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Ecole doctorale Sciences de la vie et de la santé

DOCTORAT

Pathologie et recherche clinique

Soutenu le 12 mars 2018 par

Alessandro AMADDEO

Diagnostic et prise en charge des troubles respiratoires du sommeil dans les maladies génétiques de l'enfant

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Résumé

Les troubles du sommeil chez les enfants avec une maladie génétique sont fréquents mais souvent sous diagnostiqués et sous traités. La plupart des enfants suivis dans les 40 centre de référence de maladies rares de l'Hôpital Necker peuvent présenter des troubles respiratoires et nécessiter donc d'une étude du sommeil. Ces anomalies ont besoin d'être traitées avec une prise en charge multidisciplinaire et/ou à travers une ventilation noninvasive. En plus la possibilité de développer des techniques des mesures physiologique peut aider à améliorer et simplifier le parcours diagnostique chez ces enfants.

Depuis le début de thèse j'ai suivi les deux axes principaux de ma recherche : l'exploration et le diagnostic des troubles respiratoires du sommeil chez les enfants ayant une maladie génétique et leur prise en charge. La première étude a concerné la validation chez l'enfant d'un capteur sus-sternal, capable de donner des informations concernant les efforts respiratoires pendant les études du sommeil. La deuxième étude a analysé l'utilité de réductions de l'amplitude de l'onde de pouls pendant une polysomnographie, comme mesure des réveils corticaux liés aux évènements respiratoires. J'ai aussi participé à une troisième étude concernant la validation du temps de transit de l'onde de pouls (TTP), pour la caractérisation des apnées chez l'enfant

En ce qui concerne le deuxième parti je me suis concentré sur le traitement des troubles respiratoires du sommeil. La première étude a concerné l'efficacité du traitement par PPC dans une cohorte d'enfants ayant une séquence de Pierre Robin. La deuxième étude a permis d'analyser les critères de début de ventilation noninvasive (VNI) ou PPC dans une population d'enfant ayant des maladies génétiques hétérogènes. J'ai ensuite conclu une étude sur le début d'un traitement par PPC en ambulatoire. L'étude est actuellement en révision dans une revue internationale. J'ai aussi collaboré dans l'analyse des données et dans la rédaction des plusieurs études concernant les caractéristiques des troubles respiratoires du sommeil et de leur prise en charge chez des enfants porteurs de trisomie 21, de myasthénie congénitale et d'achondroplasie.

Summary

Sleep disordered breathing (SDB) in children with genetic diseases are frequent but often underdiagnosed and not treated. Most of the patients followed in the almost 40 centers for rare diseases at Necker's Children hospital could present some kind of SDB and thus necessitate a sleep exam. For these children SDB should be treated by a multi-disciplinary team with expertise in noninvasive ventilation. Moreover, the possibility to develop simpler and efficient tool to improve the diagnosis of SDB would lead to an improvement for the care of these children. For this reason, during ma PhD program I participated in the development and validation of three tools that could simplify sleep exams in these children. The first project I developed concerned the validation of a suprasternal pressure sensor to characterize sleep apnea during sleep exam. The second project I carried out regards the use of the variations of pulse wave amplitude (PWA), a simple tool already integrated in standard respiratory sleep exam as a surrogate of cortical microarousals. This study aimed at the validation of a surrogate of cortical microarousals in order to replace the standard EEG signal for their detection and to simplify the diagnostic work up of SDB in children. During my PhD program, I also collaborate to another study concerning the use of pulse transit time (PTT) for the characterization of respiratory events during polygraphy. This study aimed at developing a simplified tool in order to increase the accuracy of standard sleep exams. The second axe of my research concerned the treatment of SDB in children with genetic and congenital disorders. The first study concerned the use of CPAP in the treatment algorithm of a series of infants with Pierre Robin sequence. This study highlighted the usefulness of CPAP in avoiding tracheostomy in this particular group of patients with severe OSAS. The second study aimed at the identification of objective criteria that lead to the initiation of CPAP or NIV in children and infants. I also collaborated to the conception, data analysis and draft redaction of a second manuscript regarding the criteria authorizing the weaning from CPAP and NIV in children. A third article concerning a program of outpatient initiation of CPAP in children is currently under revision in the Journal of Clinical and Sleep Medicine. I also collaborated in the conception, data analysis and manuscript revision of other papers regarding the description and management of SDB in children with Down syndrome, congenital myasthenia and achondroplasia.

Abbreviation list

AASM	American Academy of Sleep Medicine
AHI	Apnea hypopneas index
ATH	Adenotonsillar hypertrophy
BMI	Body mass index
BP	Blood pressure
CCHS	Congenital central hypoventilation syndrome
CHAT	Childhood Adenotonsillectomy Trial
CPAP	Continuous positive airway pressure
CSA	Central sleep apneas
CSB	Cheyne-Stokes breathing
CT	Computed tomography
DISE	Drug-induced sleep endoscopy
ECG	Electrocardiogram
EEG	Electroencephalogram
ENT	Ear nose and throat
ICSA	Idiopathic CSA
MAP	Mean arterial pressure
MDO	Mandibular distraction osteogenesis
MRI	Magnetic resonance
NIV	Noninvasive ventilation
NREM	Non-rapid eye movement
ODI	Oxygen desaturation index
OH	Obstructive hypoventilation
OHS	Obesity hypoventilation syndrome
OMA	Orthopedic mandibular advancement
OSAS	Obstructive sleep apnoea syndrome
$PetCO_2$	End-expiratory carbon dioxide
PS	Primary snoring
PSG	Polysomnography
PSQ	Pediatric Sleep Questionnaire
$PtcCO_2$	Transcutaneous carbon dioxide partial pressure
PTT	Pulse transit time
REM	Rapid eye movement
RIP	Respiratory inductance plethysmography
RME	Rapid maxillary expansion
RP	Respiratory polygraphy
SDB	Obstructive sleep disordered breathing
SpO_2	Peripheral oxygen saturation
SRBD	Sleep-Related Breathing Disorder
SWS	Slow wave sleep
TORS	Trans oral robotic surgery
TST	Total sleep time
UA	Upper airway
UARS	Upper airway resistance syndrome
UPPP	Uvulopalatopharyngoplasty

1. Definition and prevalence of sleep disordered breathing in children

a. Obstructive sleep disordered breathing in children

Obstructive sleep disordered breathing (SDB) is classically defined as a syndrome of "upper airway dysfunction during sleep, characterized by snoring and/or increased respiratory effort secondary to increased upper airway resistance and pharyngeal collapsibility "[1]. Therefore, SDB should be considered as a continuum clinical spectrum, ranging from primary snoring (PS) to upper airway resistance syndrome (UARS), obstructive hypoventilation (OH) and finally obstructive sleep apnoea syndrome (OSAS).

The prevalence of SDB is somewhat difficult to ascertain as definitions varied over time.

PS is defined as the presence of habitual snoring for more than 3 nights per weeks, in the absence of respiratory events (namely apneas and hypopneas), sleep disruption and gas exchange abnormalities. Since there is no universally accepted standard definition of snoring, its exact prevalence varies according to the different perceptions of word's meaning. As a matter of fact, differences in loudness and frequency of the phenomenon (i.e. number of nights per week, number of hours per night) have led to differences in the estimation of the prevalence of PS. The prevalence of PS, gathered via questionnaires, ranges from 1.5% to 21% in paediatric population[2] according to the different definitions. However, recent meta-analyses estimated a median prevalence of PS in children worldwide of around 11-12%[3,4]. As such, PS is common and, since its represents the less severe form of SDB, it has long time been considered as a benign disorder. However, recent data suggest a decrease of cognitive functions even in children with PS[5–7], rising the need for increased awareness regarding the consequences of the whole spectrum of SDB.

UARS has been firstly described in 1982 by Guilleminault et al[8] and is defined as the presence of snoring associated with frequent sleep arousals, but without respiratory events or gas exchange abnormalities[1]. Despite the absence of oxygen desaturations and respiratory events, UARS has been associated to daytime neurobehavioral symptoms, with a positive response to treatment similar to that of OSAS. Nevertheless, the exact prevalence of UARS has never been reported in literature, and recently this syndrome has been included in the more broaden definition of OSAS by the third international classification of sleep disorders[9], because of the impossibility to analyse separately these two entities.

OH is defined as snoring with an abnormal increase of end-expiratory ($PetCO_2$) or transcutaneous carbon dioxide partial pressure ($PtcCO_2$), without respiratory events. No data

is available on the exact prevalence of OH, since most of the studies published so far have been focused on the prevalence of OSAS. HO is frequently observed in children since the anatomical characteristics and neurological control of their upper airways generate an incomplete collapse of upper airways, with little or no repeated respiratory events, but with a continuous flow limitation resulting in carbon dioxide retention.

OSAS is the most severe form of SDB and is defined as the "recurrent partial or complete upper airway obstruction (hypopneas, obstructive or mixed apneas) with disruption of normal oxygenation, ventilation and sleep pattern"[2]. The prevalence of OSAS in children varies widely from 0.1 to 13%[4]. This variability probably derives from the different definitions and severity thresholds used over time. However, it is universally accepted that the prevalence of OSAS in children ranges between 2 to 4%[10]. OSAS is thus a relatively common disease in children.

OSAS is classically associated with tonsillar hypertrophy in otherwise healthy children, and most of the first literature data concerned this population. However, over time OSAS and SDB in general have been studied in other paediatric populations like obese children and children with congenital or genetic diseases. This revealed that OSAS is far more common in children with associated conditions like congenital craniofacial malformations, neurological and neuromuscular diseases and metabolic disorders. These children are often younger and present a multifactorial disorder that requires objective assessment and treatment of all underlying abnormalities that contribute to upper airway obstruction during sleep[11].

A disease classically associated with upper airway obstruction is Pierre Robin sequence. The original description of the sequence consists of a triad of micrognathia, glossoptosis, and airway obstruction[12] with or without cleft palate. In this population, OSAS is one of the most common and severe feature, which may need invasive maxillofacial surgery or even tracheostomy early in life. The reported prevalence of OSAS is almost 80-90%[13,14], with a greater severity than in other forms of isolated cleft palate[15].

A similar high prevalence of OSAS is observed in other craniofacial malformations[16]. In children with Goldenhar syndrome, now known as oculoauriculovertebral syndrome, OSAS is present in almost 80 to 90% of the patients [17]. Sixty percent of patients with 22q11 deletion syndrome and 65% of patients with CHARGE syndrome have OSAS. Fifty to 90% of children and 41 to 100% of adults who suffer from Treacher Collins syndrome have OSAS [18,19].

Craniosynostosis represent a heterogeneous group of disease that share a premature fusion of one or more skull sutures that may cause facial deformity. Forty percent of craniosynostosis are syndromic, with Crouzon, Apert and Pfeiffer being the most common. Almost 50% of

asymptomatic patients with non-syndromic craniosynostosis, have OSAS[20], whereas 74 to 87% syndromic patients have OSAS [16,20,21]

OSAS is also frequent in children and adults with Down syndrome with an estimated prevalence ranging between 30 and 60%[22–24], which rises to 97%[25] when including snoring.

Children with Prader Willi syndrome and with achondroplasia have an increased risk of OSAS, with a prevalence of almost 50%[26–28] and 60-90%[29,30] respectively. However, in both of these diseases, central apneas may also be present. A high prevalence of OSAS has also been reported in different subtypes of mucopolysaccharidoses[31,32].

Neuromuscular patients often exhibit OSAS in association with nocturnal hypoventilation due to progressive respiratory muscles weakness, with a prevalence of 65%[33] in children with congenital myopathy and up to 30% in adolescents with Duchenne dystrophy[34]. Even patients with Ehlers-Danlos syndrome may have OSAS, with a prevalence ranging from 32 to 100% [35,36].

In summary, SDB is quite common in otherwise healthy children but the prevalence in children with congenital and genetic diseases is higher often with a more severe form of OSAS. For this raison, given the cumulative high prevalence of these “otherwise rare” diseases, a tailored approach to the diagnosis, and a careful and specific treatment should be reserved to these children.

Table 1. Prevalence of OSAS in different congenital or genetic diseases of childhood associated with craniofacial malformations.

	Incidence	**Prevalence of OSAS**
Craniofacial abnormalities		
- *Pierre Robin Sequence*	1/8000-14000 [37,38]	80-90%[13,14,37]
- *Goldenhar syndrome*	1/5600[17]	80-90%[17,48]
- *22q11.2 deletion syndrome*	1/4000[39]	60%[49]
- *CHARGE syndrome*	1/8500[40]	65%[50]
- *Treacher Collins syndrome*	1/50000[41]	50-90%[18,19]
Craniostenosis	1/2500[42]	75-90%[16,20,21]
Down syndrome	1/700[43]	30-60%[22,23,25]
Ehler-Danlos syndrome	1/10000[44]	30-100%[35,36]
Prader Willi syndrome	1/25000[45]	50%[26–28]
Achondroplasia	1/25000[46]	60-90%[29,30,51]
Mucopolysaccharidosis	1/65000[47]	60-95%[31,32,52]

b. Definition and prevalence of central apneas in children

Although SDB classically comprises all abnormal respiratory events, including thus both obstructive and central events, obstructive respiratory events are far more common than central respiratory events in children (with the exception of the physiological central apneas in newborns and young infants). However, central sleep apneas (CSA) may be observed in some children presenting specific disorders.

Central apneas in children are defined, according to the latest American Academy of Sleep Medicine (AASM) recommendations[53], as a cessation of airflow without thoraco-abdominal movements, lasting at least 2 respiratory cycles in association with oxygen desaturation, awakenings or cortical arousal, or lasting at least 20 seconds. Additionally, in infants, central apneas could be scored if an apnea, without thoraco-abdominal movements, occurs along with a decrease in heart rate to less than 50 beats per minute for at least 5 seconds or less than 60 beats per minute for 15 seconds. It is important to highlight that brief central apneas are common in children, especially in association with movements, but they are usually not associated with a desaturation or an arousal. Thus, scoring should be performed by a reader who has a qualification and expertise in pediatric sleep in order to not overestimate the number of central apneas.

In adults, CSA is quite common in some disorders. CSA are present in almost 35-40% of patients with heart failure and a left ventricular fraction of less than 45%[54]. Idiopathic CSA (ICSA), narcotic-induced central apnoea, obesity hypoventilation syndrome (OHS), and Cheyne-Stokes breathing (CSB) are other well described forms of central apnoea in adults[55]. While the precise precipitating mechanisms involved in the various types of CSA may vary considerably, unstable ventilatory drive during sleep represent a cornerstone underlying feature.

In children, central apneas are common during the neonatal period, especially in premature newborns and may be observed as isolated apneas or as an unstable periodic breathing[56,57]. This entity is called apneas of the premature and the mechanism underlying CSA in the newborn probably involves an immature chemo-responsiveness to carbon dioxide (CO_2) and oxygen (O_2), given the spontaneous resolution between 36 to 43 weeks of gestation age[56]. With the progressive brain maturation, central apneas decrease physiologically with increasing age[58,59] but may persist in children with congenital or acquired disorders impairing ventilatory drive. One of the best example of this mechanism is congenital central hypoventilation syndrome (CCHS), a rare genetic disorder of respiratory control

characterised by an autonomic nervous system dysregulation and an impaired development of neural crest-derived cells (neurocristopathy)[60]. This disorder is caused by a polyalanine repeat expansion mutation (PARMs) of the PHOX2B gene[61] and leads in its classical form to a complete dependency on ventilatory support due to CSA and hypoventilation. However this disease is very rare[62] and only limited data have been published on other causes of CSA in children over one year of age. The estimated prevalence of CSA in children is not known, but published data indicate that only 5% of children referred for a sleep study have significant increased central apneas[63]. Diseases associated with brainstem compression or central nervous system immaturity such as Arnold–Chiari malformation[64], mucopolysaccharidosis[32] or achondroplasia[51] may be cause CSA. Moreover, CSA has been described in other diseases such as Prader–Willi[26] syndrome and hypothyroidism[65]. It has to be noted that in some of these syndrome OSAS and CSA could coexist due to the presence of upper airways obstruction and to a deficient ventilatory control. Indeed, instances whereby central respiratory events lead to obstructive respiratory events in patients with vulnerable pharyngeal anatomy, and vice versa, are observed in some sleep apnea patients. The overlap between CSA and OSAS suggests that common mechanistic traits are likely involved[66]. Typically, CSA is considered to be the primary diagnosis when ≥ 50% of apneas are scored as central in origin, whereas complex apnea syndrome is considered when central apneas are less than 50% of the respiratory events[67]. However, such thresholds are clearly arbitrary and derive from adult sleep studies performed mostly in patients with heart failure.

2. Paediatric OSAS phenotypes

Given the different clinical manifestations and physiopathological specificities, the classic clinical OSAS in children differs markedly from OSAS seen in adults. However, since the initial description by Guilleminault in 1976, the comprehension of SDB in children and its physiopathology has progressively evolved. The role of adenotonsillar hypertrophy appeared predominant in the first description of the disease. During the last three decades, the epidemic of childhood obesity had contributed to the emergence of a new phenotypic variant of OSAS in children. Indeed, OSAS was found to be highly prevalent in children with some underlying diseases affecting the upper airway. These findings led to a new classification of SDB in children into three clinical phenotypes [68] . Children with type 1 OSAS are normally pre-school aged, not obese, they do not present daytime somnolence but are rather hyperactive. They usually have adenotonsillar hypertrophy, they are more prone to recurrent ear, nose and throat infections and less prone to develop metabolic and cardiovascular morbidities. The AHI is usually moderately elevated. Adenotonsillectomy represents the first line treatment of OSAS type 1 and is generally able to cure the OSAS. Type 2 OSAS is classically seen in obese children, particularly in those with marked truncal obesity. These children have often an important daytime sleepiness, neurocognitive and mood disturbances and are more prone to cardiovascular and metabolic complications. Although hypertrophy of the adenoids and tonsils still plays a predominant role in OSAS on obese children and represents the first line treatment after weight loss, the efficacy of upper airway surgery is less effective than the type 1 OSAS[69]. The third OSAS phenotype is represented by children with congenital malformation, genetic diseases or in general with any underlying disease that may contribute to the pathogenesis of OSAS. This so-called "complex OSAS" differs from the type 1 and 2 for several reasons. First of all, no age distribution is present in this group. Children may have OSAS at any age, from infancy to late adolescence, according to the underlying disease. This has been clearly demonstrated in Prader Willi syndrome, Down syndrome, achondroplasia, Treacher Collins and other diseases[19,22,27,28]. The severity of the OSAS is usually increased[15,25,30,42] and the pathogenesis is far more complex than solely adenotonsillar hypertrophy and/or obesity. Therefore, treatment approach is also very different from OSAS type 1 and 2, since adenotonsillectomy is more likely to be insufficient to cure OSAS. Because of the presence of comorbidities, the neurological and cardiovascular consequences of OSAS are difficult to evaluate, but some evidences exist regarding the role of OSAS in the intellectual deficit of some of these patients[70]. Moreover, the complexity of clinical presentation tends to

complicate the evaluation of symptoms in these children. This explains why objective measure to ascertain the severity of OSAS are even more important in type 3 OSAS than in the other two groups.

In conclusion OSAS appears as a complex disease in children, with the presence of at least three distinct phenotypes, which differ from the physiopathology to the clinical manifestation and more important to the treatment approach which should be tailored on the underlying disease in type 3 OSAS. Furthermore, most of the studies on pediatric OSAS have focused on type 1 patients with less information on the other two groups.

Table 2. Different clinical entities of SDB in children

	Type 1	**Type 2**	**Type 3**
Age distribution	Pre-school age	School age, adolescents	Any age group
Predisposing factors	Adeno-tonsillar hypertrophy	Truncal obesity	Genetic/congenital malformations
Severity	Mild to moderate	Moderate	Severe
Behavioural and cognitive symptoms	Hyperactivity	Somnolence, depression	Difficult to determine and poorly evaluated (presence of comorbidities)
Cardiovascular consequences	Little or none	Systemic hypertension	Poorly evaluated, increased risk of pulmonary hypertension
Metabolic alterations	Little or none	Associated metabolic syndrome	Not evaluated

3. Physiopathology and risk factors for OSAS in children

The upper airway consists of the nose, pharynx, larynx, and extrathoracic trachea. The pharynx is a collapsible segment which is under the balanced control of dilator and constrictor muscles. During wakefulness, significant reduction of the airway patency is rare even in individuals with markedly enlarged tonsils, obesity, craniofacial anomalies, and/or abnormal neuromuscular tone. This is explained by the ability of the pharyngeal dilators to compensate for whatever factors that might lead to upper airway collapse. During sleep, the neuromuscular tone of the pharyngeal dilators, and their coordination with the inspiratory pump muscles, is decreased so that they are less able to compensate for this airway collapsability. Pharyngeal dilator muscles activity decreases during non-rapid eye movement (NREM) sleep in children and decreases further during rapid eye movement (REM) sleep[71]. Neuromuscular control of upper airway patency is affected by central ventilatory drive, arousal responses to respiratory occlusion (arousal threshold), and upper airway reflexes[72]. Central ventilatory drive is increased during childhood and declines gradually with age[73,74].

There is a physiological decrease in alveolar ventilation during REM sleep because lung volumes are lower, intercostal muscles do not substantially contribute to inspiratory effort, and the pharyngeal dilators are less effective than during NREM sleep. In patients with SDB these alterations lead to a sleep tracing in which:

- REM periods are often associated with hypoventilation and significant oxygen desaturations
- NREM stage N3 (slow-wave sleep) is relatively protected without desaturations
- NREM stage N2 shows modest desaturations

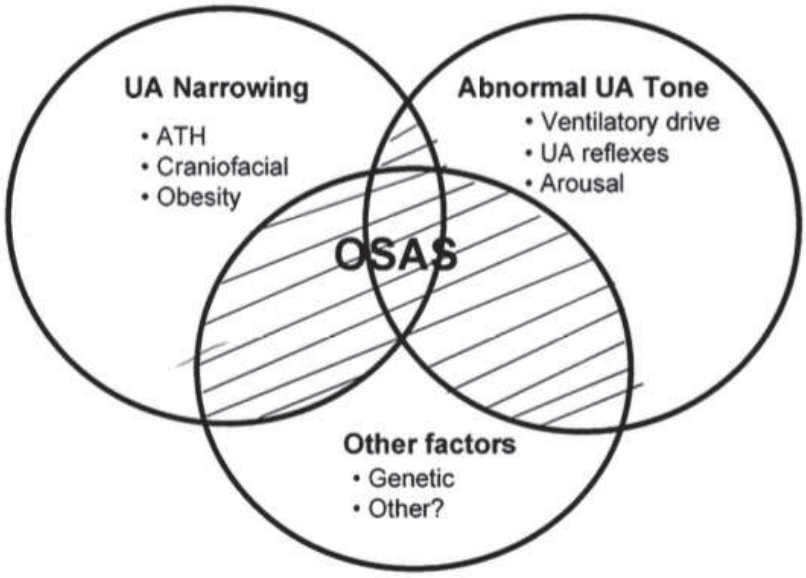
These alterations are explained by the attempt of the child to compensate for the different alterations of airway control during sleep. At sleep onset, the tone of the pharyngeal dilators decreases, leading to a decrease in airway caliber. Upper airway resistance increases consequently, resulting in a decrease in the intraluminal pressure in the pharynx. The decreased airflow, increased negative pressure, and the increase in CO_2 stimulate the pharyngeal mechanoreceptors to increase pharyngeal dilator contractions[75]. In a child without SDB, this physiological response maintains airway patency.

In children with SDB, this response in insufficient and not able to prevent upper airway collapse. In the mildest form of SDB, a modest decrease in the caliber of the pharyngeal airway leads to a turbulent airflow causing vibration of the soft palate and snoring. As the upper airway obstruction worsens, hypoventilation develops, reflected by a rise in PCO_2 and/or a

decrease in arterial oxygen saturation. This further stimulates the pharyngeal dilators and the respiratory pump muscles. In many children with OSAS, this response usually is sufficient to maintain a partially open pharyngeal airway for long periods of sleep without experiencing obstructive apneic events. By contrast, adults with OSAS are more likely to have acute obstructive apneic events, leading to arousals, because the pharyngeal dilators are less effective and/or the pharynx is more collapsible as compared to children. This increased drive during sleep accounts for the increased upper airway reflexes and tone in children, resulting in a tendency to collapse at more negative pressure than adults[76]. On the other hand, children with OSAS present a critical upper airway closure pressure close to positive values[77], which does not return to normal after adenotonsillectomy[78]. These findings suggest an impairment in maintaining an adequate pharynx dilator muscles tone in children with OSAS. Thus, given this increase in ventilatory drive, children have a specific breathing pattern of OH rather than the discrete, cyclic obstructive apneas pattern that is commonly seen in adult SDB[79].

In order to account for all the factors playing a role in OSAS in children, Marcus[80] proposed a model to explain the physiopathology of OSAS as the result of a combination of upper airway narrowing, abnormal upper airway neuromotor tone and other factors like genetic determined control of the upper airways or subtle anatomical anomalies. This model explains the multifactorial origin of OSAS in children and highlights the need for a tailored approached to this disease.

Figure 1. Pathophysiology of obstructive sleep apnea.



Abbreviations: UA: upper airway, ATH: adenotonsillar hypertrophy, OSAS: obstructive sleep apnea. *Figure from reference [63]*.

Adenotonsillar hypertrophy is universally accepted as the most common and important risk factor for OSAS children with type 1 profile. Adenoid and tonsils grow progressively during childhood[76,81], but at a faster rate than the skeletal boundaries of the upper airways. Between the ages of 3 and 8 years, the tonsils and adenoids are largest in relation to the upper airways size. In preschool children with OSAS, a reconstruction of the upper airways via computed tomography (CT) demonstrated that most children had a narrower volume and cross-sectional area at the intersection between tonsils and adenoids than healthy controls, confirming the primary role of lymphoid tissues in type 1 OSAS pathogenesis[82]. Nevertheless, as anticipated, adenotonsillar hypertrophy is not the only factor causing OSAS in children. First of all, there is lack of correlation between the tonsils and adenoids size and the severity of OSAS[83]. Secondly, if adenotonsillar hypertrophy was the only determinant of OSAS, it would be difficult to explain the high rate of persistent OSAS after adenotonsillectomy[84,85]. Subtle craniofacial abnormalities may therefore increase the risk of OSAS in non-syndromic children. A meta-analysis identified a retrusive chin, a steep mandibular plane, a vertical direction of craniofacial growth and a tendency toward class II malocclusion to be related to the presence of OSAS[86].

Some evidences suggest also familial clusters of OSAS. In particular, a history of parental adenotonsillectomy[87,88] or OSAS[89] increases the risk of OSAS in siblings. It has been speculated that some genetic factors, involved in craniofacial development and pharyngeal muscles control, may also play a role in the pathogenesis of OSAS.

Obesity represents the hallmark of type 2 OSAS in children as in adults. The severity of OSA correlates to the degree of obesity, such that for every 1 kg/m^2 increment in body mass index (BMI) beyond the mean BMI for age and gender, the risk of OSAS increases by 12%[90]. In a prospective study, OSAS was diagnosed in 4% of adolescents (16 to 19 years of age) and most of them had no signs or symptoms of OSAS during mid-childhood[91], before developing obesity. Although obesity is not as common in children as it is in adults, its prevalence is increasing worldwide, in particular in adolescents[92–94]. Because the prevalence and severity of obesity in children is increasing, it is likely to become an important cause of pediatric SDB in the future, particularly in adolescents and young adults[92–94]. Fat pad infiltration of upper airway explains the increased OSAS in obesity[4,90,95–97]. Obesity contributes to airway narrowing in several ways, including fatty infiltration of areas surrounding the airway, tongue, or fat pads lateral to the airway. Importantly, magnetic resonance studies showed that upper airway lymphoid tissue is significant increase in obese children with OSAS[98,99].

Increased adipose tissue in the abdominal wall and cavity as well as surrounding the thorax increases the global respiratory load, reducing intrathoracic volume and diaphragm excursion, particularly in the supine position, leading to hypoventilation[100]

Children with type 3 OSAS have an increased prevalence of OSAS whose physiopathology largely depends on the underlying disease.

In Pierre Robin sequence, airway obstruction has been long-time considered to be exclusively related to glossoptosis. However, more recent data suggest at least four distinct mechanisms of OSAS. In type 1 mechanism, (the most commonly seen in Pierre Robin sequence) the dorsum of the tongue moves to the posterior pharyngeal wall. In type 2, the tongue moves posteriorly and compresses the soft palate or the cleft palatal tags against the posterior pharyngeal wall. In type 3, the lateral pharyngeal walls move medially and oppose one another; and in type 4, the pharynx constricts in a circular manner[101]. Other evidences suggest also a dysfunction of the lingual and pharyngeal motor organization without any structural impairment in brainstem nuclei and pathways[14]. Children with Down syndrome have numerous factors contributing to the development of SDB such as midface hypoplasia, a high-arched palate, macroglossia, cranial base anomalies, hypotonia, laryngomalacia and enlarged adenoids[102]. SDB is also common in patients with achondroplasia. Maxillary hypoplasia, micrognathia, and a depressed nasal bridge causing narrow choanal size, adenotonsillar hypertrophy, high palate and airway muscles hypotonia in infancy are all risk factors contributing to the high prevalence of OSAS in these patients[103].

The most common neuromuscular problems contributing to SDB are alterations in muscle tone (either hypotonia or hypertonia). Given the large heterogeneity of these diseases, involving virtually any part of the nerve and muscle, the pathophysiology of SDB varies largely according to the different pathological alteration. For instance, disorders with prominent cranial nerves involvement may lead to upper airways collapse with a predominant pattern of OSAS, whereas involvement of the respiratory muscles may cause nocturnal alveolar hypoventilation in the absence of obstructive events. The normal loss of muscle tone during REM sleep decreases the rib cage contribution to the tidal volume to ~ 19%, compared to the ~ 40% observed during wakefulness and quiet sleep[104]. Susceptibility of the different respiratory motor neurons to REM atonia varies widely, with the least depression of respiratory muscle output found in the phrenic nerve and the most suppression in inspiratory laryngeal, expiratory pharyngeal, and inspiratory and expiratory intercostal nerve activities[105]. Therefore, the chest wall excursion in REM sleep depends predominantly on the preserved diaphragm function[106]. Thus, diseases with a prominent diaphragmatic

involvement manifest with predominant REM sleep hypoventilation. Finally, chronic changes in muscle tone may have significant effects on growth and development of the facial skeleton, thereby affecting upper airway patency and thus OSAS.

Finally, anthropometric and demographic variables are also correlated to OSAS in children. Male sex has been reported as a predisposing factor for OSAS by two epidemiological studies, whereas other evidences suggest a similar prevalence in both sexes[107,108]. Even if this increased prevalence in boys is not confirmed so far, a strong correlation between male sex and persistent OSAS after adenotonsillectomy has been clearly demonstrated[85,109]. Also, ethnicity predispose to the development of OSAS with African American having a higher risk of OSAS compared to Caucasian and Asian ethnicities[110].

4. Clinical manifestations of SDB

Clinical manifestations of SDB in children differ from adults. Children tend to have a much more varied constellation of symptoms, often difficult to recognize. In contrast to adults, normal children snore infrequently. This is consistent with the better preservation of upper airway patency in case of subatmospheric pressure. Excessive daytime sleepiness, which is a hallmark of poor sleep quality in adults, is rarely observed in children with SDB[111]. Rather, children tend to be hyperactive. Also, symptoms evolve and change with age as shown in Table 3. Some symptoms are observed at any age, such as night-time awakenings, while other symptoms are more common in some age groups.

Snoring is usually not present in infants, but parents report frequently a "noisy" breathing, snorting or gasping. Poor sucking or difficult feeding may be related to hypotonia, which is a risk factor for SDB in this younger age group. Stridor or gasping is often reported in the presence of layngomalacia or vocal cord paralysis. A history of brief resolved, unexplained events may be associated with the presence or the development of OSAS[11].

In toddlers, snoring may initially occur in the supine position, but as the severity of airway obstruction increases, snoring may be observed in any sleeping position. In this age, the parents may report apneas and difficult breathing, often described as paradoxical movements of thoracic cage during inspiration along with retractions. Abnormal sleep position, with hyperextension of the neck, mouth breathing, agitation during sleep and excessive sweating are also reported. Finally, parents may acknowledge staying awake during the night to monitor the breathing of their child, in order to stimulate him/her during sleep in case of abnormal breathing.

In pre-school children, symptoms of SDB are similar to those observed in toddlers. However, as the children start kindergarten and need to adapt to a sleep routine, difficult awakenings due to sleepiness become more apparent. In this age, secondary enuresis needs to be investigated.

In school-age children, snoring, night awakenings and mouth breathing are common. Learning difficulties secondary to poor concentration and impaired short-term memory become apparent. Daytime symptoms may include nasal obstruction, mouth breathing or other signs of adenotonsillar hypertrophy, which configure the so-called "adenoid-facies" (Figure 2).

In adolescents and young adults, an "adult" presentation with snoring and daytime sleepiness is common. Moreover, mood disturbances such depression and anxiety may occur and affect quality of life.

Symptoms of SDB are more difficult to detect in children with type 3 OSAS. Poor feeding is usually present at birth in Prader Willi syndrome and Pierre Robin sequence irrespectively of the presence or the severity of the upper airway obstruction. Sleep agitation and awakenings are common in children with neurological diseases such as epilepsy. Daytime agitation and intellectual disability are present in several genetic diseases such as Down syndrome and Prader Willi syndrome which hinders the evaluation of the specific impact of sleep apneas in these children.

While most children with OSAS have a normal physical examination in type 1 OSAS, several clinical abnormalities may be observed. These may provide direct or indirect evidence of increased upper airway resistance and guide the diagnosis and the potential complications of SDB.

The child's height and weight should be plotted on a standard growth chart because failure to thrive may be observed in some children with severe OSAS. Body mass index (BMI) should be calculated and evaluated following specific age-related percentiles, since overweight and obesity are an important risk factor for OSAS. Blood pressure should be measured at every physical examination as OSAS represents a recognized risk factor for systemic hypertension. Upper airway anatomy should be carefully evaluated searching for craniofacial abnormalities like midface hypoplasia, retrognathia and/or micrognathia. Mouth breathing, “adenoid” facies, nasal airflow obstruction or hyponasal speech may be features of adenoidal hypertrophy, which may contribute to or cause OSAS. Mucosal or turbinate swelling suggests chronic nasal congestion, which may be allergic. Septal deviation should also be actively searched.

Abnormal maxillomandibular development like a high-arched and narrow hard palate, a crossbite, overlapping incisors, and significant overbite should be noted. Macroglossia, as observed in Down syndrome, Wiedemann Beckwith syndrome and mucopolysaccharidoses, may reduce the caliber of the upper airway. Since tonsillar hypertrophy is a major contributor to SDB in children, tonsils size should be evaluated with the Mallampati classification and the Friedman score (Figure 3).

Clinical examination is also important in type 2 and 3 OSAS groups. However, in these cases a more comprehensive work-up is warranted. For instance, some of these children could have turbinate or lingual tonsils hypertrophy, or associated laryngeal or tracheal malformations that required an endoscopic or radiological evaluation.

Table 3. Symptoms of sleep disordered breathing in children by age

Infants (3-12 months)	*Toddlers (1-3 yr)*	*Pre-school (3-5 yr)*	*School (5-18 yr)*
- Noisy breathing - Witnessed apneas - Frequent arousals - Difficult breathing - Mouth breathing - Nocturnal sweating - Failure to thrive - Nasal congestion - Hyperextended neck - Poor sucking - Stridor - Breathholding spells	- Snoring - Witnessed apneas - Frequent arousals - Difficult breathing - Mouth breathing/dry mouth - Nocturnal sweating - Failure to thrive - Nasal congestion - Hyperextended neck - Restless sleep - Sleep terrors - Confusional arousal - Irritability - Daytime sleepiness	- Snoring - Witnessed apneas - Frequent arousals - Mouth breathing/dry mouth - Nocturnal sweating - Failure to thrive - Nasal congestion - Hyperextended neck - Sleep terrors - Confusional arousal - Sleepwalking - Daytime sleepiness/ persistent naps - Restless sleep - Enuresis - Hyperactivity, inattention - Difficulty waking up in morning - Morning headache - Sleep in knee-chest position	- Snoring - Witnessed apneas - Frequent arousals - Mouth breathing/dry mouth - Nocturnal sweating - Failure to thrive - Nasal congestion - Hyperextended neck - Nightmares - Sleeptalking - Confusional arousal - Sleepwalking - Daytime sleepiness - Restless sleep - Enuresis - Hyperactivity, inattention - Difficulty waking up in morning - Morning headache - Insomnia - Learning difficulties - Delayed puberty - Mood disorders - Hypertension

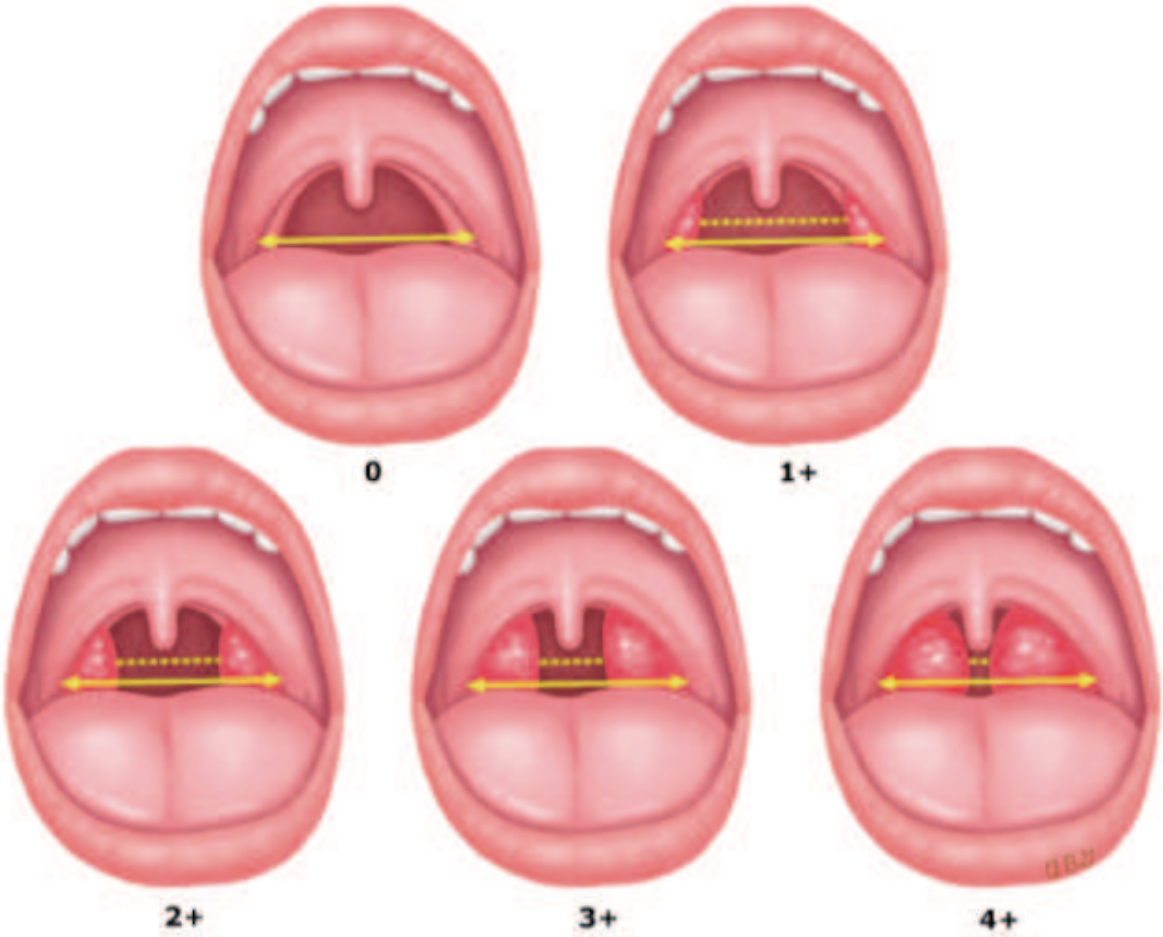
Adapted from reference [112].

Figure 2. Child with a typical “adenoids facies”.

Note the presence of narrow pinched nostrils, open mouth, everted upper lip and the loss of nasolabial folds.

Adapted from reference [113]

Figure 3. Tonsils grading by the Mallampati score



Tonsil size is graded on a scale from 0 to 5:

0 — Tonsils are entirely within the tonsillar pillar, (or previously removed by surgery).

1+ — Tonsils occupy less than 25 percent of the lateral dimension of the oropharynx, as measured between the anterior tonsillar pillars (solid yellow arrow).

2+ — Tonsils occupy 26 to 50 percent of the lateral dimension of the oropharynx.

3+ — Tonsils occupy 51 to 75 percent of the lateral dimension of the oropharynx.

4+ — Tonsils occupy more than 75 percent of the lateral dimension of the oropharynx.

Adapted from reference [114].

Figure 4: Grading of the pharyngeal space by the Friedman score.

Fig 1. Friedman Palate Position I allows visualization of the entire uvula and tonsils/pillars.

Fig 2. Friedman Palate Position II allows visualization of the uvula but not the tonsils.

Fig 3. Friedman Palate Position III allows visualization of the soft palate but not the uvula.

Fig 4. Friedman Palate Position IV allows visualization of the hard palate only.

Adapted from reference [115]

5. Consequences of SDB in children

The consequences of SDB in children are multifaceted. If untreated, or alternatively if treated late, pediatric SDB may cause substantial morbidity that affects multiple target organs and systems. Importantly, some deleterious consequences observed in children may not be completely reversible even after appropriate treatment. Obstructive SDB in children can compromise somatic growth, lead to neurocognitive disturbances, learning deficits, impaired behaviour, cardiovascular and metabolic morbidity, and decreased quality of life. However, not all children will manifest all the consequences of SDB. It is therefore reasonable to assume that in addition to the severity of the underlying sleep disorder, some genetic and environmental factors may play a critical role in the susceptibility to end-organ injury. Moreover, consequences of SDB have been well described in type 1 OSAS but much less in children of the type 2 and type 3 OSAS groups. These children often present comorbidities deriving from their underlying disease. Therefore, the exact role of OSAS related consequences and most importantly, their reversibility with treatment, represent the main concern for these two groups of patients.

Neuropsychological and cognitive problems associated with SDB

The behavioural and academic consequences of sleep fragmentation, including inattention, hyperactivity, impulsivity, and irritability, may be the primary presenting complaints in children with SDB, whatever the severity, including PS.

OSAS in children has been associated with neurobehavioral symptoms by many authors[116–120]. "Externalizing" behaviours are particularly frequent, including aggressivity, impulsivity, hyperactivity, oppositional behaviour, and conduct problems[121,122]. Oppositional-defiant disorder and conduct disorders or related disruptive behaviours such as bullying are also common consequences of pediatric SDB[123,124]. Other alterations include emotional dysregulation and "internalizing" behaviours such as irritability, mood instability, low frustration tolerance, depression/anxiety, social withdrawal, and increased somatic complaints. "Classic" symptoms of excessive daytime sleepiness (e.g., difficulty waking in the morning, falling asleep at inappropriate times, or increased napping) are common in adults with OSAS but tend to be less obvious in children, except in adolescents, obese children or those with severe SDB.

The evidence regarding the effect of OSAS on cognition is less robust than for behavioural manifestations. A number of studies have suggested an association between OSAS and impaired executive functions such as tasks involving reaction time, vigilance, and sustained and selective attention, in otherwise healthy children[116,117] and in those with underlying neurocognitive deficits such as Down syndrome[70,127]. However, other areas of impairment are not consistent across studies. Most studies have failed to find a dose-dependent relationship between pediatric OSAS severity and the degree of cognitive (or behavioural) impairment. Some cognitive deficits, such as language delay and impairment in visual perception, motor function, and memory, have been identified in very young children with only mild SDB. For example, infants with persistent habitual snoring have been found to have lower scores on a standardized measure of infant/toddler development (Bayley scores)[128].

However, it is likely that the association between OSAS and behavioural or cognitive dysfunction may have been confounded by other factors that also increase the risk of cognitive impairment, including comorbid conditions (prematurity, underlying disorders and co-occurrence with other sleep disorders); environmental and sociocultural influences (short sleep duration, exposure to environmental smoke, and economic disadvantage); and genetic susceptibility.

Metabolic consequences

Insulin resistance, dyslipidaemia, hypertension, and obesity represent a cluster of conditions included in the definition of "metabolic syndrome". Obesity is a risk factor of metabolic syndrome even in the paediatric population, since every 0.5 unit increment in BMI (converted to a Z score) increases the risk of metabolic syndrome by nearly 50%[130]. OSAS has been identified as an important risk factor for the occurrence of metabolic syndrome in adult patients[130,131] but not in children[132,133]. However, similar to adults when obesity and OSAS coincide in children, these two conditions contribute to induce metabolic disturbances[134,135]. Conflicting data exist on the role of OSAS-driven inflammation in the cardiovascular morbidity of OSAS in children. Serum uric acid, a reliable marker of oxidative stress, was found elevated in a group of overweight children, with a significant relationship between the severity of OSAS and serum uric acid levels[136], and a normalisation of uric acid after treatment[137]. An independent interaction between nocturnal intermittent hypoxia and increased white blood cell and neutrophil levels in overweight and obese children and adolescents has also been demonstrated[138].

Nevertheless C-reactive protein (CRP), a marker of systemic inflammation often elevated in adults with OSAS, was found to be normal in these children.

Cardiovascular comorbidities

Cardiovascular complications are a major OSAS morbidity in adults. In children, data are scarce, and the long-term effects of OSAS are difficult to assess given the lack of long term follow-up. However, children with severe untreated OSAS, defined as an AHI of more than 5 events/h, have an increased prevalence of systemic hypertension with an odd ratio of 3.9 for systolic and 3.3 for diastolic hypertension[139]. Interestingly, in a group of 101 children, aged 6 to 13 years, severe OSAS (defined as an AHI higher than 5 events/h) was associated with a lower right ventricular ejection fraction, increased left ventricular diastolic dysfunction and cardiac remodeling with larger interventricular septal thickness index on the echocardiogram, independent of the presence of obesity[140]. Furthermore, some of the cardiovascular comorbidities associated with OSAS tend to improve with treatment. Indeed, the regular use of CPAP for 6 months in children with OSAS was able to significantly reduce systolic pressure[141]. Concerning the possible contribution of OSAS to cardiovascular diseases, it has been shown that lipid peroxidation levels correlated with the degree of intermittent hypoxia in children[142], possibly contributing to endothelial dysfunction[143,144] and to later cardiovascular morbidity.

OSAS may lead to pulmonary hypertension or cor-pulmonale[145,146]. The overall prevalence is unknown, but the prevalence of symptomatic pulmonary hypertension is very low in children. This may be explained by the timely diagnosis and treatment of severe OSAS. The possibility of a different response of pulmonary circulation to hypoxemia in children may not be excluded. However, an increase risk of pulmonary hypertension has been reported in children with type 3 OSAS. In particular, children with several underlying diseases like craniosynostosis[147], Duchenne muscular dystrophy[148], achondroplasia[29,149,150], Down syndrome[151,152] or mucopolysaccharidosis[52,153] have an increased risk of symptomatic pulmonary arterial hypertension.

Growth

Severe OSAS has been classically associated with failure to thrive, especially in infants and toddlers. But growth delay is multifactorial. It has been postulated that severe OSAS leads to

increased energy expenditure due to elevated work of breathing during sleep, in particular during REM sleep[154,155]. Nocturnal growth hormone secretion, which peaks during slow wave sleep (SWS)[156], may be decreased in children with sleep fragmentation due to increased upper airway resistance [157]. Moreover, tonsillar hypertrophy may lead to a reduction of food intake due to mechanical obstruction[158]. The positive effect of adenotonsillectomy on growth and in particular on weight has been reported[3,155] in non-obese children. However this effect has also been observed in obese children, with a consequent increased risk of residual OSAS after adenotonsillectomy [159]. However, although reported, failure to thrive is rarely observed nowadays, probably due to an increased awareness and diagnosis of OSAS.

6. Diagnosis of SDB in children

Nocturnal, attended, laboratory polysomnography (PSG) is the gold standard for diagnosis of SDB. However, due to limited resources and in an effort to simplify the diagnosis of OSAS, other simpler measurements have been proposed over time. Nevertheless, the diagnosis of OSAS in children derives from the combination of history, symptoms, clinical examination, and a sleep study. According to the recommendations of the AASM, the diagnostic criteria for OSAS in children, which includes also upper airway resistance syndrome and obstructive hypoventilation, are:

Clinical criteria ("A criteria") – The presence of one or more of the following clinical symptoms (reported by the parents or caregivers):

- Snoring
- Laboured, paradoxical, or obstructed breathing during the child's sleep
- Sleepiness, hyperactivity, behavioural problems, or learning problems

Polysomnographic criteria ("B criteria") – The PSG demonstrates one or both of the following:

- One or more obstructive apnoea, mixed apnoea, or hypopnoeas, per hour of sleep.
- A pattern of obstructive hypoventilation, defined as at least 25 percent of total sleep time spend with hypercapnia ($PtcCO_2$ >50 mmHg) in association with one or more of the following:
- Snoring
- Flattening of the nasal pressure waveform
- Paradoxical thoraco-abdominal motion

AHI is calculated as the total number of apneas and hypopneas scored during the recording, divided by the total sleep time. This index is universally used to assess the severity of OSAS. Normative referenced values for healthy children have been published and have led to the following grading of OSAS severity [58,160,161].

The following categories are classically used as an index of severity[162]:

- Mild OSAS – AHI 1 to 4.9 events/h,
- Moderate OSAS – AHI 5 to 9.9 events/h
- Severe OSAS – AHI >10 events/h

As these cut off values have not been validated against end-organ morbidity in children in the literature, especially in infants and toddlers, some authors consider that a AHI of more than 5 events/h should be considered as severe[1]. The main raisons for this lower cut-off is that even children with an AHI >5 events/h may have an increased risk of elevated blood pressure as compared with healthy controls[163] and a lower rate of spontaneous improvement as demonstrated in the CHAT study[85] .

Clinical data and Questionnaires

Patient's clinical history and physical examination are less reliable than PSG to diagnose OSAS. Parents should be asked about the presence of snoring, agitated sleep, apneas, mouth breathing, awakenings and enuresis. Moreover, clinical characteristic such as tonsillar hypertrophy, dental occlusion class or the presence of other craniofacial malformations should be actively searched.

In an attempt to assist the diagnostic algorithm, several questionnaires have been developed. These questionnaires may be used for clinical screening or assessment when access to full PSG is limited but also to prioritise children for a PSG.

The Sleep-Related Breathing Disorder (SRBD) scale from the Pediatric Sleep Questionnaire (PSQ) is a well-known and worldwide used questionnaire[164]. SRBD generates a score that aims to predict improvement in behaviour, quality of life, and sleepiness after adenotonsillectomy. In the original validation study, the questionnaire correctly classified 86 and 85 percent of children and had a sensitivity of 0.85 and 0.81, with specificity of 0.87 in pediatric population[164]. The total score on the PSQ ranged from 0.0 to 1.0, and a score ≥0.33 suggested a high probability of OSAS.

Only few questionnaires used in adults are applicable in children. The Epworth Sleepiness Scale has been modified for children and may be helpful to assess sleepiness in disorders such as OSAS or narcolepsy, or to follow the response to treatment[120] and a modified pediatric version is available[165].

Scores combining the patient's history and clinical findings are also available and seem to yield better results as questionnaires alone. As an example, the sleep clinical record proposed by Villa et al[166] has a sensitivity of 96% and a positive likelihood value of 2.91.

However, no questionnaire may substitute PSG for the diagnosis of OSAS and therefore these tools are nowadays mainly used for the screening and for prioritizing children for a PSG.

Imaging and ENT endoscopy

Children with type 3 OSAS have a high risk for airway abnormalities, and in particular cases should be evaluated with airway imaging in order to assess the presence of respiratory obstruction and its level. Historically plain radiography or cephalometry (a lateral radiograph of the head and neck) has been used to evaluate upper airways. However, these techniques are not so informative and therefore (CT) or magnetic resonance (MRI) of the upper airway are preferred nowadays. Some patients may warrant an ENT endoscopy or a drug-induced sleep endoscopy (DISE) in order to identify the site of obstruction during sleep. These tests quantify the degree and site of obstruction and help with planning for surgical procedures, such as adenotonsillectomy, but they are not indicated in the routine diagnostic evaluation of children with suspected OSAS.

Nocturnal Oximetry

Overnight continuous pulse oximetry consists of the simultaneous monitoring of pulse rate, pulse amplitude, and SpO_2. Ideally an analysis of trend with an averaging time of 3 seconds should be performed. According to the McGill criteria, patients may be divided in 4 groups based on the minimal SpO_2 and on the number of clusters of 4% oxygen desaturation[167] (Table 4).

Table 4: McGill oximetry score

Oximetry score	Comment	Criteria			Other
		Number of SpO_2 drops < 90%	Number of SpO_2 drops < 85%	Number of SpO_2 drops < 80%	
1	Normal	< 3	0	0	SpO_2 stable (<3 clusters) and > 95%
2	Mild OSAS	≥ 3	≤ 3	0	≥ 3 clusters of desaturation
3	Moderate OSAS	≥ 3	> 3	≤ 3	≥ 3 clusters of desaturation
4	Severe OSAS	≥ 3	> 3	> 3	≥ 3 clusters of desaturation

Abbreviations: SpO2: pulse oximetry, OSAS: obstructive sleep apnea.

Adapted from reference [168]

In children undergoing adenotonsillectomy, the presence of an abnormal oximetry correlates with a PSG-confirmed moderate to severe OSAS[168]. Moreover, the night to night variability of nocturnal oximetry is very low with a good night–to-night agreement[169]. However, the presence of non-conclusive or normal results does not rule out OSAS[168]. Other studies have demonstrated that a oximetry score of 3 or 4 effectively identifies OSAS in children with Down syndrome, although a score of 2 could derive from central apneas in some patients[170]. Recently, a more complex automated signal processing algorithm has been developed to improve the accuracy of nocturnal oximetry for the diagnosis of OSAS but, despite promising results, the algorithm is not yet available for the use in current practice[171].

Besides the analysis of the trend of nocturnal oximetry, oxygen desaturation index (ODI) has been also used to try to predict the presence of OSAS. Normative values for ODI of 3% have been published and do usually not exceed 1.2 events/h in healthy children[160]. However, different ODI cut-off values are able to predict the severity of OSAS in children aged 3 to 12 years[172] with a sensitivity and specificity of almost 80%. Tsai and colleagues found that the optimal ODI cut-off values for predicting the occurrence of mild, moderate, and severe OSAS were 2.05 (sensitivity: 77.7%; specificity: 88.9%), 3.50 (sensitivity: 83.8%; specificity: 86.5%) and 4.15 (sensitivity: 89.1%; specificity: 86.0%), respectively[172].

In conclusion, although simple, cheap, and easy to interpret, nocturnal oximetry has a relatively low accuracy to predict OSAS and is not able to accurately estimate OSAS severity, in particular mild to moderate OSAS. However, in the absence of PSG, a practical approach combining nocturnal oximetry with questionnaires and clinical symptoms is recommended, as pointed out in the recent European Respiratory Society statement[1].

One of the main limitation of simple oximetry is that it lacks information about hypoventilation and hypercapnia. Since obstructive hypoventilation in children is frequent it should be actively searched, therefore a study analysing the predictive value of a combination of SpO_2 and $PtcCO_2$ measurement is worth to be performed.

Polysomnography and respiratory polygraphy

As stated above, nocturnal attended PSG represents the gold standard for the diagnosis of SDB in children. Night-to-night variability is minimal therefore one PSG is usually sufficient in the majority of children[173,174].

Multiple sensors are used during PSG[175] which include:

- Nasal and mouth airflow: nasal pressure transducer to score hypopnoeas and oronasal thermistance to score apnoeas.
- Respiratory effort: esophageal manometry, abdominal and thoracic respiratory inductance plethysmography (RIP) belts
- Oxygen saturation: SpO_2, with an averaging time of ≤2 sec.
- Microphone for snoring,
- Body movements,
- Body position (not required by the AASM)
- EEG recordings based on the international 10-20 system: placement of electrodes should be in frontal, central and occipital zones with standard reference at the left mastoid (M1). Recommended derivations are F4-M1, C4-M1 and O4-M1 (left derivations). Backup electrodes should be placed at F3-M2, C3-M2 and O3-M2 (right derivations). The recording of eye movements, electromyography of the chin and electrocardiogram is recommended.

Sleep stages are scored according to the AASM recommendations[175] and are divided in wake (W), N1, N2 and N3 (slow wave sleep) and rapid eye movements (REM) sleep.
Respiratory events are scored, according to AASM updated recommendation[53], as follows:
Apnea is defined by a drop of the flow signal of >90% of the pre-event baseline and should be classified as:

- Obstructive if it meets apnea criteria for the duration of at least 2 breaths during baseline breathing and is associated with the presence of respiratory effort throughout the entire period of absent airflow.
- Mixed if it meets apnea criteria for the duration of at least 2 breaths during baseline breathing and is associated with no respiratory efforts during one portion of the event and the presence of inspiratory effort in another portion, regardless of which portion comes first.
- Central if it meets apnea criteria, is associated with absent inspiratory effort throughout the entire duration of the event, and (1) last at least 20 seconds or (2) lasts at least the duration of two breaths during baseline breathing and is associated with an arousal or ≥ 3% oxygen desaturation or (3) in infants younger than 1 year old the event lasts at least the duration of two breaths and is associated with a decrease in heart rate to less than 50 beats per minute for at least 5 seconds or less than 60 beats per minute for 15 seconds.

Hypopnea is defined by a drop of peak flow of at least 30% of pre-event baseline signal, the duration of the drop is at least 2 breaths during baseline respiration and there is ≥ 3% desaturation from pre-event baseline or the event is associated with an arousal. The events should be classified as obstructive in the presence of respiratory efforts during the events and central in the absence of inspiratory efforts.

Alveolar hypoventilation in children is defined as a PCO_2 value > 50mmHg for at least 25% of total sleep time.

Three alternatives help diagnose hypoventilation during sleep exam:

1. Arterial CO_2 ($PaCO_2$) represents the standard for CO_2 measurement. However, this technique is invasive and does not allow continuous monitoring but only punctual values. The AASM states that elevated $PaCO_2$ obtained immediately after waking may provide evidence of hypoventilation during sleep[176]. However a significant number of children with nocturnal hypoventilation may not be identified by $PaCO_2$ after waking[177].
2. Monitoring of exhaled CO_2 (End tidal CO_2/$PetCO_2$) is widely used in pediatric population. The most used method, side stream, consists on a device that suctions gas through a nasal cannula worn by the patient. Room air is suctioned during inhalation (PCO_2 = 0) while CO_2 is measured during exhalation. The difference between $PaCO_2$ and $PetCO_2$ is usually 2 to 7 mmHg, and is higher in patients with lung disease. The accurate value corresponds to the plateau $PetCO_2$. The major pitfall of $PetCO_2$ is the inaccuracy of the measurement during mouth breathing, in case of low tidal volume or high respiratory rates. Nasal cannula with a "mouth guide" to allow sampling of gas exhaled through the mouth are available. $PetCO_2$ is not accurate during oxygen therapy or noninvasive ventilation (NIV). Finally, since $PetCO_2$ depends on the airflow, it is considered as an alternative sensor for detecting apnea by the AASM.
3. Transcutaneous CO_2 monitoring ($PtcCO_2$) consists on the continuous measurement of CO_2 via a non-invasive transcutaneous sensor. $PtcCO_2$ values allow a more reliable estimation of PaCO2 as compared to $PetCO_2$[178,179]. The main advantage of this technique is that the measurement is independent of mouth breathing, lung disease, oxygen therapy or NIV. However, the signal has an important lag time not allowing the detection of variations directly related to a given respiratory event or breath to breath differences.

The AASM recommendation[176] defines four levels of sleep studies, based on the number of channels and on the presence or not of a sleep technologist during the exam:

- Level 1: attended PSG performed in a sleep laboratory with the presence of a sleep technologist and the recording of a minimum of seven channels including electroencephalography (EEG), electrooculography (EOG), submentalis (chin) electromyography (EMG), electrocardiogram (ECG)/heart rate, and pulse oximetry (SpO2).
- Level 2: PSG recorded unattended, in or out of a sleep laboratory.
- Level 3: RP (respiratory polygraphy) recorded unattended, and defined by the recording of a minimum of four channels, including ventilation, oximetry, ECG, or heart rate, at home or outside of the sleep laboratory,
- Level 4: unattended recording of two to three cardiorespiratory signals (most often airflow, SpO_2, and heart rate),

Since level 1 PSG is time consuming, expensive, poorly available and difficult to interpret only a limited number of children will undergo a PSG. It is thus absolutely mandatory to develop new informative, noninvasive and child-friendly alternatives to PSG.

Two studies evaluated comprehensive sleep studies ("type 2" devices with more than seven channels) in school-aged children, applied by a technologist in the home setting. The tolerance was reported as good but not optimal by the patients and families[180,181]. In the first study, only seventeen percent of parents noted a sensor fell off [180] The most frequent problems were noted with the nasal pressure signal, with a satisfactory signal for more than 75 percent of recording time in less than two-thirds of the children. The second study revealed similar results, with the nasal cannula and the thermistance being satisfactory for more than 6 hours in less than 60% of the sleep studies[181].

Nap PSG is an abbreviated study that records sleep and breathing in the sleep laboratory during a daytime nap. This type of study is limited by the short recording time and the possible absence of REM sleep. For this raison, it should be limited to infants younger than 6 months of age, who still have REM sleep during nap sleep, with a study that should be only validated in case of at least 2 REM periods. Nap PSG has a good positive predictive value (77 to 100 percent) but a poor negative predictive value (17 to 49 percent) for identifying OSAS in children[182]. As a result, a normal nap study cannot exclude an OSAS requiring thus a full PSG.

In Europe, the vast majority of pediatric sleep laboratories perform level 3 and 4 exams[183,184], which are more acceptable by infants and young children.

RP consists in the detection of oronasal flow, chest and abdomen movements by impedance plethysmography, body position by sensor position, snoring by microphone, and heart rate

and blood oxygen saturation by means of pulse oximetry. The absence of EEG makes this technique easier to install on children and better tolerated. However, the absence of EEG has the following drawbacks:

1. Data about sleep quality, sleep fragmentation and arousal are not available.
2. The result of sleep exam is normally calculated as the mean number of events per hours (total number of respiratory events divided by total sleep time (TST)). TST is indeed the effective sleep time during night, defined as the time in bed minus periods of awakening. It derives that, without the EEG signals, the exact TST cannot be calculated and total recording time is used instead. For this reason, the AHI calculated via RP may be underestimated. However, sleep and wakefulness can be quite accurately estimated in children using cardiorespiratory and/or videotape recordings.
3. For the scoring of hypopnoeas, a 3% oxygen desaturation or an arousal are required along with the > 30% reduction of respiratory flow. In the absence of EEG signal, hypopnoeas associated with arousal but without a desaturation are missed which may underestimate the AHI.

For these reasons, RP may underestimate the AHI scored on a PSG, but it has been demonstrated that the difference concerns mainly children with mild and moderate OSAS (1< AHI < 10/h)[185], a subgroup in whom even modest variations of AHI determine different treatment approaches.

In conclusion, the diagnosis of OSAS in children is based on a combination of symptoms, clinical signs, and PSG results. Alternative exams like nocturnal oximetry may an alternative for severe OSAS, while in mild to moderate cases the predictive value of SpO_2 is reduced. As such, PSG remains the gold standard for the diagnosis of OSAS but the limited availability of paediatric sleep labs equipped to perform a type 1 exam constitute a major problem worldwide. Efforts are therefore needed in order to simplify sleep studies in children while maintaining a good reliability. Moreover, PSG often represents a problematic exam especially in young infants; hence we need new tools able to deliver useful and reliable information without being too invasive.

Pulse transit time

Pulse transit time (PTT) is the time period the pulse wave takes to travel between the aortic valve and the vessels in the finger and is calculated as the interval between the R wave of the

electrocardiogram (ECG) and the arrival of the photoplethysmographic pulse at the finger[186]. PTT is considered a noninvasive surrogate marker of blood pressure (BP) changes since the speed at which a pulse travels between two arterial sites is influenced by mean arterial pressure (MAP) and the distance between the two sites. When the MAP rises, the arteries become tenser thus allowing a pulse wave to travel faster, leading to a shortening of the PTT. Conversely, when the MAP decreases, the pressure pulse wave travels slower and PTT lengthens. This intrinsic interaction between changes in BP and the PTT explains the three potential application of this technique. First of all, PTT may be used to monitor changes of BP and thus acting like a surrogate of BP. Secondly, PTT has been proposed as a valid tool to detect cortical and non-cortical sleep arousal. As a matter of fact, arousals could be graded in four different levels with the first two levels corresponding to Delta and K waves burst that are integrated in the brainstem in order to generate a sympathetic activation[187]. This phenomenon leads to a rapid change in BP, which may be detected by a shortening of PTT. Finally, the measurement of swings in esophageal pressure by means of an esophageal catheter is the current gold standard technique for detecting respiratory effort but, given the invasive nature of this exam its use is limited to research purpose. Surrogate measures of respiratory effort like respiratory inductance plethysmography (RIP) are thus used in clinical practice. When an obstructive respiratory event occurs, the inspiratory effort increases, leading to an increase of Pes. This elevation of Pes generates a progressive more negative intrathoracic pressure that a transient reduction of BP that could be detected by PTT[188]. Thus, PTT reflects respiratory effort and arousals and has been used for the diagnosis of SDB in adults[189,190] and children[191,192], with good sensitivity and specificity. However, the high percentage of artefacts represents the main drawback of PTT and limits its use in current practice.

7. Treatment of OSAS in children

Once the diagnosis of OSAS has been made, the decision to initiate treatment is taken on an individual basis. Anticipated benefits and risks of treatment must be carefully weighed. Classically, an AHI of more than 5/h is considered as the cut-off for treatment, irrespective of the presence of comorbidities. However, as stated before, recent evidences suggest that even primary snoring may be associated with neurocognitive dysfunction and cardiovascular stress[109,193]. On the other hand, the decision to treat is challenged by the fact that a large group of pre-adolescent with OSAS (and without obesity) improve spontaneously over time[85,109]. Finally, important considerations include the child's age, the severity of PSG abnormalities, and any underlying issue or complications related to OSAS. In conclusion, the decision to treat a child with OSAS relies on several factors and the best treatment strategy should be decided by a clinician having an expertise in pediatric sleep-related respiratory abnormalities.

Adenotonsillectomy

Since adenotonsillar hypertrophy is the main cause of OSAS in otherwise healthy children, adenotonsillectomy represents the treatment of choice in this age group. In the past, this approach was largely based upon clinical experience. In 2013, a randomized trial (Childhood Adenotonsillectomy Trial, CHAT) demonstrated an advantage of a watchful waiting for children with moderate, uncomplicated OSAS who were candidates for adenotonsillectomy[85]. Specifically, adenotonsillectomy provided a better improvement in daytime behavior, sleep apnoea symptoms, subjective sleepiness, and quality of life. However, no differences emerged in cognitive measures of attention or executive functions that were the primary outcomes of the study.

Adenotonsillectomy is associated with a low complication rate in most children with type 1 OSAS, and is usually performed as an outpatient procedure. Postoperative pain and poor oral intake are the most frequent adverse effects following intervention. More severe complications may include bleeding, infection, esthetic complications, respiratory failure, velopharyngeal incompetence, and subglottic stenosis. Two techniques are currently available. Extracapsular tonsillectomy (also known as complete, total, or sub-capsular tonsillectomy) consists of the removal of the entire palatine tonsils and the surrounding fascia or capsule with either cold or hot techniques. Intracapsular tonsillectomy (also known as subtotal or partial tonsillectomy, or "tonsillotomy") is nowadays increasingly used for the

treatment of obstructive SDB. In this technique, microdebriders, bipolar electrosurgical scissors, or radiofrequency ablation (including "coblation") devices are used to debulk the obstructing portions of the tonsil parenchyma[194–196]. Some evidence suggests that the technique speeds the recovery compared with traditional tonsillectomy, and reduces the risk of postoperative hemorrhage. However, there is a risk of tonsillar regrowth, which usually is clinically insignificant but which may occasionally require a revision surgery. It appears though that adenotonsillotomy should be the treatment of choice in those children who have a type 1 OSAS. In this group of patients adenotonsillar hypertrophy represents the most important physiopathological mechanism of OSAS and therefore, adenotonsillectomy is more likely to be curative.

Regarding adenotonsillectomy post-operative complications, the severity of OSAS predicts the incidence of respiratory complications. An AHI >26 events/h and more than three drops in oxygen saturation of haemoglobin below 90% have been shown to be significant predictors of post-operative respiratory complications[197,198]. However, in the CHAT study, the frequency of respiratory complications in school-aged children without comorbidities was low (1.4%) and was not predicted by OSAS severity[85]. Due to the lack of studies analysing the association between the level of CO_2 and postoperative complication, experts recommend that every child with a maximum PCO_2 level of > 60 mmHg should be treated as an inpatient. Patients with type 3 OSAS have been shown to have a higher rate of post-operative complications. In particular cerebral palsy, seizures, age of less than 3 years, congenital heart disease and prematurity have been identified as important predictors of a complicated postoperative outcome[199]. Moreover, children with medical comorbidities such as craniofacial anomalies, genetic syndromes, and neuromuscular disease are also at high risk of post-operative complications and need postoperative inpatient monitoring[2]. Furthermore, the presence of an ongoing upper airways infection represents a contra-indication for any anaesthesia because of the risk of episodes of breath-holding, desaturation <90% and bronchospasm [200].

Despite the efficacy of adenotonsillectomy, 20% to 70% of the children may present residual OSAS, in particular in patients with type 2 and 3 OSAS. These results may be in part explained by the different definitions of residual OSAS used by the authors. Moreover, it has to be noticed that the presence of other risk factors of OSAS (ie. obesity) may explain the high rate of children with little or no benefit from adenotonsillectomy [69,201] in some studies. Indeed, obesity represents one of the major risk factor for persistent OSAS in children. Obese children have a 3.2 to 4.7 increased risk of persistent OSAS after adenotonsillectomy compared to

otherwise healthy children[202,203]. Male sex and African American ethnicity are also risk factors for persistent OSAS after adenotonsillectomy [1].

Age is also a risk factor for persistent OSAS. In infants younger than 3 years the risk of adenotonsillectomy failure was as high as 65% in one study[204]. It has to be noticed that in this age group a large number of patients had an underlying disease like craniofacial malformation or chromosomal abnormality which may explain the high risk of adenotonsillectomy failure [205]. In children older than 7 years, the risk of persistent OSAS is also increased[204], even when obesity is taken in account[189,190]. It appears that children younger than 3 years old and older than 7 have the least benefit from adenotonsillectomy , probably because in these two age groups the role of adenotonsillar hypertrophy is less important.

Finally, the pre-existing severity of OSAS predicts the post-adenotonsillectomy outcome. Indeed, patients with severe OSAS have a higher probability of residual OSAS after AT than patients with moderate or mild OSAS[206].

Even if a higher rate of complications and treatment failure exists, adenotonsillectomy represents also the first line therapy for children with type 3 OSAS if appreciable adenotonsillar tissue is present. The rationale is that adenotonsillectomy may improve upper airway patency enough to cure or improve OSAS, even if it is not able to intervene on associated anatomical abnormalities. Despite a high rate of residual OSAS after adenotonsillectomy is in children with craniofacial abnormalities or neurological disorders including neuromuscular disorders and neurodisability, some patients may have good results[29,147,151].

Other upper airway surgeries

Surgical procedures other than adenotonsillectomy may be indicated for treating OSAS in children with type 2 and 3 OSAS. Indeed, in these children, the cause of OSAS is usually multifactorial and not related exclusively to adenotonsillar hypertrophy. Based on the type and site(s) of obstruction the most commonly alternative approaches include turbinectomy, lingual tonsillectomy, supraglottoplasty, uvulopalatopharyngoplasty (UPPP), mandibular distraction osteogenesis (MDO), tongue base procedures and tongue-lip adhesion. Tracheotomy represents the last solution for children with severe OSAS who have failed to respond to all other treatment approaches.

Laryngomalacia is the most frequent congenital anomalies of the larynx[207]. It is characterized by an inspiratory prolapse of prominent mucosal folds on the accessory cartilages above the

arytenoids resulting in a dynamic, inspiratory supraglottic obstruction. Symptoms are inspiratory stridor without or with intercostal retractions, episodes of cyanosis, feeding difficulties responsible of poor weight gain and growth delay. According to the morphology of supraglottic area, laryngomalacia may be classified into three types. Type 1 is defined by a prolapse of supra arytenoid floppy tissues. Type 2 is characterised by shortened aryepiglottic folds associated with a long tubular epiglottis that curls on itself while in type 3 epiglottis is retroflexed and collapses posteriorly during inspiration[208]. Symptoms usually appear during the first days of life and progress with a peak at 2-5 months of age. Most of the children improve spontaneously with a resolution before the age of 2 years[205]. However, between 10 to 20% of the patients require an endoscopic supraglottoplasty[210,211]. The intervention is effective for treating children with laryngomalacia with OSAS with an overall success rate ranging from 90% to 12% according to the different definitions of residual OSAS[212–214]. However children with type 3 laryngomalacia, prematurity, concomitant airways lesions and comorbidities have higher failure rate[214] and may require additional treatment(s).

MDO had been used with success to treat severe OSA due to mandibular hypoplasia, particularly in infants with congenital mandibular hypoplasia such as Pierre Robin sequence or Treacher Collins[215–217]. MDO consists in the application of internal or external distraction devices that are placed on each mandibular branch. The distraction devices move the mandible forward at a rate of 1 to 2 mm/day until the desired advancement is achieved. Successful treatment of airway obstruction (defined as either tracheotomy avoidance or decannulation, no need for CPAP, or significant improvement or absence of OSAS symptoms) is reported in almost 90% of children by a recent meta-analysis[218]. Of note, no data are available on OSAS documented on a PSG before and after MDO. Also, the rate of post-operative complications is high, with more than 20% of patients having infection, abscess, open bite deformity, nerve injuries, or hypertrophic scarring. Furthermore longitudinal data on the objective long-term efficacy of this technique are lacking and recurrence of OSAS after MDO has been reported[219,220]. These data suggest that MDO may be an option for severe OSAS in selected patients with mandibular hypoplasia from congenital craniofacial defects, but the high complication rate mandates careful consideration when choosing this procedure.

UPPP is a technique widely used for the management of OSAS in adults but not in children. It has mainly been used in children at high risk for persistent upper airway obstruction after adenotonsillectomy alone, including children with Down syndrome or with neuromuscular disorders[221–223]. However, the small sample size of the studies, absence of control groups, and paucity of validated outcome measures preclude concluding on the utility of this procedure in

a broader pediatric population. Potential complications include nasopharyngeal stenosis, palatal incompetence, and speech difficulties.

The use of nasolaryngoscopy, cine MRI and DISE has increased the recognition of obstruction at the base of tongue as a cause of persistent OSAS after adenotonsillectomy. This is especially important in children with obesity, Down syndrome, and craniofacial or neuromuscular disorders[102,224–228]. Newer minimally invasive techniques and technical improvements have made procedures that aim to reduce tongue tissue, advance tongue musculature, or ablate lingual tonsil tissue more feasible. Endoscopic-assisted coblation lingual tonsillectomy is an effective technique to treat tongue base collapse in children with OSAS. Two recent meta-analysis concluded that the efficacy in terms of reduction of AHI after lingual tonsillectomy is moderate, with a mean reduction of the AHI of 8.9 events/h. The overall reported success rate is 17% (95% CI, 7%-35%) for a postoperative AHI less than 1 event/h and 51% (95% CI, 25%-76%) for a postoperative AHI less than 5 events/h[213]. Newer techniques like trans oral robotic surgery (TORS) allow a more accurate view of lingual base and a better and more efficient dissection of tissues. This may improve the efficacy of the procedure as shown in a retrospective case series of patients with syndromic and non-syndromic persistent OSAS after adenotonsillectomy or on continuous positive airway pressure (CPAP) failure [229]. In this selected population, DISE allowed to identify tongue base and lingual tonsillar hypertrophy as the unique site of obstruction. Subsequent lingual tonsillectomy resulted in a reduction of 50% of AHI in all of the patients[229], demonstrating that the precise identification of the site of obstruction is crucial for an optimal individualised treatment. Other techniques like frontofacial monobloc advancement, or Lefort type 2 or 3 are reserved to particular cases of faciocraniodysostosis[230–233].

Tracheotomy is an invasive technique that represents the last option in children with persistent severe, life threatening OSAS despite surgical intervention(s) especially if they are intolerant to CPAP therapy or if this therapy is not sufficient. Although tracheotomy is an effective treatment for OSAS and airway obstruction, it is associated with complications in as many as 43 to 77 percent of children[234], including bleeding, tracheoesophageal fistula, accidental decannulation, tube occlusion or even death[235]. Therefore, even if life–saving in some cases, the decision for a tracheotomy should be carefully discussed with a multidisciplinary team and the parents.

Individualised treatment approach

The presence of multiple sites of obstruction may explain the high incidence of residual apneas in children, especially in those with type 3 OSAS. The region of the soft palate, tongue base with lingual tonsillar hypertrophy, the supraglottis, inferior turbinates, and the adenoid region with regrowth of adenoids are all possible alternative sites of UA obstruction. The diagnostic work-up should therefore include a thoughtful clinical examination searching for tonsillar hypertrophy, nasal obstruction, macroglossia or other craniofacial abnormalities. In addition, awake flexible laryngoscopy, and in some cases, lateral neck plain films, are usually performed in order to detect adenoid hypertrophy, lingual tonsil hypertrophy, laryngeal malformation (i.e. laryngomalacia) or other possible upper airway anomalies. However, nor the laryngoscopy neither the lateral neck films accurately detect the site of obstruction during sleep or sedation. Indeed, it is crucial to evaluate also the associated dynamic component of UA obstruction during sleep. For these raisons, cine magnetic resonance imaging (MRI) and sleep endoscopy have been introduced. These two techniques aim at providing information on the site of obstruction, allowing for a better selection of patients who will benefit from adenotonsillectomy[31,32,52]. However, the limitation of both techniques is that these procedures are performed during drug-induced sedation or sleep, with the consequence that the anaesthetic agent itself may affect the pattern of UA obstruction or collapsibility.

Cine MRI have been shown to be a useful tool for the management of children with type 3 OSAS, with some authors reporting a change in the management decisions in up to 50% of cases[226,236,237]. However, cine MRI is most commonly used in patients who have failed previous surgical management, such as tonsillectomy and adenoidectomy, or have an underlying syndrome that predisposes them to multiple potential causes of persistent or recurrent OSAS. Indeed, the majority of studies were performed in patients with Down syndrome, in whom the most common factors associated with residual AT were macroglossia, glossoptosis, recurrent enlargement of the adenoid tonsils, and enlarged lingual tonsils[102,236].

DISE allows a dynamic examination of the site(s) of obstruction and is usually performed during the same anaesthesia that preceed ear-nose-throat (ENT) surgery. One of the main problems of this technique was the heterogeneity of the scoring [101,238,239]. Recently, a standardised scoring system has been proposed by Lam et al[240]. This score divides the UA into six regions: 1) nasal airway between inferior turbinates and septum 2) nasopharynx 3) velopharynx 4) oropharynx 5) hypopharynx and 6) arytenoids. For each level, the operator scores the degree of obstruction ranging from 0 (no obstruction) to 2 (complete obstruction).

When performed by skilled ENT, DISE may guide the surgical decision[241] and change the type of intervention in up to 30% of infants and 25% of children with a higher rate of success compared to standard treatment[242].

Finally, more advanced techniques that may predict the outcome of individualised treatments, like functional respiratory imaging, are currently under development[82]. Correlation between CT scan functional imaging and DISE findings is a promising area of research and may provide in the future a noninvasive tool able to predict treatment success[243].

Orthodontics

Rapid maxillary expansion (RME) is an orthodontic treatment that widens the palate and nasal passage, thereby increasing airway caliber and reducing nocturnal UA obstruction. The technique can only be used prior to midline fusion of the maxilla, which generally occurs shortly prior to puberty. RME is proposed after the 4th year of life, when the second deciduous molars of the upper jaw have erupted, and the device is usually removed after a period of 12 months [241]. RME should be restricted to children with OSAS and a narrow palate (crossbite) who have little adenotonsillar tissue, or for those with residual OSAS after AT. Two recent meta-analysis highlighted the overall efficacy of RME but also the large heterogeneity of the studies[245,246].

Orthopedic mandibular advancement (OMA) aims to correct dental and skeletal retrognathia by re-directing the mandible into a more forward and downward position. This aims at increasing the opening of the oropharyngeal airway during wake and sleep. In adults, OMA has shown its efficacy to correct moderate OSAS[247], even if some data highlight its role even in moderate to severe OSAS[248]. Despite its large use in adults as an alternative to CPAP[247,249] only few studies analysed this treatment in children. In young adolescents, OMA has been shown to be an effective technique to correct moderate OSAS with a reduction of the AHI of almost 5 events/h[246].

Medical and adjuvant therapy

Weight loss should be the first line therapy for obese children with OSAS[1,2]. However, the presumption that weight loss is beneficial to obese children who have OSAS is based primarily upon evidence from adults. This may be explained by the difficulty to achieve a sufficient weight loss in the large majority of children with type 2 OSAS. There are few studies of the effect of weight loss on OSAS in children with morbid obesity. These suggest that OSAS is

likely to improve if a sufficient weight loss can be achieved. Verhulst et al demonstrated that in a group of obese teenagers attending a residential treatment centre, weight loss was able to treat OSAS in 62% of the patients[250]. Similar results were reported by Siegfried and colleagues in a similar setting of obese adolescents admitted to a rehabilitation center[251]. However, it has to be noted that conclusions resulting from weight loss achieved in a rehabilitation centre may not be extended to the general population of obese patients. For adolescents with morbid obesity and OSAS and/or other obesity-associated morbidities , weight loss surgery may be an option[252,253].

Intranasal corticosteroids or leukotriene modifier therapy may be useful to treat mild surgery naïve OSAS or mild residual OSAS after adenotonsillectomy. No clear guidelines exist on the optimal duration of therapy but most studies showed an efficacy after 3 months of treatment. Several studies have shown beneficial effects of intranasal steroids for children with mild OSAS. During a randomized trial of 25 children treated with intranasal corticosteroids or placebo, the group receiving intranasal steroids for six weeks had a modest improvement in OSAS, with a mean an AHI reduction from 11 to 6 events/h[254]. Similar findings were observed in double-blind randomized crossover trial of 48 children with mild OSAS treated with intranasal budesonide with 50% of the children normalising their PSG data during budesonide treatment. In many of the children, the positive effects were sustained up to eight weeks after discontinuation of treatment[255]. Montelukast (Singulair®) appears to modestly reduce AHI and adenotonsillar size in children with mild OSAS[256]. The combination of montelukast and intranasal corticosteroids was also effective in several studies. In a retrospective review of 752 children with mild OSAS who were treated with a combination of intranasal corticosteroids and montelukast, more than 80 percent experienced beneficial effects. Among those who underwent a follow-up PSG, the AHI normalized in 62 percent[257]. The combination was also effective in a group of children who had mild residual OSAS after adenotonsillectomy[258]. Despite the mild effect of local corticosteroids, systemic corticosteroids do not appear to be effective, probably due to the short length of utilisation[259].

Other therapies

Positional therapy may be considered when a school-aged child, adolescent, or older teenager present an abnormal AHI exclusively or predominantly (x2) in the supine position as compared to the other positions. Several tools such as pillows and belts are commercially

available. Additionally, the head of the bed can be raised to ease breathing. Positional therapy has not been well evaluated in children.

The nasal expiratory resistor device consists of a 0.25-inch diameter one-way valve attached externally to each nostril with adhesive tape. The valve allows easy inhalation but on exhalation produces expiratory resistance acting similarly to a CPAP device during sleep. The only pediatric study published was a randomized, double-blind, placebo controlled, crossover study in which 14 obese teenagers with mild OSAS. The children showed a variable response; older children and children with less hypercapnia showed a better response to therapy. Thus, nasal expiratory resistor devices may be an option in older children with OSAS who do not respond to or are unable to tolerate other treatments but additional studies are warranted[260].

Myofunctional reeducation consists of exercises designed to strengthen the tongue and orofacial muscles, and repositioning facial muscles into the appropriate position. In a retrospective review of 24 children with residual OSAS after adenotonsillectomy who were referred for myofacial reeducation services, those who completed myofacial reeducation improved their AHI and minimum SpO_2 on a follow-up PSG as compared with those who did not complete the myofacial reeducation[261].

8. Continuous positive airway pressure and noninvasive ventilation

The respiratory system may be represented as a balance between the respiratory load, the respiratory muscles capacity and central ventilatory drive. An alteration of one or more of these factors may translate into SDB. Upper airway obstruction is a classic example of increased respiratory load, whereas neuromuscular disorders decrease respiratory muscles capacity. Finally, congenital diseases affecting central nervous system (i.e. Ondine's curse) or acquired lesions may impair central ventilatory drive. The choice of the type of noninvasive ventilatory support depends of the pathophysiology of the respiratory failure. CPAP is indicated in case of "isolated" obstruction of the upper or lower airways. Indeed, in case of airway obstruction, the other components of the respiratory balance (i.e. the respiratory muscles and the central ventilatory drive) are normal and the restoration of a sufficient airway patency throughout the entire breathing cycle normalises breathing. On the contrary, when the muscles or the central ventilatory drive are affected, NIV is indicated in order to assist the weak respiratory muscles or to "take over" a deficient ventilatory drive. However, and overlap exists and in some diseases like mucopolysaccharidosis, achondroplasia, Prader Willi or Down syndrome a combination of two or more factors may lead to complex SDB due to the alteration of different components of the respiratory balance.

Two forms of noninvasive ventilatory support are available. The first is continuous airway positive pressure (CPAP), which consists in the delivery of a continuous pressure to the airways trough a noninvasive interface. The aim of CPAP is to maintain upper airway patency during the entire breath cycle and it is therefore largely used in children with severe and/or persistent OSAS despite all other treatment. Bilevel pressure may be proposed to children who do not tolerate high CPAP pressures whereas NIV is required to those presenting alveolar hypoventilation. In this latter form of respiratory support, the ventilator assists the breath of the patient by delivering a volume of air at each breathing cycle.

CPAP was first described in adults with OSAS, almost 36 years ago, by Sullivan and colleagues[262] and since, it has progressively become the mainstay of severe OSAS in adults. Even if a pediatric patient was initially included in the first report of Sullivan, this treatment has been used almost exclusively in the acute neonatal setting for decades. Only recently, technological advances have made this technique readily available for home setting and now CPAP and NIV are increasingly used in children of every age worldwide[263–267].

CPAP is recommended in children with residual OSAS (AIH > 5 events/h) after adenotonsillectomy and OSAS related to obesity, or to craniofacial abnormalities. In patients

with obstructive nocturnal hypoventilation, an initial trial of CPAP should be offered, with a rapid switch to NIV in case of persistent hypoventilation.

Indeed, CPAP or NIV are almost exclusively reserved for patients with type 2 and 3 OSAS. Literature data from national survey or experienced centres indicate that more than 80% of the children treated with long term CPAP or NIV have congenital or acquired underlying diseases[263–266].

Indications of CPAP and NIV

There are no evidence-based criteria to start CPAP or NIV therapy in children with SDB. This is in part due to the large heterogeneity of the spectrum of SDB in children, ranging from "simple" type 1 OSAS to type 2 and 3 OSAS with or without alveolar hypoventilation. Underlying diseases predisposing to SDB are also extremely heterogeneous. Moreover, treatment of SDB should aim at reducing morbidity but, due to the absence of reliable indicators of end organ morbidity, and given the presence of important and confounding comorbidities in children with SDB, it is difficult to assess which parameters should guide decision to treat. In an attempt to standardise treatment, the ERS statement on obstructive sleep disordered breathing[1] in children suggest that CPAP or NIV should be started in the presence of:

- residual OSAS after adenotonsillectomy (AHI >5/h)
- OSAS related to obesity, craniofacial abnormalities or neuromuscular disorders.

Concerning the ventilator mode: if nocturnal hypoventilation occurs ($PetCO_2$ >50 mmHg for >25% of total sleep time or peak $PetCO_2$ ⩾55 mmHg) NIV is preferred

These recommendations have the merit of proposing an early, "aggressive" treatment approach in children with underlying diseases. Each therapeutic intervention in a child with OSAS should be evaluated after 6 weeks to 12 months. In practice, CPAP is prescribed in children with complex OSAS due to anatomical or structural abnormalities of the upper airways such as craniofacial malformations, Down syndrome, Prader Willi syndrome or morbid obesity [6,38,39]. BiPAP is indicated if nocturnal hypoventilation persists despite optimal CPAP[37]. CPAP is associated with an improvement in sleep parameters such as the AHI and gas exchange, attention deficits, behaviour, sleepiness and quality of life[6].

According to the British Thoracic Society guidelines[268], NIV should be start in children with neuromuscular diseases when daytime hypercapnia or of symptoms of nocturnal hypoventilation are present. Symptoms of nocturnal hypoventilation are not specific and may

not reflect objective hypoventilation[269]. Also, NIV may be justified without any complementary investigation when the child presents episodes of acute respiratory failure triggered by a respiratory infection or an anaesthetic procedure, as these events are markers of an insufficient respiratory reserve[268]. The type of neuromuscular disorder should be taken into account as nocturnal hypoventilation occurs preferentially in disorders characterised by a prominent diaphragmatic weakness. The criteria that are used to define "nocturnal hypoventilation" are highly variable which has practical consequences, as long term NIV indication relies upon hypoventilation detection[270]. The scoring of PSG in patients with neuromuscular disease requires a specific expertise. Indeed, instead of apneic and hypopneic events, these patients may present a progressive simultaneous decrease in airflow and thoracic and abdominal movements accompanied or not by a change in gas exchange, suggestive of global inspiratory muscle weakness. Paradoxical breathing with opposition phase on the thoracic and abdominal belts may be the consequence of diaphragmatic dysfunction or weakness of the intercostal muscles and should not be falsely interpreted as "obstructive events"[271–273]. In clinical practice, periods of "reduced ventilation" or paradoxical breathing, more than obstructive and/or central apnea-hypopneas, especially during rapid-eye movement sleep, associated with a SpO_2 < 90% and/or a $PtcCO_2$ value > 50 mmHg are indicative of an insufficient respiratory muscle performance and justify long term NIV in children with neuromuscular disease. In clinical practice, however, many children with a progressive neuromuscular disease such as spinal muscular atrophy or Duchenne muscular dystrophy are started on NIV empirically.

There are neither validated indications for NIV in children with cystic fibrosis. Like adult patients with chronic obstructive pulmonary disease, NIV is recommended as a first line treatment for an acute hypercapnic respiratory exacerbation, without any evidence from prospective randomised studies[274–276]. NIV is also largely prescribed for patients on the lung transplant list and those with an insufficient improvement with oxygen therapy[277].

Efficacy of CPAP and NIV

No randomized trials have compared CPAP to placebo or sham CPAP therapy in children with OSAS, mainly because of ethical concerns. Observational studies suggest that CPAP improves OSAS symptoms, signs, and the AHI in at least 85 percent of children:

In a series of 80 children (≤15 years old) with OSAS, Waters and colleagues[278] observed that nasal CPAP administered at a mean pressure level of 8 cmH_2O for an average of 15 months

eliminated the symptoms, signs, and PSG abnormalities of OSAS in 90 percent of the children. The AHI decreased from a mean of 27.3 to 2.6 events/h. Approximately 80 percent of the children in the series had undergone previous adenotonsillectomy, and one-half had a congenital syndrome or malformation. In a multicenter series of 94 children (<19 years old) with OSAS, of whom 75 percent had undergone previous adenotonsillectomy, CPAP therapy, administered at a median pressure level of 8 cm H_2O, was effective in 86 percent of children[279]. Effectiveness was defined as resolution of clinical symptoms, normal SpO_2 during sleep, and improvement of PSG abnormalities. Poor adherence was the primary reason of CPAP failure.

Different CPAP modes are available. Constant CPAP is the simplest mode and has proven its efficacy in children with severe upper airway obstruction[278,280–282]. Auto-titrated CPAP is a mode during which the positive airway pressure is automatically adjusted between a minimal and a maximal airway pressure set by the prescriber, according to an analysis of the flow curve and airway resistance by the device software. More sophisticated modes, associating a moderate decrease in airway pressure at the onset of expiration, or a variable increase in the airway pressure during inspiration are also available[283]. As all CPAP devices have been designed for adult patients, manufacturers recommend a minimal weight, usually between 10 and 30 kg, for the use of these CPAP modes. The few studies that have compared constant CPAP to more complex CPAP modes have not been able to demonstrate a superiority of these modes with regard to comfort or efficacy as compared to constant CPAP[284,285].

CPAP adherence represents a major challenge of CPAP. Behavioural therapy may improve adherence to CPAP in children[286,287]. CPAP adherence may be influenced by perception of benefit, degree of structure in the home, and social reactions, among other factors. Only one study has investigated so far the prognostic factors influencing CPAP adherence and found that CPAP adherence in children and adolescents is related primarily to family and demographic factors rather than severity of OSAS or measures of psychosocial functioning[288].

Initiation of CPAP or NIV in a specialised paediatric inpatient unit with experienced staff may improve adherence. Good adherence in the first week of treatment is a predictor for the long-term use over 2–3 months[289]. A strict follow up with frequent home visits by a trained home care provider seems to improve adherence[290].

The large use of NIV in children with neuromuscular disease contrasts with the few studies that have evaluated the benefits of NIV in children. Studies involving a small number of patients have shown that NIV is associated with normalisation of nocturnal and daytime gas exchange, improved sleep quality, and reduced symptoms associated with sleep-disordered

breathing[291–293]. NIV, associated with mechanical insufflation-exsufflation has been shown to prevent thoracic deformities and consequent thoracic and lung hypoplasia in young children with neuromuscular disease[294]. Concerning cystic fibrosis, there is a large gap between the expected and proven benefits, Indeed, a recent Cochrane review that concluded that the improvement of nocturnal gas exchange and less oxygen desaturation and respiratory muscle fatigue during chest physiotherapy were the only proven benefits of NIV in cystic fibrosis[295].

Initiation in children

Ideally, chronic CPAP or NIV should be initiated during an in-hospital titration sleep study. Guidelines are available for the titration of CPAP in adults and children with OSAS[296]. Pressure should be adjusted progressively if at least 1 obstructive apnea is observed for patients <12 years or if at least 2 obstructive apneas are observed for patients ≥12 years. The goal should be the complete disappearance of respiratory events with the lowest airway pressure. If the patient is uncomfortable or intolerant on high airway pressures, he/she may be switched to NIV. In case of persistent obstructive respiratory events at 15 cmH_2O of CPAP during the titration study in patients < 12 years old and 20 cmH_2O for patients > 20 years, the patient may be switched to NIV.
Device and interface choice should be carefully chosen with the patient and the caregivers. Therapeutic education should be provided to the patient and the caregivers in order to enable them understand, adhere and to be confident with the treatment. Troubleshooting of common problems with the interface and the device should be anticipated.

Technical considerations

CPAP and NIV equipment comprises the interface, the circuit and the device. Important improvements have been made in interfaces available for children. Interfaces may cover the nose (nasal mask), the nose and the mouth (nasobuccal mask), the face (total face mask) and exceptionally the mouth only (mouthpiece). Interfaces can be vented, meaning that they incorporate intentional leaks to be used with a single circuit and a minimal positive expiratory pressure, and non-vented masks, which can be used with a double circuit, a circuit with an expiratory valve, and with or without a positive expiratory pressure. The ideal interface should be minimally invasive, light, hypoallergenic and should guarantee an optimal pressurisation without unintentional leaks. Patient's age, nasal permeability and the presence

of mouth breathing are also parameters that determine the choice of the interface. Nasal masks are the only type of interfaces available for infants, and some models can be used in newborns from 3kg weight. Nasal pillows (or prongs or cannulas) are minimal contact interfaces, which are available for school-aged children and very well tolerated[290]. Children with maxillofacial deformities and mouth-breather such as patients with Treacher Collins syndrome generally need a nasobuccal mask.

The choice of the device depends on different considerations. Ventilators can be divided into CPAP devices, BIPAP ventilators and life support ventilators. Moreover, there have been dramatic improvements in the technology of home CPAP devices over last decade. The in-built software of CPAP devices can now provide a large amount of data regarding treatment compliance and efficacy, even in young children[297]. Manufactures aim to produce "light" weighted device with little or no alarms, no batteries and with various algorithm for improving patients' tolerance or auto titrating CPAP[298]. Following manufactures indications, most of these ventilators are recommended for patients weighting > 30 kg (Table 5), meaning that the software is not able to detect the airflow generated by children weighting < 30 kg. For this reason data about efficacy and objective compliance to treatment may be inaccurate[299], and most important, the auto titrating CPAP algorithm are not reliable in young children. For children < 30 kg, the choice of the ventilator should therefore take into account manufactures' recommendations

Table 5. Recommended minimal weight and modes of ventilation for some home ventilators.

Devices	**Autotitrating CPAP**	**Bilevel PAP**	**Minimal weight**
Resmed			
Airsense 10 Elite	yes	no	30kg
Lumis	yes	yes	13kg
Stellar	no	yes	13kg
Astral	no	yes	5kg
Respironics			
PR 1	yes	no	30kg
BIPAP A40	no	yes	10kg / 20kg
Trilogy	no	yes	5kg
Fisher & Paykel			
Icon	Yes	No	30kg
Lowenstein			
PrismaVent	no	yes	10kg

Monitoring and follow up

There are no validated guidelines for the monitoring or long-term follow up of children treated with CPAP or NIV. The timing of the follow up visits depends on the age and the medical condition of the child. Ideally, a sleep study with CPAP or NIV should be performed one month after the initiation of treatment, and then every 2 to 6 months. Check-up visit should include measurement of SpO_2 with $PtcCO_2$ recording, as numerous asymptomatic patients remain hypercapnic during CPAP or NIV despite a normal overnight SpO_2 and normal daytime blood gases[300]. Analysis of the in-built software of the ventilator and the overnight gas exchange gives useful information on important issues such as objective compliance, the level of unintentional leaks, respiratory rate, airway pressure and respiratory events[301,302]. But, as underlined above, the majority of the devices are designed for adults and the accuracy of this information is not always reliable in children. Systematic polygraphic studies are

recommended during NIV as residual respiratory events, such as patient-ventilator asynchronies, unintentional leaks, persistent obstructive events with or without reduction in central drive, and persistent central or mixed events, are common in stable asymptomatic children and may be associated with desaturations and/or arousals[303].

Monitoring the efficacy of CPAP/NIV but also the need to continue or not is crucial in children since SDB may improve in some children, either spontaneously or after specific therapeutic procedures. Indeed, a significant number of children may be withdrawn from their ventilator support over time. Conditions such as Pierre Robin syndrome or bronchopulmonary dysplasia improve spontaneously with increasing age. Other conditions may improve after upper airway, maxillofacial or neurosurgery such as tracheal or laryngeal stenosis, Treacher Collins syndrome, or craniofaciostenosis. There are no recommendations or guidelines for the withdrawal of ventilator support. After a corrective surgery, a minimal delay corresponding to the timing associated with the maximal benefit is recommended. This delay may last from approximately two to six months, according to the type of surgery. In case of a spontaneous improvement, a sleep study without CPAP or NIV is recommended after a withdrawal of at least 2 to 4 weeks of ventilator support because of the long-lasting effects of CPAP and NIV. In any case, long-term follow up is recommended because of the possibility of recurrence of SDB.

Side effects

Serious side effects from CPAP or NIV, like pneumothorax, are rare. The most common problems encountered are pressure skin sores from the interface, aerophagia, mucosal dryness and the discomfort caused from mask leaks. Pressure sores may improve with the change of the mask. Nasal obstruction may occur but, in most cases, can be effectively treated by humidification or topical nasal sprays. Central apnea or hypoventilation have been reported in some patients with high pressure level[304]. If treatment with CPAP or NIV is implemented before completion of full facial growth, the pressure of the mask on the growing maxillary area may lead to midface hypoplasia[305].

9. Presentation of the research project

My research project concerns the "Diagnosis and treatment of SDB in children with genetic diseases". The entire project was developed at the NIV and sleep unit of Necker Children Hospital in Paris.

The first aim of my research project is focused on the development and improvement of new tools to diagnose SDB in children. As pointed out before, PSG remains the gold standard for the diagnosis of SDB, but this exam is expensive, time consuming, difficult to interpret and most important, not available in most paediatric centres. Moreover, PSG quality is often affected by the involuntary displacement or loss of sensors or by the intolerance of the different sensors by the child. Given these considerations, one of the main challenges in paediatric sleep medicine is the development and validation of simplified tools, able to improve the tolerance issues while assuring a high and reliable accuracy.

The first project I developed concerned the validation of a suprasternal pressure sensor to characterise sleep apnoea during respiratory polygraphy. This study was published in the Journal of Clinical Sleep Medicine in December 2016. A second part of this study is currently ongoing and explores the usefulness of the same sensor for the detection of respiratory events without the signals of the nasal cannula and the thermistance. The aim of this two-part project is to demonstrate the validity of this sensor for the detection of airflow and respiratory efforts in children, thus allowing complementary analysis to nasal cannula and thoraco abdominal belts.

The second project I carried out regards the use of the variations of pulse wave amplitude (PWA) as a surrogate of cortical microarousals. This study aimed at the validation of a surrogate of cortical microarousals in order to replace the standard EEG signal for their detection and to use PWA as a simple tool for the scoring of hypopneas during respiratory polygraphy. This study was published in Sleep Medicine in June 2017.

During my PhD program, I also collaborate to another study concerning the use of pulse transit time (PTT) for the characterisation of respiratory events during polygraphy. This study was published in Sleep and Breathing in March 2017.

The second axe of my research concerned the treatment of SDB in children with genetic and congenital disorders. The first study concerned the use of CPAP in the treatment algorithm of a series of infants with Pierre Robin sequence. This study highlighted the usefulness of CPAP in avoiding tracheostomy in selected patients with severe OSAS due to Pierre Robin sequence. This paper was published in Plastic and Reconstructive Surgery in February 2016. The second

study aimed at the identification of objective criteria that lead to the initiation of CPAP or NIV in children and infants. This study was published in Pediatric Pulmonology in September 2016. I also collaborated to the conception, data analysis and draft redaction of a second manuscript regarding the criteria authorising the weaning from CPAP and NIV in children. This paper was published in Pediatric Pulmonology in September 2017. A third article concerning the feasibility and efficacy of an outpatient initiation of CPAP in children is currently under revision in the Journal of Clinical and Sleep Medicine.

I also collaborated in the conception, data analysis and manuscript revision of other papers regarding the description and management of SDB in children with Down syndrome, congenital myasthenia and achondroplasia.

Finally, I am the first investigator of a study concerning sleep structure and sleep related respiratory events in girls with Rett syndrome.

10. Improvement and development of new diagnostic tools for SDB in children

a. Validation of a Suprasternal Pressure Sensor for Sleep Apnea Classification in Children.

The detection and characterisation of sleep respiratory events is crucial to a correct interpretation of sleep exam. Even if a pneumotachograph is the gold standard for the detection of airflow, its use is limited due to practical reasons. According to the AASM, an oronasal thermal airflow sensor and a nasal pressure transducer should be both used during a diagnostic sleep study. The first represent the reference for the detection of apneas, whilst the latter is the preferred sensor for the detection of hypopneas[53]. On the other hand, the correct characterisation of obstructive versus central events relies on the detection of a respiratory effort. Oesophageal pressure monitoring is the gold standard for the detection of intrathoracic pressure swings, which depend on respiratory muscles activity[306]. However this technique is invasive, not well tolerated and may lead to sleep disturbances[307]. Therefore, in most of the sleep centres around the world, respiratory inductance plethysmography (RIP), via thoracoabdominal belts represents the standard for the detection of respiratory efforts. However, even if this tool is accurate in most of the cases, it may underestimate obstructive events[308–310]. This is mostly seen in patients with truncal obesity who present little or no thoracoabdominal movements during obstructive events or in young children and infants. The PneaVoX sensor consists of a microphone and a pressure sensor inserted inside a 28-mm diameter and 15-mm thick protective housing. The surface of the transducer attached to the skin comprises a 2 mm-thick cuff, designed to ensure an airtight cavity between the skin of the suprasternal region and the transducers. Sounds in the cavity related to respiratory flow and snoring are recorded by the microphone. Static pressure variations in this cavity, related to increasing deformation of the suprasternal notch during obstructed inspirations, are measured. According to the intensity and frequency, three different signals are therefore recorded from the PneaVoX sensor:

- Respiratory effort is recorded from the suprasternal sensor (SSP) with a frequency range between 0.02 and 20 Hz;
- Snoring is recorded from the microphone with a frequency range between 20 Hz and 200 Hz and is defined by an acoustic intensity greater than 76 decibels in the transducer chamber;

- Respiratory flow (in and out flows) is recorded from the microphone with a frequency range between 200 and 2000 Hz during inspiration and expiration.

This sensor has been validated in adults for the characterization of apneas but not in children[311].

The aim of the study was to validate the PneaVoX to RIP and oronasal thermal for the characterization of sleep apneas in children.

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SCIENTIFIC INVESTIGATIONS

Validation of a Suprasternal Pressure Sensor for Sleep Apnea Classification in Children

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Study Objectives: The recognition and characterization of respiratory events is crucial when interpreting sleep studies. The aim of the study was to validate the *PneaVoX* sensor, which integrates the recording of respiratory effort by means of suprasternal pressure (SSP), respiratory flow, and snoring for the classification of sleep apneas in children.

Methods: Sleep recordings of 20 children with a median age of 7.5 (0.5–16.5) years were analyzed. Scoring of apneas according to the American Academy of Sleep Medicine (AASM) guidelines using nasal pressure, oronasal thermal sensor and respiratory efforts by means of respiratory inductance plethysmography (RIP), was compared to a scoring using the *PneaVoX* sensor and nasal pressure, without the oronasal thermal sensor nor RIP, during a dual blind study.

Results: The percentage of sleep time recording without artifacts was 97%, 97%, 87%, 65%, and 98% for the respiratory flow and SSP from the *PneaVoX* sensor, oronasal thermal sensor, nasal pressure, and RIP, respectively. As compared to the AASM scoring with RIP, sensitivity and specificity of the SSP for the scoring of central apneas were 75% and 99% for the first reader, and 70% and 100% for the second reader, respectively. Sensitivity and specificity for the scoring of obstructive apneas were 98% and 75%, and 100% and 70%, respectively. A significant number of apneas scored as central by RIP were scored as obstructive by the SSP.

Conclusions: The *PneaVoX* sensor has a high degree of scorability in children. The *PneaVoX* sensor is a useful adjunct for characterizing apneas.

Keywords: polygraphy, respiratory effort, suprasternal pressure, respiratory inductance plethysmography, central apnea, obstructive apnea, child

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INTRODUCTION

The recognition and characterization of respiratory events is crucial when interpreting sleep studies. According to the 2012 recommendations of the American Academy of Sleep Medicine (AASM), the standard sensor for apnea detection is an oronasal thermal sensor whereas a nasal pressure transducer is recommended for the scoring of hypopneas.[1]

Monitoring of respiratory effort is paramount in the classification of respiratory events as obstructive, central, or mixed. Increased respiratory effort is a sign of obstructive sleep-disordered breathing and may be recorded from mechanical, electrical, and electromechanical signals.[2] Monitoring of esophageal pressure is the gold standard, as the pressure signal directly reflects the respiratory muscle force,[2] but this method is invasive and usually poorly tolerated and may cause sleep disturbances.[3] Characterization of respiratory efforts by means of esophageal pressure is thus not used in routine care. Respiratory inductance plethysmography (RIP) is used as an alternative method to detect respiratory efforts but underestimation of obstructive events is possible. Indeed, in 9% of a study population of 54 adult patients, chest wall motion evaluated by RIP suggested central apneas but esophageal swings revealed obstructive apneas.[4] In another study which analyzed data from 22 adult patients, re-scoring with esophageal pressure led to a decrease in central apneas (10 vs. 6 events/h), an increase in obstructive apneas (34 vs. 42 events/h), and a moderate increase in mixed apneas (4 vs. 5.5 events/h).[5] More recently, approximately 30% of apneic events considered to be central using data generated by uncalibrated RIP were classified differently when examined using diaphragmatic electromyography and esophageal pressure.[6]

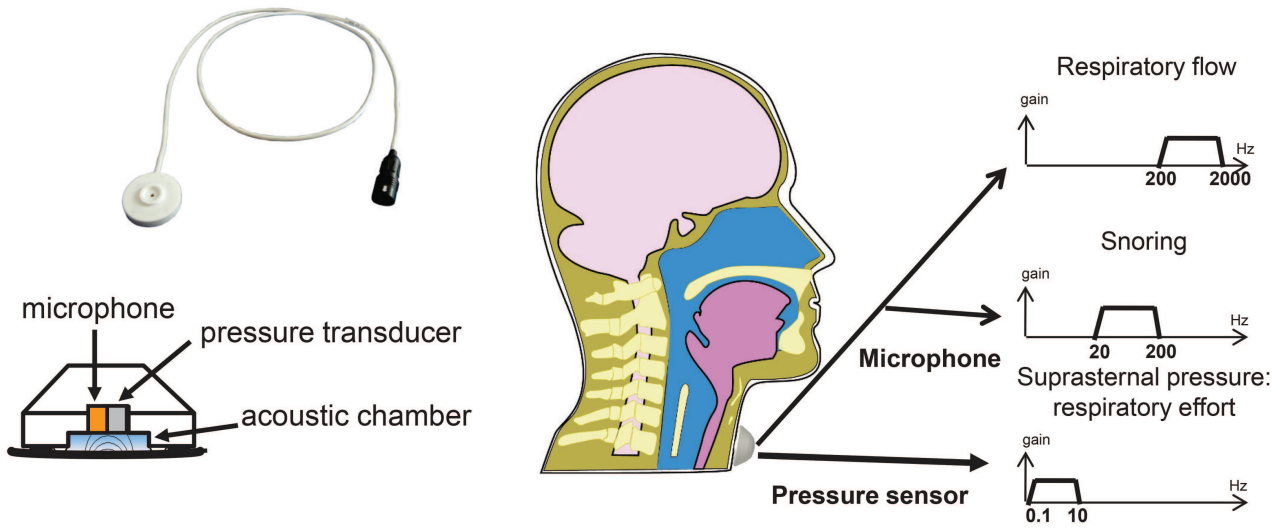
Acceptance and tolerance of sensors is an important practical issue of sleep studies in children. Airflow sensors have been shown to have the poorest tolerance with the lowest hours of scorable signal free from artifact and the highest equipment discomfort.[7] Sensors that are minimally invasive and the least

BRIEF SUMMARY

Current Knowledge/Study Rationale: The PneaVox suprasternal pressure sensor had a high sensitivity and sensibility for the classification of apneas in children. A significant number of apneas scored as central by respiratory inductance plethysmography were scored as obstructive by the PneaVox suprasternal pressure sensor.

Study Impact: The PneaVoX suprasternal pressure sensor has a high degree of scorability in children. The PneaVoX suprasternal pressure sensor is a useful adjunct for characterizing apneas in children.

Figure 1—The PneaVoX sensor.



uncomfortable are thus preferred. In order to overcome the removal of sensors or signal artifacts, the use of well-tolerated, stable, and different sensors that may give additional and/or complementary information on airflow and respiratory effort is recommended.[1]

A sensor placed over the trachea in the sternal notch (*PneaVoX*), which enables the recording of suprasternal inspiratory pressure related to inspiratory effort (SSP), but also of tracheal sounds and snoring, has been shown to have a good sensitivity (99.4%) and specificity (93.6%) for the evaluation of respiratory efforts in adults when compared to esophageal pressure.[8] However, this *PneaVoX* sensor has never been validated in children.

The aim of the present study was to compare a similar *PneaVoX* sensor to the oronasal thermal sensor with RIP for the characterization of sleep apneas in children.

METHODS

Patients

The study was conducted at the noninvasive ventilation and sleep unit at Necker university Hospital in consecutive children who underwent a polygraphy (PG) for a suspicion of obstructive sleep apnea syndrome (OSA). The protocol was approved by the local ethical committee (CPP Ile de France II, n° 2014-03-09 SC).

Sleep Recordings and the PneaVoX Sensor

PGs were performed using CID 102* (Cidelec, Angers, France). The recorded data included airflow via a nasal pressure transducer and an oronasal thermal sensor, body position, actigraphy, thoracic and abdominal movements assessed with RIP, and pulse oximetry (SpO_2).

Each study was performed with the *PneaVoX* sensor (**Figure 1**). The *PneaVoX* sensor was placed above the sternal notch, over the trachea. The transducer was attached to the skin by an adhesive tape and then secured with an adhesive band. Incorrect application of the transducer, not ensuring an airtight cavity between the skin and the transducer, resulted in the absence of the suprasternal negative pressure signal; therefore, the quality and amplitude of the signal was verified before starting the recording.

The *PneaVoX* sensor consists of a microphone and a pressure sensor inserted inside a 28-mm diameter and 15-mm thick protective housing. The surface of the transducer attached to the skin comprises a 2 mm-thick cuff, designed to ensure an airtight cavity between the skin and the transducers (**Figure 1**). Sounds in the cavity related to respiratory flow and snoring are recorded by the microphone. Static pressure variations in this cavity, related to increasing deformation of the suprasternal notch during obstructed inspirations, are measured by the SSP. According to the intensity and frequency, three different signals are therefore recorded from the *PneaVoX* sensor:

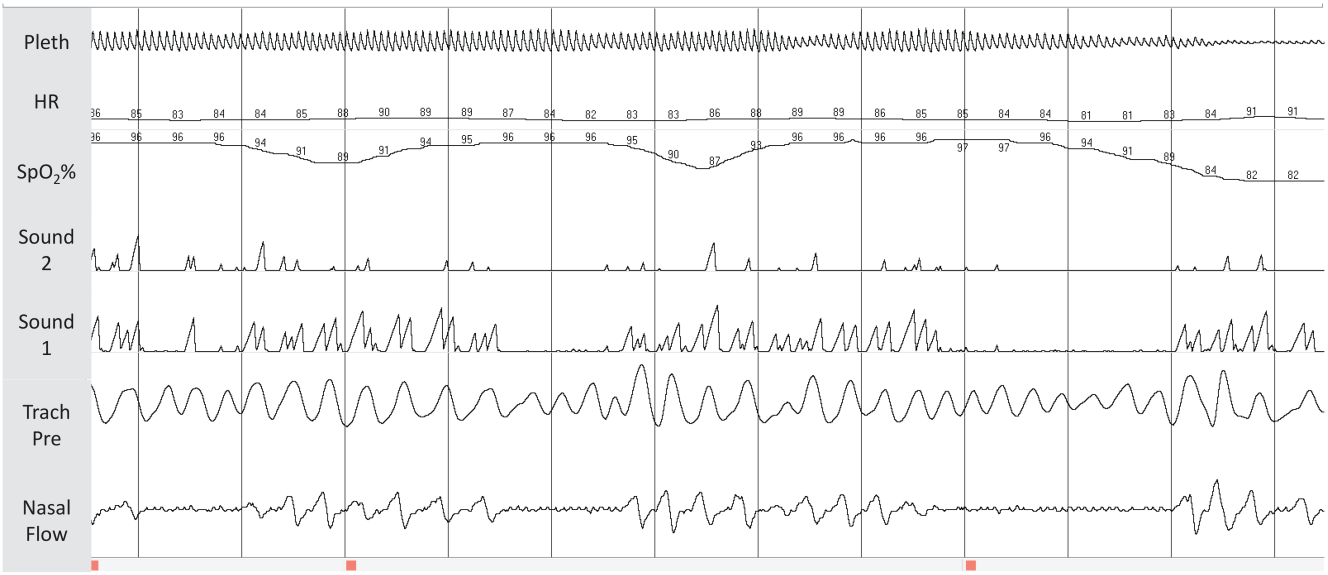
- Respiratory effort is recorded from the SSP with a frequency range between 0.02 and 20 Hz;
- Snoring is recorded from the microphone with a frequency range between 20 Hz and 200 Hz and is defined by an acoustic intensity greater than 76 decibels in the transducer chamber;
- Respiratory flow (in- and outflows) is recorded from the microphone with a frequency range between 200 and 2000 Hz during inspiration and expiration.

Validation of the PneaVoX Sensor for the Classification of Apneas

In the absence of the esophageal pressure, the SSP was compared to RIP which was considered as the "gold standard" for the classification of sleep apneas. A dual blind analysis of each anonymized PG was performed by two independent experienced readers. The dual blind analysis consisted of:

1. one scoring using the oronasal thermal sensor, the nasal pressure transducer and RIP, *without the PneaVoX,* (*Therm-RIP scoring*), representing

Figure 2—Obstructive apnea with suprasternal pressure sensor.



Contemporary reduction in nasal flow and tracheal sound 1 and 2, with persistence of respiratory effort on the suprasternal pressure sensor. Note the presence of concomitant oxygen desaturation. Two-minute epoch. Pleth, pulse wave plethysmography; HR, heart rate; SpO_2, pulse oximetry; Trach Pre, suprasternal pressure.

the reference sensor set according to the AASM recommendations.[1]

2. another scoring using the *PneaVoX* sensor, including the SSP, tracheal sounds and snoring, respiratory flow, and the nasal pressure transducer, *without the oronasal thermal sensor nor RIP* (*PneaVoX scoring*).

For the *Therm-RIP scoring,* an obstructive apnea was defined as ≥ 90% reduction of oronasal thermal sensor for a duration > 2 breaths with the persistence of respiratory efforts on the RIP (**Figure S1** in the supplemental material). Central apnea was defined as ≥ 90% reduction of oronasal thermal sensor for a duration > 2 breaths without any respiratory efforts on RIP, associated with an oxygen desaturation of ≥ 3% or with an event duration > 20 seconds (**Figure S2** in the supplemental material).

For the *PneaVoX scoring*, an obstructive apnea was defined as ≥ 90% reduction of tracheal sounds for a duration > 2 breaths with the persistence of respiratory efforts on the SSP (**Figure 2**). Central apnea was defined as ≥ 90% reduction of tracheal sounds for a duration > 2 breaths without any respiratory efforts on the SSP, associated with an oxygen desaturation of ≥ 3% or with an event duration > 20 seconds (**Figure 3**).

Each PG was prepared for the *Therm-RIP scoring* and *PneaVoX scoring* by a third examiner who was not involved in the scoring of the PGs (GB). GB prepared the anonymized PG and selected the sleep periods for the scoring by the two readers. Each reader then scored the anonymized *Therm-RIP scoring* and *PneaVoX scoring* in a random order. The comparison of the results obtained with the two *scorings* was performed by the third blind-examiner (GB). Three examples of agreement or non-agreement between the *Therm-RIP scoring* and *PneaVoX scoring* are shown on **Figure 4**, **Figure 5** and **Figure 6**, respectively.

Statistical Analysis

Data are presented as median and range. The sensitivity and specificity of the *PneaVoX* sensor to detect obstructive or central apneas, compared to RIP (considered as the reference method) were calculated according to the following formulas:

- Sensitivity = [true positives] / [true positives + false negatives] * 100;
- Specificity = [true negatives] / [true negatives + false positives] * 100.

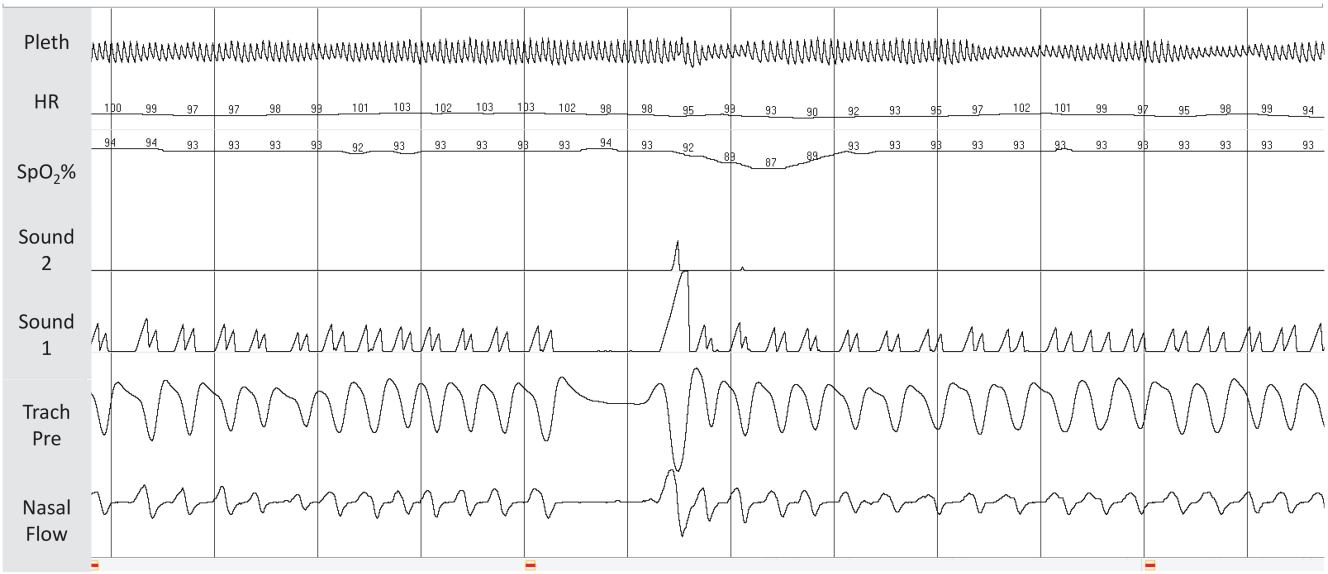
RESULTS

The PGs of 20 children with a median age of 7.5 (0.5–16.5) years were analyzed. Median total recording time was 6.6 hours. Percentages of total sleep time with a scorable signal free of artifacts were 97%, 97%, 87%, 65%, and 98% for the respiratory flow and SSP from the *PneaVoX* sensor, the oronasal thermal sensor, the nasal pressure, and RIP, respectively. No differences according to age were observed.

The concordance between the *Therm-RIP scoring* and the *PneaVoX scoring* for the first and second reader are shown on **Table 1**. A total number of 563 apneic events were scored by the first reader, and 596 by the second reader. For the first reader, the sensitivity of the SSP was 75% for central apneas, and 98% for obstructive apneas. The specificity for detecting these two types of apneas was 98% and 75%, respectively. For the second reader, the sensitivity of the SSP was 70% for central apneas, and 100% for obstructive apneas. The specificity for the detection of these two types of apneas was 100% and 70%, respectively.

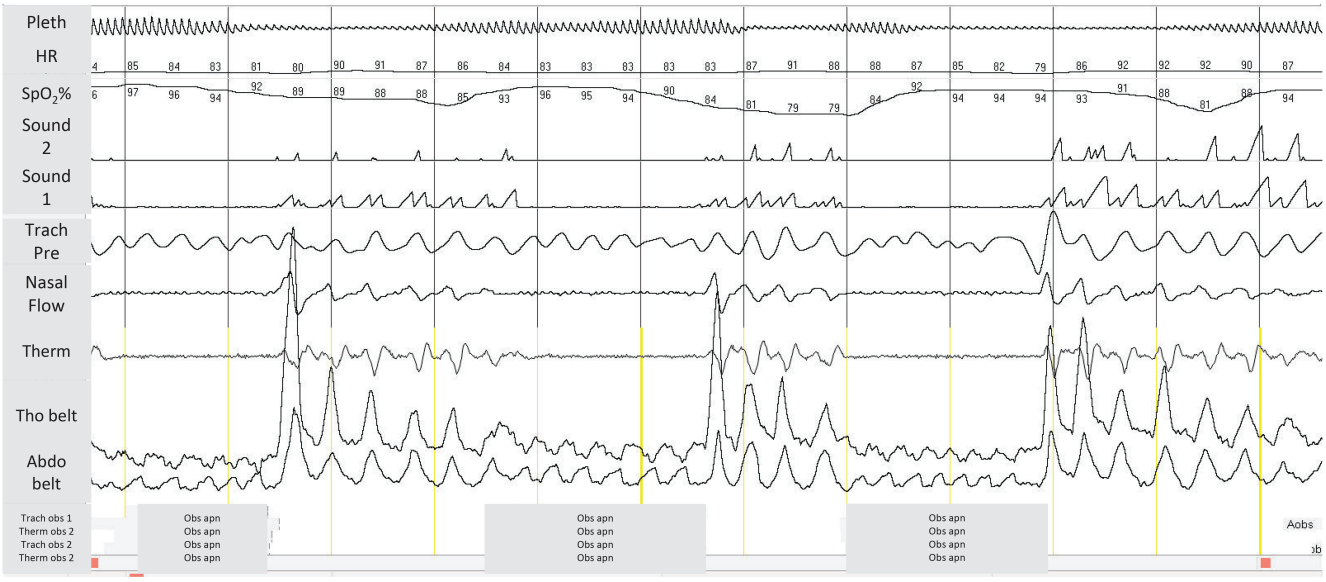
For the first reader, 16 of the apneas classified as central on the *Therm-RIP scoring* were apneas with persistence of respiratory effort on the SSP. This number increased to 29 for the second reader. On the contrary, only 10 of the apneas classified as

Figure 3—Central apnea with suprasternal pressure sensor.



Contemporary reduction in nasal flow and tracheal sound 1 and 2, with abolition of respiratory effort on suprasternal pressure sensor. Note the presence of concomitant oxygen desaturation. Two-minute epoch. Pleth, pulse wave plethysmography; HR, heart rate; SpO_2, pulse oximetry; Trach Pre, suprasternal pressure.

Figure 4—Obstructive apnea concordance between tracheal sounds and oronasal thermal sensor.



Contemporary abolition in nasal flow, oronasal thermal sensor, tracheal sound 1 and 2, with persistence of respiratory effort on the suprasternal pressure sensor and on abdominal and thoracic belts. Note the concordance between the two readers for the analysis with the PneaVox sensor and oronasal thermal sensor. Two-minute epoch. Pleth, pulse wave plethysmography; HR, heart rate; SpO_2, pulse oximetry; Trach Pre, suprasternal pressure; Therm, oronasal thermal sensor; Tho belt, thoracic belt; Abdo belt, abdominal belt; Trach obs, suprasternal pressure sensor analysis for observer 1 or 2; Therm obs, oronasal thermal sensor analysis for observer 1 or 2; Obs apn, obstructive apnea.

obstructive on the *Therm-RIP scoring* were classified as central based on the SSP by the first reader, and 1 by the second reader.

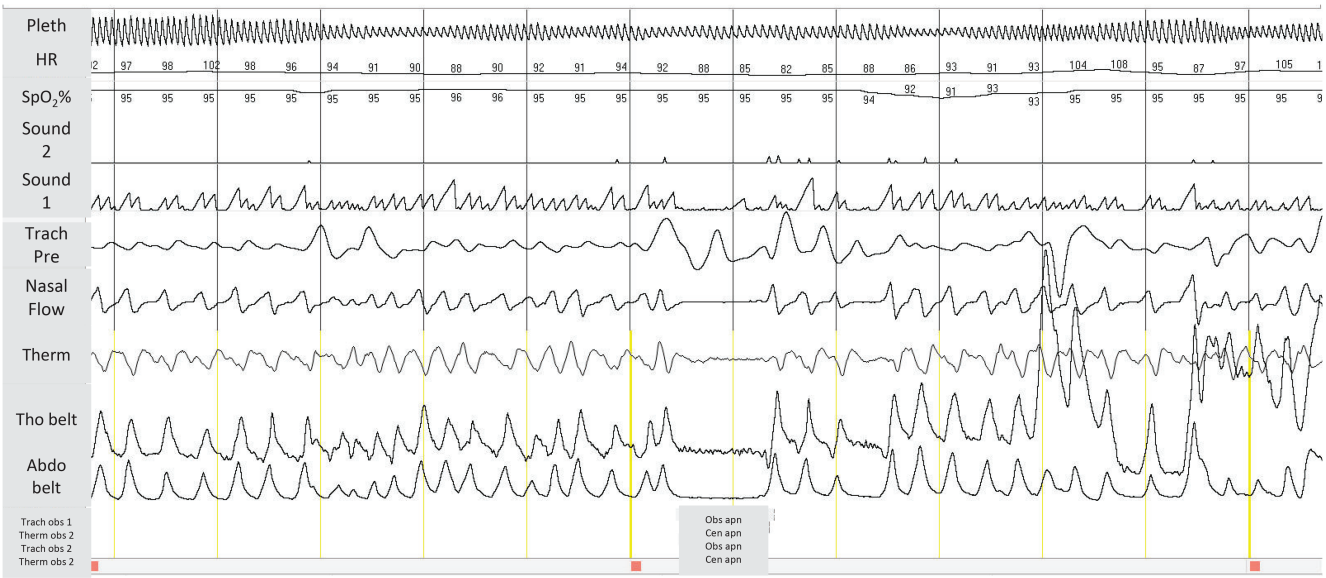
DISCUSSION

Our study is the first to evaluate the usefulness of a *PneaVoX* sensor integrating respiratory effort, in- and outflows, and snoring in children. The *PneaVoX* sensor showed a high degree of scorability and was very well tolerated and accepted by the children regardless of their age. The agreement between the *PneaVoX* sensor and the sensors recommended by the AASM, i.e., oronasal thermal sensor and RIP, was good with high levels of sensitivity and specificity for the classification of apneas. However, a significant number of apneas scored as central by the oronasal thermal sensor and RIP were scored

Figure 5—Central apnea concordance between tracheal sounds and oronasal thermal sensor.

Contemporary abolition in nasal flow; oronasal thermal sensor; tracheal sound 1 and 2; with abolition of respiratory effort on the suprasternal pressure sensor and on abdominal and thoracic belts. Note the concordance between the two readers for the analysis with the PneaVox sensor and oronasal thermal sensor. Two-minute epoch. Pleth, pulse wave plethysmography; HR, heart rate; SpO_2, pulse oximetry; Trach Pre, suprasternal pressure; Therm, oronasal thermal sensor; Tho belt, thoracic belt; Abdo belt, abdominal belt; Trach obs, suprasternal sensor analysis for observer 1 or 2; Therm obs, oronasal thermal sensor analysis for observer 1 or 2; Cen apn, central apnea.

Figure 6—Discordance between tracheal sounds and oronasal thermal sensor analysis.



Contemporary abolition in nasal flow, oronasal thermal sensor, tracheal sound 1 and 2, with persistence of respiratory effort on the suprasternal pressure sensor but abolition of abdominal and thoracic belts movements. Note the discordance between the two readers for analysis with the suprasternal sensor and oronasal thermal sensor, with both observers scoring the same event as obstructive on the suprasternal sensor analysis and as central on the oronasal thermal sensor analysis. Two-minute epoch. Pleth, pulse wave plethysmography; HR, heart rate; SpO_2, pulse oximetry; Trach Pre, suprasternal pressure; Therm, oronasal thermal sensor; Tho belt, thoracic belt; Abdo belt, abdominal belt; Trach obs, suprasternal pressure sensor analysis for observer 1 or 2; Therm obs, oronasal thermal sensor analysis for observer 1 or 2; Obs apn, obstructive apnea; Cen apn, central apnea.

as obstructive by the *PneaVoX*, as observed previously in adult patients.[8]

Qualification of respiratory events as obstructive or central is of major importance for the analysis of sleep studies in children. Chest and abdominal chest wall movements recorded by RIP are usually taken as surrogates of respiratory effort for diagnostic purposes.[1] However, RIP can underestimate respiratory effort because chest and abdominal wall motion may be influenced by lung volume and posture. The sensor bands on the chest and the abdomen may move up or down during

Table 1—Comparison of the classification of apneas by the oronasal thermal sensor, nasal cannula, and respiratory inductance plethysmography (Thermal sensor-RIP scoring) and the *PneaVoX* sensor, integrating a supra-sternal pressure transducer (SSP), and nasal cannula (without the oronasal thermal sensor nor RIP, *PneaVoX* scoring) by the two readers.

		Thermal sensor-RIP scoring (with nasal cannula)	
		Central apneas (RIP) Reader 1 / Reader 2	Obstructive apneas (RIP) Reader 1 / Reader 2
PneaVoX scoring (with nasal cannula)	Central apneas (SSP) Reader 1 / Reader 2	**49 / 67**	10 / 1
	Obstructive apneas (SSP) Reader 1 / Reader 2	16 / 29	**488 / 499**

The numbers in each box represent the number of apneas scored by reader 1 / reader 2; the bold numbers represent the number of concordant scoring and the plain numbers those of discordant scoring.

the night, leading to an overestimation of central sleep apnea events. RIP may also be unreliable when the amplitude of the chest wall movements is small,[4] which may be the case in very young children or older children with truncal obesity. Monitoring of movements of the suprasternal fossa has previously been proposed as a noninvasive method for the estimation of pleural pressure, showing that pressure variations in the suprasternal area reflect esophageal pressure.[9,10] When using the *PneaVoX* sensor, we also found that the SSP showed a good agreement with RIP for apnea classification. And importantly, the scoring with the SSP increased the number of obstructive apneas, similarly to previous studies that used the esophageal pressure.[4–6]

The *PneaVox* sensor also comprised a microphone that records in- and outflows. The recording of tracheal sounds for the detection of apneas in children is not new. Indeed, more than 30 years ago, Beckerman and Wegmann used a miniature microphone/amplifier system to sense breath sounds over the trachea in order to detect central and obstructive apnea episodes in infants and children.[11] In a later study, they used a microphone breath sound detector, coupled to the analysis of chest wall motion by transthoracic impedance in 10 sleeping infants and children for the detection of normal respirations, and central and obstructive apneas.[12] However, they did not observe any statistically significant difference between breath sounds and airflow in the ability to detect obstructive apnea.

The acceptance and the scorability of the different sensors used during sleep studies in children are important issues. Indeed, technical problems such as displacement or refusal of sensors by a restless, irritable or non-cooperative child are common, especially for the airflow sensors. Studies analyzing the comfort and hours of artifact-free signal for different respiratory sensors showed that airflow sensors were associated with the lowest tolerance and "scorability."[7] The *PneaVoX* sensor has the advantage over other devices that sense airflow (thermistors, carbon dioxide sampling catheters) that it is not easily dislodged during restless sleep.[8] This sensor is also less sensitive to position and remains reliable even in the prone position.[8]

The major limitation of our study is that we did not measure the esophageal pressure for the characterization of apneas because of its discomfort and poor acceptance. As the *PneaVox* sensor used in the present study is similar to the sensor used in comparison to the esophageal pressure in adult patients, in the study by Meslier et al.,[8] we may reasonably assume that the agreement between the SSP and the esophageal pressure is similar in children. The difference in the number of events scored by the two readers may be explained by an inter-scorer variability, as recently assessed in large study by Rosenberg et al.[13] As the PneaVox sensor has not been validated for detecting hypopneas; therefore, we only included apneic events in our analysis.[8]

In conclusion, the SSP of the *PneaVoX* sensor is useful for the classification of apneas in children. This sensor is also well accepted and associated with a high scorability. As such, the *PneaVoX* sensor is a useful adjunct for detecting airflow and obstructive apneas in children.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
abdo belt, abdominal belt
cen apn, central apnea
HR, heart rate
obs apn, obstructive apnea
OSA, obstructive sleep apnea
PG, polygraphy
pleth, pulse wave plethysmography
SpO_2, pulse oximetry
RIP, respiratory inductance plethysmography
SSP, suprasternal inspiratory pressure
therm, oronasal thermal sensor
trach pre, suprasternal pressure
tho belt, thoracic belt
trach obs, suprasternal pressure sensor analysis

REFERENCES

1. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 2012;8:597–619.
2. Vandenbussche NL, Overeem S, van Dijk JP, Simons PJ, Pevernagie DA. Assessment of respiratory effort during sleep: esophageal pressure versus noninvasive monitoring techniques. Sleep Med Rev 2015;24:28–36.

3. Chervin RD, Aldrich MS. Effects of esophageal pressure monitoring on sleep architecture. Am J Respir Crit Care Med 1997;156:881–5.
4. Staats BA, Bonekat HW, Harris CD, Offord KP. Chest wall motion in sleep apnea. Am Rev Respir Dis 1984;130:59–63.
5. Boudewyns A, Willemen M, Wagemans M, De Cock W, Van de Heyning P, De Backer W. Assessment of respiratory effort by means of strain gauges and esophageal pressure swings: a comparative study. Sleep 1997;20:168–70.
6. Luo YM, Tang J, Jolley C, et al. Distinguishing obstructive from central sleep apnea events: diaphragm electromyogram and esophageal pressure compared. Chest 2009;135:1133–41.
7. Goodwin JL, Enright PL, Kaemingk KL, et al. Feasibility of using unattended polysomnography in children for research--report of the Tucson Children's Assessment of Sleep Apnea study (TuCASA). Sleep 2001;24:937–44.
8. Meslier N, Simon I, Kouatchet A, Ouksel H, Person C, Racineux JL. Validation of a suprasternal pressure transducer for apnea classification during sleep. Sleep 2002;25:753–7.
9. Tobin MJ, A JG, Watson H, Sackner MA. Noninvasive measurement of pleural pressure by surface inductive plethysmography. J Appl Physiol Respir Environ Exerc Physiol 1983;55:267–75.
10. Moavero NE, Lipton DS, Jenouri GA, Pine J, Schneider A, Sackner MA. Non-invasive semi-quantitative measurements of tidal pressure-volume and flow relations of lung in COPD patients. Bull Eur Physiopathol Respir 1984;20:333–9.
11. Beckerman RC, Wegmann MJ, Waring WW. Tracheal breath sounds for detection of apnea in infants and children. Crit Care Med 1982;10:363–6.
12. Beckerman RC, Wegmann MJ. A comparison of tracheal breath sounds, airflow, and impedance pneumography in the detection of childhood apnea. Sleep 1985;8:342–6.
13. Rosenberg RS, Van Hout S. The American Academy of Sleep Medicine Inter-scorer Reliability Program: respiratory events. J Clin Sleep Med 2014;10:447–54.

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DISCLOSURE STATEMENT

Dr. Baffet is fully employed by Cidelec and contributed to the study design, the preparation of the anonymized data and the manuscript with regard to the description of the PneaVox sensor, he was not involved in the analysis of the data and the conclusions of the study which are the full responsibility of the other authors. The authors have indicated no financial conflicts of interest.

The results of the present study confirm that the PneaVoX sensor is a valuable tool for the characterisation of sleep apneas in children. First of all, the PneaVox sensor had a high scorability meaning that the sensor is well tolerated in children. Secondly, there was a good agreement between the characterisation of apneas via the PneaVox sensor versus the standard signals of RIP and oronasal thermal sensor. The greatest discrepancy was seen for central events. Indeed, some events scored as central by RIP were scored as obstructive by the PneaVox sensor. Since the overestimation of central events is one of the problems with RIP, one could speculate that PneaVox was more accurate in the characterisation of sleep apneas.

In conclusion, this study demonstrated that the PneaVoX sensor is accurate for the characterisation of sleep apneas in children and that it is well accepted. It may thus be considered as an interesting adjuvant tool for sleep studies in children.

b. Pulse wave amplitude reduction as a surrogate for cortical arousal during sleep hypopnea in children

PSG represents the gold standard for the diagnosis of SDB in children and adults. However, as stated, this exam is time consuming, expensive, poorly available and difficult to interpret. For this reason, simplified tests are needed in order to provide access to sleep studies to a large population of children. One of the main alternatives to PSG is RP. This technique consists in a limited channel cardiorespiratory recording without EEG signals. The absence of the EEG electrodes facilitates the set-up of exam and its interpretation but the absence of EEG signals has three major drawbacks:

1. Data about sleep quality, sleep fragmentation and arousal are not available.
2. Indexes of respiratory events are normally calculated as the mean number of events per hour of sleep (total number of respiratory events divided by total sleep time (TST)). TST represents the effective sleep time during night, defined as the time in bed minus periods of awakening. It derives that, without the EEG signals, the exact TST cannot be calculated and total recording time is used instead. For this reason, RP may underestimate the "real" AHI. However, sleep and wakefulness can be quite accurately estimated in children using cardiorespiratory and/or videotape recordings.
3. For the scoring of hypopnoeas, a 3% oxygen desaturation or an arousal are required along with an at least 30% reduction of respiratory flow. In the absence of EEG signal, hypopnoeas associated with an arousal but without a desaturation are missed which may underestimate the "real" AHI.

Arousals cause central autonomic activation, which leads to increased sympathetic activity and peripheral vasoconstriction. The changes on peripheral vascular bed are detectable via variations of the pulse wave amplitude (PWA) and may increase the diagnostic accuracy of RP when used as a surrogate marker of cortical arousal[312–314]. The aim of our study was to evaluate the diagnostic value of PWA changes as a surrogate for cortical arousals in children.

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Original Article

Pulse wave amplitude reduction as a surrogate for cortical arousal during sleep hypopnea in children

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ABSTRACT

Objectives: The accuracy of respiratory polygraphy (RP) is limited because of the absence of electroencephalography (EEG). Pulse wave amplitude (PWA) reduction has been shown to be a marker of autonomic activation during arousal, and may represent a substitute for obstructive respiratory-related cortical arousal (RRCA). This study tested the hypothesis that PWA could be a surrogate for RRCA in detecting obstructive hypopnea (OH) in a pediatric population.
Materials and methods: Two experienced readers scored 30 consecutive polysomnographies (PSG) using standard scoring rules. Automatic software detected every 20–90% reduction in PWA. A second scoring of respiratory events using PWA reduction as a surrogate for RRCA was performed (RP with PWA) for each percentage of PWA reduction. The final analysis consisted of determining the concordance between the two methods of detecting OH.
Results: A total of 987 episodes of ≥30% flow reduction were analyzed: 330 with RRCA only, 205 with desaturation (DS) only, 134 with both, and 318 without RRCA or DS. As the percentage of reduction in PWA increased, the sensitivity of PWA as a substitute for RRCA decreased, but the specificity increased. For a decrease in PWA of 60% or 70%, the sensitivities of PWA as a substitute for RRCA were 79% and 57%, and the specificities 51% and 76%, respectively.
Conclusion: Pulse wave amplitude reduction lacks sensitivity and specificity to be used as a surrogate for RRCA to detect OH in children. Polysomnography remains the gold standard for the diagnosis of sleep disordered breathing in children.

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1. Introduction

Overnight polysomnography (PSG) represents the gold standard for diagnosing obstructive sleep apnea syndrome (OSAS) in children and adults [1–3]. However, due to practical and economic reasons, limited channel recordings without electroencephalography (EEG) (respiratory polygraphy (RP), or type III recordings) are increasingly used in adults [4,5]. RP has been shown to underestimate the apnea–hypopnea index (AHI) in children when compared to PSG [6], mainly because of an incorrect estimation of total sleep time (TST). However, sleep and wakefulness can be accurately determined in children by using cardiorespiratory and videotape recordings [7], which reduce this discrepancy between PSG and RP. A second major problem when scoring obstructive respiratory events with RP is the absence of EEG, which precludes the detection of respiratory-related cortical arousals (RRCA) for the scoring of obstructive hypopneas. According to the American Academy of Sleep Medicine (AASM), obstructive hypopneas (OH) are defined in children as a drop of at least 30% of respiratory flow, lasting at least

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two breaths, associated with a ≥3% oxygen desaturation (DS) and/or a RRCA [8]. Therefore, in the absence of EEG tracings, hypopneas not associated with DS are not scored, which may underestimate the AHI [8].

Arousals cause central autonomic activation, which leads to increased sympathetic activity and peripheral vasoconstriction [9]. Pulse wave amplitude (PWA) reduction has been shown to reflect sympathetic activation during sleep [10–12] in adults, but also to improve the diagnostic value of conventional PSG in obstructive sleep apnea syndrome (OSAS) by better detecting respiratory events and RRCA [13]. However, studies in children and studies assessing PWA as a surrogate for RRCA for respiratory event detection are still lacking.

The aim of the present study was to verify if PWA reduction could be a surrogate for RRCA for the scoring of OH in children referred to a sleep laboratory for suspected OSAS.

2. Material and methods

2.1. Polysomnography

The PSG of 50 consecutive children who were referred to the sleep unit of Necker University Hospital in Paris for a suspicion of OSAS, between March 2014 and March 2015, were analyzed. PSG was performed using CID 102* (Cidelec, Saint Gemmes sur Loire, France). The recorded data included airflow (nasal pressure transducer and oronasal thermistance), body position, body movements, thoracic and abdominal movements assessed with inductance belts, pulse oximetry (SpO_2), and PWA using the Nonin pulse oximeter (Nonin Medical, Inc., Plymouth, MN) with a sampling frequency of 64 Hz. The EEG recordings were based on the international 10–20 system, which includes the placement of electrodes in positions F1-A2, F2-A1, C3-A2, C4-A1, O1-A2, O2-A1, recording of eye movements, electromyography of the chin and electrocardiogram. Sleep stages were obtained manually using standard criteria [14]. Sleep arousals were defined as an abrupt shift in EEG frequency, including a theta-alpha pattern and/or a frequency >16 Hz lasting ≥3 s with ≥10 s of stable sleep preceding the event. Respiratory events were scored according to the AASM manual and following update [8,14]. Oxygen desaturation index (ODI) was defined as the number of DS per hour of PSG recording.

2.2. Data analysis

PSG was analyzed using the Cidelec 2.2.2 software; they were retained for analysis if sleep time lasted at least 4 h of TST and if there were no artifacts in the EEG, PWA, and respiratory flow tracings.

A first standard PSG scoring using the AASM scoring manual [14] was performed by two experienced readers: the first reader scored the PSG and the second validated the analysis. Percentage of PWA reduction was added by mean of specific software developed by Cidelec (GB), which scored each 20%–90% reduction in PWA. Maximal PWA percentage reduction was calculated according to the baseline amplitude of the signal within the previous 5 s. Each PWA reduction was graphically represented with corresponding bars on the PSG tracing (Fig. 1a). Only reductions in PWA occurring at the time of a respiratory event or during the 5 s following the event were retained for analysis. All the reductions in PWA caused by artifacts of the pulse wave signal were discarded.

The second scoring, performed in a random order, consisted of a "blind" RP scoring, without the EEG tracings but with the graphical representation of the decrease in PWA. The two readers were thus aware of the different percentages of reduction in PWA (from 20% to 90%). Every ≥30% decrease of airflow (nasal pressure transducer) was scored as an OH if it was associated with DS and/or a reduction in PWA. Decreases in airflow, ≥30% but <90%, not associated with DS or PWA reduction, were marked as respiratory events. The first reader scored the RP scoring and the second validated the analysis (Fig. 1b).

Lastly, the two scorings were integrated in the same tracing (Fig. 2). A third reader, who was unaware of the results of the first two scorings, performed a manual comparison between the two scorings for each percentage of maximal reduction in PWA.

The protocol was approved by the local ethical committee (CPP Ile de France II, n° 2014-03-09 SC).

2.3. Statistical analysis

Data were presented as median and range. The sensitivity and specificity of every percentage level of PWA reduction to detect AASM hypopnea were calculated according to the following formulas:

$$Sensitivity = [true\ positives]/[true\ positives + false\ negatives] * 100$$
$$Specificity = [true\ negatives]/[true\ negatives + false\ positives] * 100$$

Table 1 shows the process for the calculation of the sensitivity and specificity of PWA as a surrogate for a RRCA to score OH. The same table was completed by the third reader, for each percentage of maximal reduction in PWA from 20 to 90%.

3. Results

3.1. Polysomnographies

Thirty out of the 50 PSGs were retained for analysis, due to the presence of artifacts or insufficient sleep time (TST <4 h) in 20 PSGs. Clinical and demographic characteristics of the patients (16 males) are shown in Table 2. Mean age was 11.9 ± 4.6 years old. The most frequent diagnosis was Prader–Willi syndrome (14/30). Thirty percent of patients were obese, with a body mass index (BMI) ≥95% centile [15]. None of the patients were using drugs that could have effect on the EEG or PWA results. The results of the PSG are shown in Table 3. The total number of OH retained for analysis from the 30 PSGs was 669, with 3145 RRCA and 1160 DS.

The total number of ≥30% decreases in respiratory flow was 987: 134 events were associated with a DS and RRCA, 205 events were associated with a DS only, 330 events were associated with RRCA only, and 318 events were not associated with a DS nor with a RRCA (Table 4). The distribution of these 318 "respiratory events" not associated with RRCA or DS, but only with a decrease in PWA ("false positives") is shown in Fig. 3.

3.2. Analysis of the agreement between pulse wave amplitude and respiratory-related cortical arousal

Figs. 4 and 5 show the sensitivity and specificity values for every given level of PWA reduction to predict an RRCA for OH scoring, with and without DS. During episodes of ≥30% respiratory flow reduction with RRCA and no DS (which defines hypopnea not detected on RP), as the percentage of decrease in PWA increased, the sensitivity of PWA to substitute for RRCA decreased, but the specificity increased (Fig. 4). The best compromise of sensitivity and specificity values were found for a decrease in PWA between 60% and 70%. The sensitivities of PWA to predict RRCA were 79% and 57%, respectively, and the specificities 51% and 76%. Comparable results were observed for episodes of ≥30% respiratory flow reduction with RRCA and DS (Fig. 5).

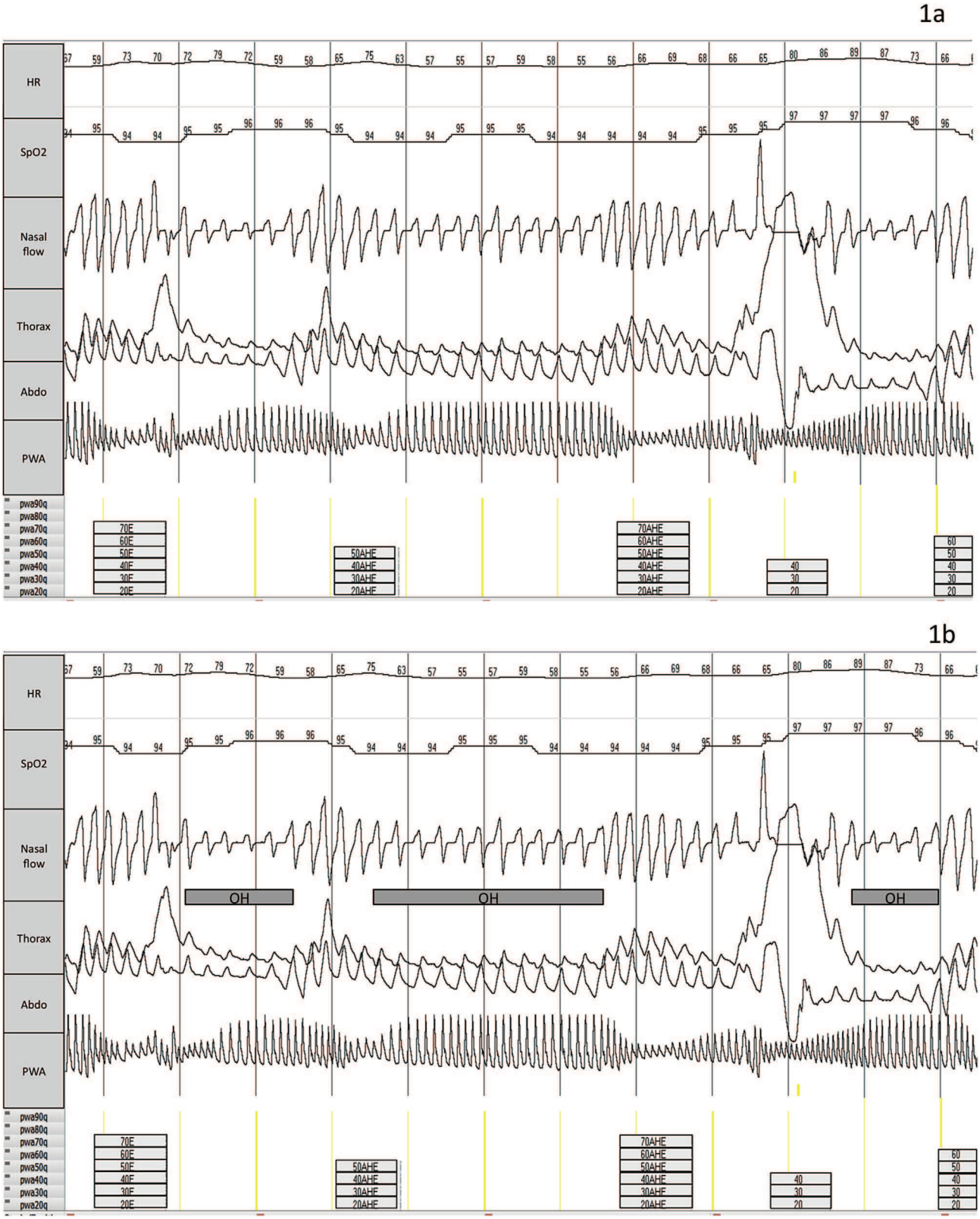

Fig. 1. Examples of the procedures. **1a**. An example of the graphical presentation of % of reduction in PWA. **1b**. An example of the scoring of PWA reduction related events. Abbreviations: Abdo, abdomen; HR, heart rate; OH, obstructive hypopnea; PWA, pulse wave amplitude; SpO_2, peripheral oxygen saturation.

As an example, Table 5 shows the difference between the HI obtained on PSG and RP according to the different levels of reductions of PWA as a surrogate for RRCA. This table shows that the HI ranged from 1.9 events/hour for a 90% reduction in PWA to 3.9 events/hour for a 20% reduction in PWA. Bland–Altmann plots for the HI corresponding to a 60% and 70% reduction in PWA, which were associated with the best sensitivity and specificity, are shown in Fig. 6a and b, respectively. As compared to a 60% reduction in

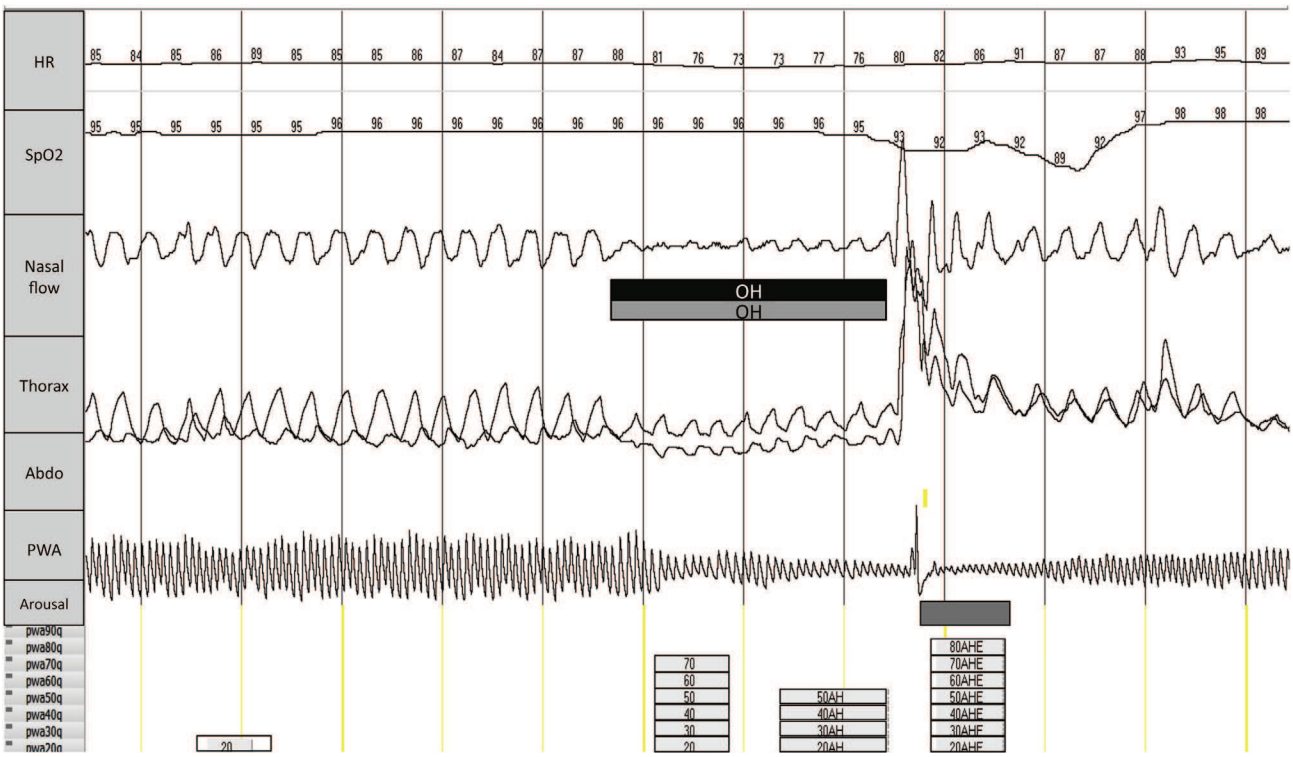

Fig. 2. Example of integration of the two scores. Black bar (OH) represents a respiratory event scored according to AASM scoring rules (PSG first scoring); Gray bar (OH) represents a respiratory event scored according to PWA reduction scoring (second scoring). Abbreviations: AASM, American Academy of Sleep Medicine; Abdo, abdomen; HR, heart rate; OH, obstructive hypopnea; PWA, pulse wave amplitude; PSG, polysomnography; SpO2, peripheral oxygen saturation.

Table 1
Calculation of sensitivity and specificity of pulse wave amplitude as a surrogate for respiratory-related cortical arousal.

	RRCA	No RRCA
Decrease in PWA	*With a DS*	*With a DS*
	=hypopnea	=hypopnea
	=true positive	=false positive
	Without a DS	*Without a DS*
	=hypopnea	=no hypopnea
	=true positive	=false positive
No decrease in PWA	*With a DS*	*With a DS*
	=hypopnea	=hypopnea
	=false negative	=true negative
	Without a DS	*Without a DS*
	=hypopnea	=no hypopnea
	=false negative	=true negative

DS, ≥3% oxygen desaturation; PWA, pulse wave amplitude; RRCA, respiratory-related cortical arousal.

Table 2
Clinical and demographic characteristics of the patients ($n = 30$).

Age, years (median and range)		13 (4–19.5)
Female to male ratio		16/14
BMI (centile)		62 (±38)
Underweight (<5th percentile)		17%
Obese (≥95th percentile)		30%
Diagnosis	Prader–Willi syndrome	14
	Non co-morbid OSAS	2
	Bronchopulmonary dysplasia	2
	Polymalformative syndrome	2
	Spinal muscular atrophy type 2	2
	Vocal cord palsy	2
	Rett syndrome	1
	Cerebral tumor	1
	Duchenne muscular dystrophy	1
	Sickle cell disease	1
	Silver-Russell syndrome	1
	Neurofibromatosis type 1	1

BMI, Body mass index (Kg/m^2); OSAS, obstructive sleep apnea syndrome.

Table 3
Sleep study data ($n = 30$). Data are expressed as mean and standard deviation.

TST, minutes (median, range)	480.5 (332–681)
Sleep stage duration, minutes (median, range)	
N1	35 (0–91)
N2	227 (161–764)
N3	101 (32–186)
REM	91 (8–167)
Arousal index, events/hour (median, range)	11 (5–34)
Respiratory events, events/hour (median, range)	
AHI	3.6 (1–46)
OAI	0.2 (0–5)
CAI	0 (0–46)
Mean SpO_2%, (mean ± SD)	96 (±1.3)
Minimal SpO_2%, (mean ± SD)	89 (±4.4)
ODI events/hours, (mean ± SD)	4.5 (±6.2)

AHI, apnea–hypopnea index; CAI, central apnea index; OAI, obstructive apnea index; ODI, oxygen desaturation index; REM, rapid eye movements; SpO_2, pulse oximetry; TST, total sleep time.

PWA, a 70% reduction in PWA seemed to have a better agreement with the RRCA scoring.

4. Discussion

This study is the first to compare OH scoring using PWA vs RRCA, and shows that the reduction in PWA reduction lacks sensitivity and specificity to be used as a surrogate for RRCA in a pediatric population referred for OSAS. Indeed, an inverse relationship between sensitivity and specificity was observed for the ability of PWA to substitute for RRCA, with increasing levels of PWA reduction. For the scoring of hypopneas in children, PSG remains the gold standard.

The results show that the percentage of decrease in PWA cannot be used as a reliable surrogate for RRCA in children. Indeed, an

Table 4
Total number of ≥30% decreases in respiratory flow retained for the study.

		Number	
≥30% decrease in respiratory flow with 3%DS	With RRCA	134	"AASM" hypopneas
	Without RRCA	205	
≥30% decrease in respiratory flow without 3%DS	With RRCA	330	
	Without RRCA	318	No "AASM" hypopneas

Abbreviations: 3%DS, ≥3% oxygen desaturation; AASM, American Academy of Sleep Medicine; RRCA, respiratory-related cortical arousal.

inverse trend was observed between sensitivity and specificity for every level of PWA reduction. Table 5 shows the potential changes in the AHI according to a given PWA threshold. As children usually have low AHI, even a small change in the AHI may thus potentially impact the therapeutic decision [3].

Vat and colleagues [16] compared four different definitions for scoring hypopnea in adults, using 3% or 4% desaturation associated or not with a PWA reduction. Using a PWA reduction of at least 30%, they found an increase in the estimation of the HI, but a lack of specificity due to poor correlation between EEG arousal and PWA drops. Delessert and colleagues [12] analyzed ≥20% decreases of PWA and associated changes in EEG power density and cortical activity during sleep in an adult population. They found a sensitivity of 64.7% and a predictive value of 70.9% of PWA reduction to predict an arousal. By performing an EEG power density analysis, they observed that a reduction in PWA was associated with an arousal, but also to subtle EEG power changes in all bands. These findings, along with other experiences [17,18], suggest that increased power density with an autonomic reaction such as a PWA drop may represent a central nervous system mechanism to prevent arousal and promote sleep continuity. It can thus be

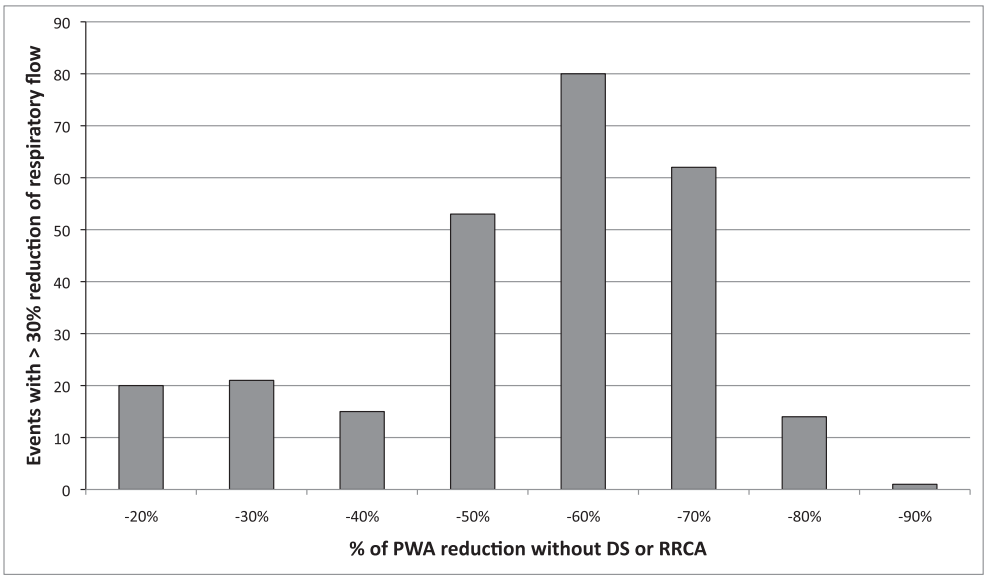

Fig. 3. Number of respiratory events with ≥30% decrease in respiratory flow, associated with pulse wave amplitude reduction, but without a respiratory-related cortical arousal or ≥3% oxygen desaturation. Abbreviations: DS, oxygen desaturation; PRRCA, respiratory-related corcial arousal; PWA, pulse wave amplitude.

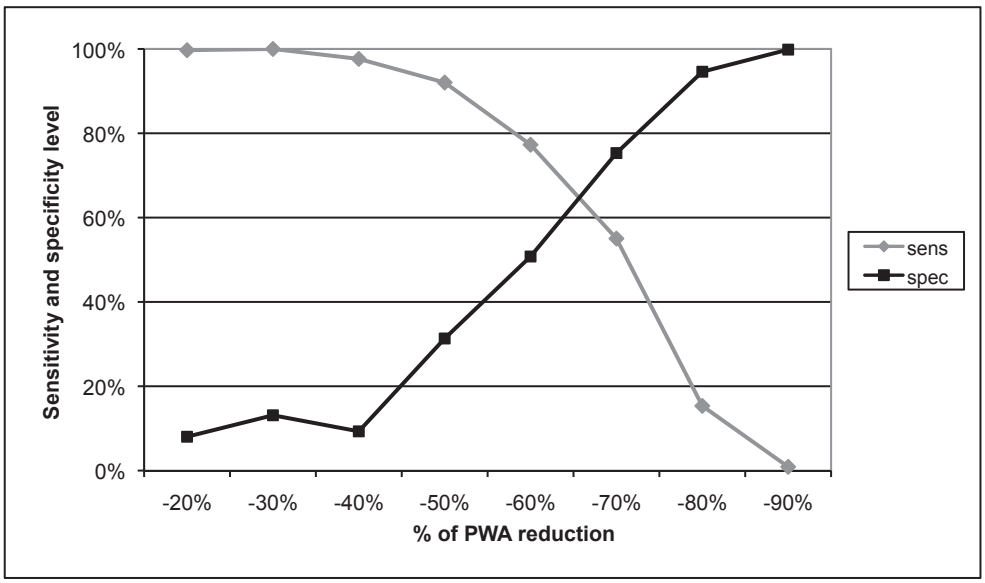

Fig. 4. Sensitivity and specificity level for every % of pulse wave amplitude reduction with desaturation. Abbreviations: PWA, pulse wave amplitude; sens, sensitivity; spec, specificity.

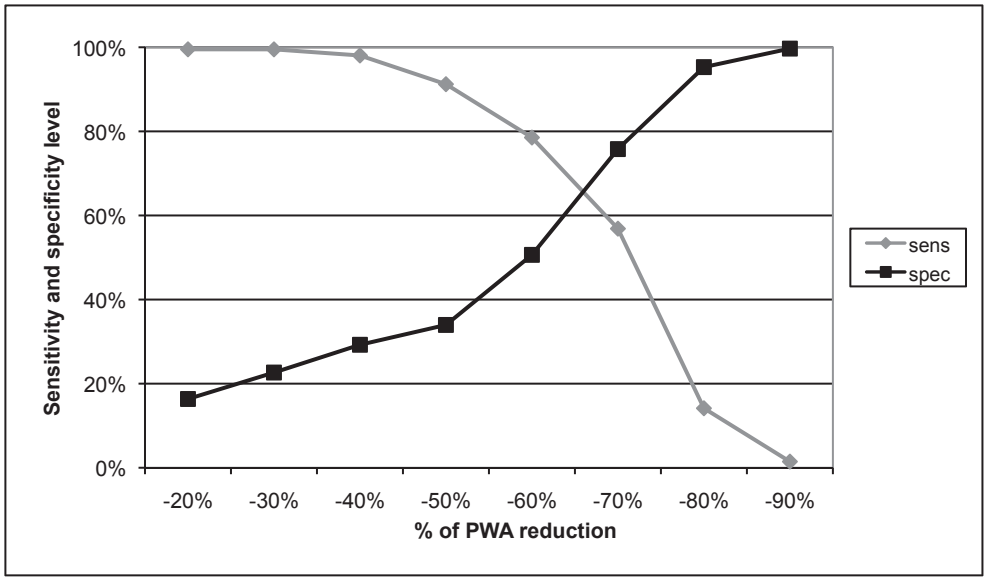

Fig. 5. Sensitivity and specificity level for every % of pulse wave amplitude reduction without desaturation. Abbreviations: PWA, pulse wave amplitude; sens, sensitivity; spec, specificity.

Table 5
Comparison of the hypopnea index on polysomnography and respiratory polygraphy, according to the different levels of reductions of pulse wave amplitude as a surrogate for respiratory-related cortical arousal.

HI on PSG (events/hour)	HI on RP, according to the different levels of reduction in PWA (events/hour)							
	90%	80%	70%	60%	50%	40%	30%	20%
2.8	1.9	2.1	2.7	3.2	3.6	3.7	3.8	3.9

HI, hypopnea index; PSG, polysomnography; PWA, pulse wave amplitude; RP, respiratory polygraphy.

speculated that PWA changes represent a more subtle analysis of sleep fragmentation; they are able to detect autonomic activations not necessarily followed by cortical arousal. Even if these autonomic activations had been linked to deleterious consequences on daytime functions [19], they are currently not taken into account for the scoring of arousal during respiratory events that still rely on classical EEG findings [14]. This observation may contribute to an explanation of the poor concordance between RRCA and PWA changes in the present study. Moreover, in another study of adults treated by noninvasive ventilation, a 30% reduction in PWA was found to have a 87% positive predictive value for detecting EEG arousals [20]. As in the present study, the specificity was low (40.7%), but the sensitivity was higher (89%). It could therefore be speculated that these results highlight the extreme sensitivity of PWA changes for "sub-cortical" arousals that are not recorded by conventional EEG, but only by spectral analysis. Finger PWA could probably be more sensitive in detecting autonomic arousals than standard EEG, and therefore does not represent the ideal parameter to substitute EEG-scored arousals [21]. Moreover PWA itself could offer additional information regarding the effects of upper airway obstruction on the central nervous and cardiovascular systems. More recently, Karmakar and colleagues [10] proposed a complex arousal detection model derived from finger photoplethysmography, taking into account PWA and area–area under peak. They found 68% sensitivity and 95% specificity of this model to detect respiratory arousals in a group of 10 adult patients with sleep-disordered breathing.

The present study had some limitations. For instance, it was a single-center study with the majority of children having

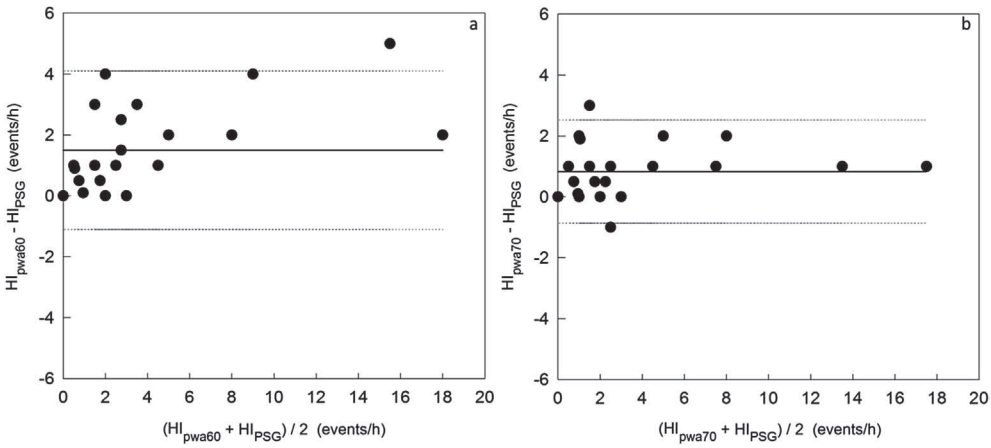

Fig. 6. Bland–Altman plots between the hypopnea index (HI) corresponding to a 60% reduction in pulse wave amplitude (PWA) (a), the HI corresponding to a 70% reduction in PWA (b) and the HI scored on a polysomnography (PSG). The thin lines represent the limits of agreement and the continuous bold line represents the bias (mean of the difference).

Prader–Willi syndrome, which was due to the presence of a Prader–Willi reference center at the hospital. This may have affected the results, since it has been shown that these patients may have some alterations of sleep architecture [22] and autonomic dysfunctions [23] with imbalanced sympathetic and parasympathetic activity. However, children with Prader–Willi are routinely referred to a sleep laboratory due to high prevalence of OSAS. This study did not analyze the accuracy of the PWA according to the different sleep stages. Indeed, PWA reductions not associated with RRCA are more frequent during REM sleep [11,12,17,18,24], which is the most vulnerable sleep stage for obstructive respiratory events. It could be argued that PWA could perform better in predicting RRCA during NREM sleep stages. Nevertheless, the aim of the present study was to evaluate if RP could be used instead of PSG, and thus EEG, by using other noninvasive surrogates of RRCA. Since the scoring of sleep stages relies on EEG signals, as it is for arousals, this data seem non-relevant when searching for a parameter that could be used instead of EEG tracings.

However, an important strength of the study was the use of an automated analysis of the reduction in PWA, the dual PSG scoring, and the final analysis by an independent reader. Great care was taken to use the same pulse oximeter sensor for all recordings. It is well known that pulse oximetry accuracy varies from one manufacturer to another [25], especially during hypoxemia.

In conclusion, this study showed that PWA reduction is not a reliable surrogate for RRCA, and therefore could not substitute EEG tracings for scoring OH. Future studies should aim at improving comprehension of the relationship between other markers of autonomic activation and deleterious consequences of sleep disordered breathing in children.

Disclosure statement

Dr. Baffet is fully employed by Cidelec and contributed to the study design and preparation of the PWA data. He was not involved in the analysis of the data and the conclusions of the study, which are the full responsibility of the other co-authors. The authors have indicated no financial conflicts of interest.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2017.02.027.

References

[1] Epstein LJ, Kristo D, Strollo Jr PJ, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med 2009;5:263–76.
[2] Marcus CL, Brooks LJ, Ward SD, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2012;130:e714–55.
[3] Kaditis AG, Alonso Alvarez ML, Boudewyns A, et al. Obstructive sleep disordered breathing in 2- to 18-year-old children: diagnosis and management. Eur Respir J 2016;47:69–94. http://dx.doi.org/10.1183/13993003.00385-2015.
[4] Collop NA. Portable monitoring for the diagnosis of obstructive sleep apnea. Curr Opin Pulm Med 2008;14:525–9. http://dx.doi.org/10.1097/MCP.0b013e328312ed4a.
[5] El Shayeb M, Topfer LA, Stafinski T, et al. Diagnostic accuracy of level 3 portable sleep tests versus level 1 polysomnography for sleep-disordered breathing: a systematic review and meta-analysis. CMAJ 2014 Jan 7;186(1):E25–51. http://dx.doi.org/10.1503/cmaj.130952.
[6] Tan HL, Gozal D, Ramirez HM, et al. Overnight polysomnography versus respiratory polygraphy in the diagnosis of pediatric obstructive sleep apnea. Sleep 2014 Feb 1;37(2):255–60. http://dx.doi.org/10.5665/sleep.3392.
[7] Morielli A, Ladan S, Ducharme FM, et al. Can sleep and wakefulness be distinguished in children by cardiorespiratory and videotape recordings? Chest 1996;109:680–7.
[8] Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 2012 Oct 15;8(5):597–619. http://dx.doi.org/10.5664/jcsm.2172.
[9] Zou D, Grote L, Eder DN, et al. Obstructive apneic events induce alpha-receptor mediated digital vasoconstriction. Sleep 2004;27:485–9.
[10] Karmakar C, Khandoker A, Penzel T, et al. Detection of respiratory arousals using photoplethysmography (PPG) signal in sleep apnea patients. IEEE J Biomed Health Inf 2014;18:1065–73. http://dx.doi.org/10.1109/JBHI.2013.2282338.
[11] Haba-Rubio J, Darbellay G, Herrmann FR, et al. Obstructive sleep apnea syndrome: effect of respiratory events and arousal on pulse wave amplitude measured by photoplethysmography in NREM sleep. Sleep Breath 2005;9:73–81. http://dx.doi.org/10.1007/s11325-005-0017-y.
[12] Delessert A, Espa F, Rossetti A, et al. Pulse wave amplitude drops during sleep are reliable surrogate markers of changes in cortical activity. Sleep 2010;33:1687–92.
[13] Zacharia A, Haba-Rubio J, Simon R, et al. Sleep apnea syndrome: improved detection of respiratory events and cortical arousals using oxymetry pulse wave amplitude during polysomnography. Sleep Breath Schlaf Atm 2008;12:33–8. http://dx.doi.org/10.1007/s11325-007-0126-x.
[14] Iber C, Ancoli-Israel S, Chesson A, et al. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. 1st ed. Westchester, Illinois: American Academy of Sleep Medicine; 2007.
[15] Rodd C, Metzger DL, Sharma A. Extending World Health Organization weight-for-age reference curves to older children. BMC Pediatr 2014;14:1.
[16] Vat S, Haba-Rubio J, Tafti M, et al. Scoring criteria for portable monitor recordings: a comparison of four hypopnoea definitions in a population-based cohort. Thorax 2015;70:1047–53. http://dx.doi.org/10.1136/thoraxjnl-2014-205982.
[17] Poyares D, Guilleminault C, Rosa A, et al. Arousal, EEG spectral power and pulse transit time in UARS and mild OSAS subjects. Clin Neurophysiol 2002;113:1598–606.
[18] Black JE, Guilleminault C, Colrain IM, et al. Upper airway resistance syndrome: central electroencephalographic power and changes in breathing effort. Am J Respir Crit Care Med 2000;162:406–11.
[19] Martin SE, Wraith PK, Deary IJ, et al. The effect of nonvisible sleep fragmentation on daytime function. Am J Respir Crit Care Med 1997;155:1596–601. http://dx.doi.org/10.1164/ajrccm.155.5.9154863.
[20] Adler D, Bridevaux PO, Contal O, et al. Pulse wave amplitude reduction: a surrogate marker of micro-arousals associated with respiratory events occurring under non-invasive ventilation? Respir Med 2013;107:2053–60. http://dx.doi.org/10.1016/j.rmed.2013.10.010.
[21] Catcheside PG, Chiong SC, Mercer J, et al. Noninvasive cardiovascular markers of acoustically induced arousal from non-rapid-eye-movement sleep. Sleep 2002;25:797–804.
[22] Lin H-Y, Lin S-P, Lin C-C, et al. Polysomnographic characteristics in patients with Prader–Willi syndrome. Pediatr Pulmonol 2007;42:881–7. http://dx.doi.org/10.1002/ppul.20673.
[23] DiMario FJ, Dunham B, Burleson JA, et al. An evaluation of autonomic nervous system function in patients with Prader-Willi syndrome. Pediatrics 1994;93:76–81.
[24] Lavie P, Schnall RP, Sheffy J, et al. Peripheral vasoconstriction during REM sleep detected by a new plethysmographic method. Nat Med 2000;6:606.
[25] Robertson FA, Hoffman GM. Clinical evaluation of the effects of signal integrity and saturation on data availability and accuracy of Masimo SE and Nellcor N-395 oximeters in children. Anesth Analg 2004;98:617–22.

In conclusion, the present study demonstrated that PWA changes are not sufficiently reliable to be used as a surrogate for respiratory-related cortical arousals, and therefore may not substitute EEG signals for scoring obstructive hypopneas. We observed an inverse correlation between sensitivity and specificity with increasing levels of PWA reduction. This means that the more profound the decrease of PWA, the more sensitive this tool is for the detection of a cortical arousal. However, one could argue that even little variations of the PWA correspond to a discernible event that is not associated with a cortical arousal. Indeed, arousals may be graded into four different levels with the first two levels corresponding to Delta and K waves bursts that are integrated in the brainstem in order to generate a sympathetic activation[187]. These events do not "reach" the cortex, probably to maintain sleep continuity. However, their importance in determining cardiovascular risk related to SDB has never been determined. Future studies should aim at improving the understanding of the relationship between other markers of autonomic activation and the deleterious consequences of SDB in children.

c. Pulse transit time as a tool to characterize obstructive and central apneas in children

The characterisation of respiratory events as obstructive or central is crucial when interpreting sleep studies. The gold standard for the measurement of respiratory effort is the variation of the swing of oesophageal pressure, detected via an oesophageal catheter. However, this technique is not only invasive and difficult to accept by most of the patients, but may also disrupt sleep quality and consequently PSG results. Surrogate measures of respiratory effort are thus warranted and the AASM recommends dual thoracoabdominal RIP belts in children.

Pulse transit time (PTT) is defined as the time period the pulse wave takes to travel between the aortic valve and the vessels in the finger. It is calculated as the interval between the R wave of the electrocardiogram (ECG) and the arrival of the photoplethysmographic pulse at the finger and depends on the difference in mean arterial pressure (MAP). As during an obstructive respiratory event, intrathoracic pressure becomes more negative, MAP progressively decreases and this variation is detected by the PPT as a typical "crescendo" aspect. This tool has already been validated against oesophageal pressure in adults[188–190] whereas only one study compared PTT to thoracoabdominal RIP in children[191] with a good sensitivity and specificity. In this last study, a standalone system was used to detect PTT. The aim of the present study was to evaluate the usefulness of PTT, estimated via an automated integrated software, for the characterisation of apneas in children with SDB.

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ORIGINAL ARTICLE

Pulse transit time as a tool to characterize obstructive and central apneas in children

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Abstract
Purpose The characterization of apneas during polysomnography (PSG) as obstructive or central is a key element of a sleep study. Pulse transit time (PTT) has demonstrated its potential as a noninvasive surrogate marker for inspiratory efforts**.** The aim of the study was to assess the ability of PTT to classify apneas as central or obstructive, as compared to respiratory inductance plethysmography (RIP) in children.
Methods Overnight PSG with simultaneous PTT recording was performed on 11 consecutive children (mean age 8.9 years, range 1–18.2 years). The same observer scored the apneas using two blinded configurations: (1) the *RIP scoring* used the nasal pressure, thermistors, thoracic and abdominal movements, and pulse oximetry signals: (2) the *PTT scoring* used PTT in combination with all the other signals *without* the thoracic and abdominal movements.
Results One hundred fourteen apneas out of a total of 520 respiratory events were analyzed. With RIP, 58 (51%) apneas were scored as obstructive and 56 (49%) as central. Using PTT, 77 (68%) of the apneas were scored as obstructive and 37 (32%) as central. When using PTT, 30 apneas scored as central by RIP were scored as obstructive. PTT was highly sensitive (81%) but poorly specific (46%) in scoring 58 apneas as obstructive. PTT was less sensitive (46%) but highly specific (81%) to score 56 apneas as central.
Conclusion PTT may be used as an additional tool to RIP to improve the scoring of apneas as obstructive or central in children. The high percentage of artifact is a limitation of PTT.

Keywords Pulse transit time · Polysomnography · Respiratory inductance plethysmography · Apneas · Child

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Introduction

The characterization of respiratory events during sleep as obstructive or central is a key element of a sleep study, as misclassification can lead to inappropriate treatment. Increased respiratory effort is a sign of obstructive sleep-disordered breathing and may be recorded from mechanical, electrical, and electromechanical signals [1].

The measurement of swings in esophageal pressure (Pes) by means of an esophageal catheter is the current gold standard technique for detecting changes in inspiratory effort. However, the placement of an esophageal catheter is uncomfortable and difficult to accept especially in children. Moreover, it may modify the upper airway dynamics and induce sleep disruption [2]. According to the 2012 recommendations of the American Academy of Sleep Medicine (AASM), respiratory inductance plethysmography (RIP) can be used as an alternative method to detect respiratory efforts [3]. RIP is a noninvasive, well-tolerated, and reproducible method. However, this technique is difficult to standardize as variation may occur with body position, sleep stage, and the degree of obesity. Obstructive events may thus be underestimated by RIP [4–6].

Pulse transit time (PTT) is a measure of respiratory effort and arousal that has shown promise in the diagnosis of sleep-

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disordered breathing in adults [7–9] and children [10]. PTT is the time period the pulse wave takes to travel between the aortic valve and the vessels in the finger and is calculated as the interval between the R wave of the ECG and the arrival of the photoplethysmographic pulse at the finger [11]. Several studies have shown a good correlation between the PTT and the Pes swings in adult patients [9, 12, 13],

Few studies have evaluated PTT in children [10, 14–17]. The majority of these studies, including one study which used Pes [14], evaluated the usefulness of PTT to improve the detection of arousals associated with respiratory events [14–17]. Only one study assessed the usefulness of PTT with a standalone system to classify respiratory events as central or obstructive, with encouraging results [10].

The aim of the present study was to assess the ability of PTT, recorded with an automated integrated software, to classify apneas as central or obstructive, as compared to RIP, which is the recommended scoring by the American Academy of Sleep Medicine (AASM) [3] in patients referred to a pediatric university hospital sleep unit.

Material and methods

Population

This study was conducted at the Noninvasive Ventilation and Sleep Unit of Necker University Pediatric Hospital in Paris. Consecutive children with sleep-disordered breathing, who were referred for a scheduled PSG, were enrolled. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the local ethical committee (CPP Ile de France II, no. 2014-03-09 SC). Informed consent was obtained from all parents and patients >6 years included in the study.

Polysomnography

All the children underwent a full-night polysomnography. Continuous recordings were performed using an electroencephalogram (EEG) with electrode positions C3/A2-Cz/O1 of the International 10–20 Electrode Placement System, electrooculogram, chin electromyogram, and electrocardiogram (ECG). Thoracic and abdominal movements were recorded by RIP. Airflow was measured by means of nasal pressure, associated with the sum of buccal and nasal thermistor signals. Pulse oximetry (SpO_2) was also measured. All the recordings were performed with the PSG system Alice 6 LDxS (Philips Respironics, Carquefou, France). Sleep studies were scored manually using standard techniques and criteria of the AASM [3].

Method of PTT measurement

PTT was recorded simultaneously from the automated integrated software of the Alice 6 LDxS (Philips Respironics, Carquefou, France). The PTT refers to the time period the pulse wave takes to travel between two arterial sites, from the moment the pulse leaves the aortic valve, identified by the R wave on the ECG, to the time when it reaches the vessels in the finger, identified by the pulse wave detected by the SpO_2 sensor. The speed at which this arterial pressure wave travels is directly proportional to blood pressure. An acute rise in blood pressure causes vascular tone to increase, and hence, the arterial wall becomes stiffer causing the PTT to shorten. Conversely, when blood pressure falls, vascular tone decreases and PTT increases [18]. PTT can quantify respiratory effort by detecting changes in the blood pressure oscillations associated with pleural swings ("pulsus paradoxus") [15]. PTT was calculated as the interval between the ECG R wave and the point corresponding to 50% of the height of the maximum value on the pulse wave form detected by photoplethysmography at the finger level. PTT values are available with every heartbeat and are measured with an accuracy of 2 ms. The signal is typically oversampled at 5 Hz to ensure no values are neglected. Normal PTT is approximately 200 to 300 ms when using the finger probe.

Procedure

The analysis was only done on apneas. Hypopneas and respiratory events occurring during the time period of artifacts on the ECG, RIP, or SpO_2 signals were discarded.

The study was designed as a blinded PSG study: patients underwent an overnight multichannel PSG with simultaneous PTT recording. The same observer scored the PSG respiratory events using two scoring configurations. The *RIP scoring* used the nasal pressure, thermistors, thoracic and abdominal movements, and SpO_2 signals. The *PTT scoring*, blinded to the first scoring, used PTT in combination with all the other signals without the thoracic and abdominal movements. Obstructive apnea (OA) was defined as the absence of nasal airflow for at least two breaths, with continued chest wall and abdominal movements on the *RIP scoring* or an increase in PTT on the *PTT scoring*. (Fig. 1) Central apnea (CA) was defined as the absence of airflow lasting more than 20 s or of shorter duration and associated with an arousal and/or a 3% oxygen desaturation with the cessation of respiratory effort on the *RIP scoring* or (no change) near disappearance/reduction in PTT on the *PTT scoring* [10].

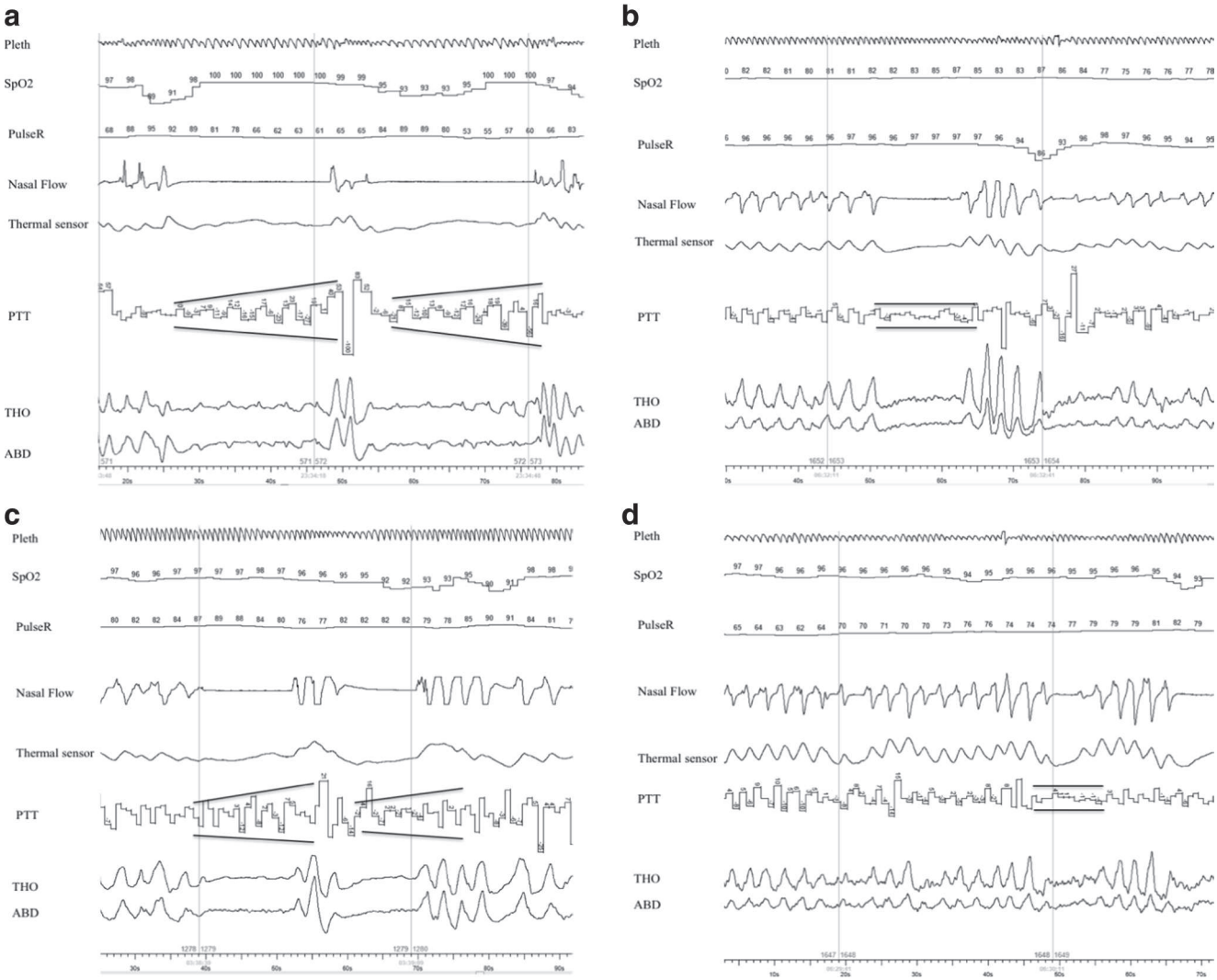

Fig. 1 One-minute sections of PSG tracings with pulse transit time (PTT) and RIP (THO-ABD) in four different patients. **a** Concordance in obstructive apneas: the apneas can clearly be seen on both signals with a pattern of increase in the PTT swings and phase opposition on RIP. **b** Concordance in central apneas: determination of a central event is made from the near disappearance of the PTT swings or the respiratory movements on RIP. **c** Misclassification of a central apnea by the PTT: there is an obvious pattern of increase in the PTT swings whereas there are no respiratory oscillations on RIP. **d** Misclassification of an obstructive apnea by the PTT: there are no PTT oscillations whereas there are still respiratory movements on RIP

Statistical analysis

Statistical calculations were performed using the Excel 2010 (Microsoft Corp, Seattle, WA) program. The sensitivity and specificity of PTT to detect obstructive or central respiratory events, compared to RIP (considered as the reference method) were calculated according to the following formulas: Sensitivity = [true positives]/[true positives + false negatives]*100; Specificity = [true negatives]/[true negatives + false positives]*100. Positive predictive value was calculated as [true positives]/[true positives + false positives]*100. Negative predictive value was determined as [true negatives]/[true negatives + false negatives]*100.

Results

Patient population

Eleven children (four boys) were included in the study (Table 1). Mean age was 8.9 years (range 1–18.2 years). All the patients had an underlying disease: Prader-Willi syndrome (n = 4), achondroplasia (n = 3), Bardet Biedl syndrome (n = 1), Down's syndrome (n = 1), Fallot tetralogy (n = 1), and juvenile polyarthritis (n = 1). The mean apnea-hypopnea index (AHI) was 6.9 events/h (range 2.5 to 11.3 events/h) and the mean apnea index (AI) 2.5 events/h (range 0 to 7.4 events/h).

Table 1 Characteristics of the population

	Gender	Age (years)	Pathology	AHI (events/h)	AI (events/h)
Patient 1	F	8.3	Prader-Willi	9.6	1.7
Patient 2	F	7.8	Prader-Willi	3.9	1.5
Patient 3	F	8.9	Prader-Willi	10.3	7.1
Patient 4	F	9.4	Prader-Willi	2.5	1
Patient 5	M	8.2	Achondroplasia	11.3	7.4
Patient 6	F	8.2	Achondroplasia	3.9	0.6
Patient 7	F	7.9	Achodronplasia	3.6	0.7
Patient 8	M	14.9	Bardet Biedl syndrome	11	0
Patient 9	M	4.8	Fallot tetralogy	10.8	2
Patient 10	M	18.2	Juvenile polyarthritis	6	4.3
Patient 11	F	1.0	Down syndrome	4	0.9

F female, *M* male, *AHI* apnea-hypopnea index, *AI* apnea index

Respiratory events

Five hundred twenty respiratory events were scored using the RIP. Among these events, 180 were apneas and 340 were obstructive hypopneas. Among the 180 apneas detected using RIP, 66 (37%) apneas were excluded because of artifacts on the ECG, RIP, or SpO_2 signals. One hundred fourteen apneas remained available for a comparison of scoring between RIP and PTT.

Accuracy of PTT for distinguishing central and obstructive apneas

With RIP, 58 (51%) apneas were scored as obstructive and 56 (49%) as central (Table 2). Using PTT, 77 (68%) of the apneas were scored as obstructive and 37 (32%) as central. When using PTT, 30 apneas scored as central by RIP were scored as obstructive. An agreement for obstructive and central apneas was observed in only 73 (64%) of the 114 apneas. When RIP was taken as the reference scoring, PPT was highly sensitive (81%) and poorly specific (46%) in scoring 58 apneas as obstructive (Table 2). The positive predictive value was 61% and the negative predictive value was 70%. PTT was less sensitive (46%) but highly specific (81%) to score 56 apneas as central. The positive predictive value was 70% and the negative predictive value was 61% (Table 2).

Discussion

Our results show that a scoring of apneas with PTT (without RIP) on the automated integrated software of a commercial PSG device, led to a greater number of obstructive apneas as a scoring based on RIP, as recommended by the AASM. However, 37% of the apneas could not be used for analysis because of artifacts.

The aim of the study was to evaluate the ability and accuracy of PTT to classify apneas as obstructive or central in children. Because we were not able to compare PTT to Pes which is the gold standard, we compared PTT to RIP, which is used to assess respiratory efforts in routine care [3]. However, it is well known that RIP may underestimate respiratory effort, because chest and abdominal wall movements may be influenced by lung volume and posture. The sensor bands on the chest and the abdomen may move up or down during the night, leading to an overestimation of central sleep apnea events. RIP may also be unreliable when the amplitude of the chest wall movements is small, as may be observed in very young children or in older children with obesity. Similarly to studies that used Pes or diaphragmatic EMG, we found more obstructive apneas with a *PTT scoring* (68%) as compared to a *RIP scoring* (51%) [5, 6]. PTT has been compared to Pes in three adult studies [9, 12, 13] and one pediatric study [14]. All these studies demonstrated an excellent correlation between the changes in Pes and PTT. Indeed, the analysis of 177 respiratory events by Argod et al.

Table 2 Comparison of the classification of apneas (n = 114) by respiratory inductance plethysmography (RIP) technique (comprising RIP, nasal pressure, thermistors, and pulse oximetry) and pulse transit time (PTT) technique (comprising nasal pressure, thermistors, and pulse oximetry *without* RIP)

		RIP technique	
		Obstructive apneas (RIP)	Central apneas (RIP)
PTT technique	Obstructive apneas (PTT)	47	30
	Central apneas (PTT)	11	26

showed that PTT had a 93% specificity and a 100% sensitivity for the detection of central apneas, and a 99% specificity and a 85% sensitivity for the detection of obstructive apneas as compared to a Pes scoring [12]. Katz et al. performed a polysomnography with Pes and PTT in 24 symptomatic children and 10 normal controls to assess if PTT could increase the detection of respiratory arousals [14]. They observed also a good correlation between the change in Pes and PTT. Foo et al. performed a study quite similar to ours in 33 children comparing a scoring of respiratory events by RIP and PTT [10]. They found that PTT had a 90% sensitivity and 82% specificity to detect obstructive events and a 90% sensitivity and 80% specificity to detect central events. The main limitation was the effect of motion artifacts with only 334 events out of 993 (34%) events being considered as valid for the PTT analysis. We can thus reasonably assume that PTT may be useful to "correct" the scoring of some central apneas by RIP as obstructive apneas and that PTT is more sensitive than RIP for the scoring of obstructive apneas.

Despite these results, the PTT is not used on a routine basis for the scoring of respiratory events during sleep. The main limitation of PTT is artifact [10, 18, 19]. This is mostly due to interference with the photoplethysmographic signal at the finger, or chest wall movements which disturb the ECG leads. There is also a significant variation in PTT between individuals as a result of differences in blood pressure and vascular compliance [19]. This may partially explain why 11 apneas scored as obstructive by the *RIP scoring* were scored as central by the *PTT scoring* in the present study (Table 2). Artifacts are more likely to occur during rapid eye movement sleep (REM) as this sleep state is associated with large variations in respiratory drive. This is particularly troublesome as REM sleep is a period associated with an increased incidence of respiratory events. REM sleep is also associated with a labile hemodynamic state, with an increase in sympathetic activity causing fluctuations in pulse rate and blood pressure, affecting the stability of the PTT signal. Finally, PTT cannot be considered as a quantitative measure as a PTT recording is only available with each cardiac cycle; measurement may thus fall on either side of the peak or trough of the blood flow pressure oscillation associated with respiratory effort, resulting in a tendency to undersample. The change in PTT may therefore not represent the real value of the change in respiratory effort.

Our study has several limitations. The major limitation is the lack of comparison with the gold standard, i.e., Pes. Such a study would be difficult to perform in our population of children with severe underlying diseases for which repeated and often invasive procedures are commonly required. A second limitation is the small number of apnea events. This is explained by the fact that the study was performed in children, in whom the number of apneas is generally lower than in adults. We did not compare the scoring of hypopneas because our patients had only obstructive hypopneas. Finally, PTT analysis was performed by an automated integrated software of a commercially available equipment whereas most previous studies used a standalone system [9, 10, 12, 17]. We found only one study in children using the Alice software, but the aim of this study was to evaluate the usefulness of PTT for the detection of respiratory-related arousal [14]. Part of the high variability of the PTT signals may indeed be explained by the quality of the recorder data processor device.

Conclusion

Scoring of apneas with PTT (without RIP) on the automated integrated software of a commercial PSG device, led to a greater number of obstructive apneas as a scoring based on RIP. As previous studies using Pes have shown that PTT can be used as an accurate semi-quantitative estimate of respiratory effort, PTT could be used as an additional tool with RIP to improve the scoring of apneas as obstructive or central in children. However, the high percentage of artifact is a limitation of PTT. Finally, a study validating PTT against Pes would definitely be able to confirm the value of PTT in children.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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References

1. Kaditis AG, Alonso Alvarez ML, Boudewyns A, Alexopoulos EI, Ersu R, Joosten K, Larramona H, Miano S, Narang I, Trang H, Tsaoussoglou M, Vandenbussche N, Villa MP, Van Waardenburg D, Weber S, Verhulst S (2016) Obstructive sleep disordered breathing in 2- to 18-year-old children: diagnosis and management. Eur Respir J 47:69–94
2. Chervin RD, Aldrich MS (1997) Effects of esophageal pressure monitoring on sleep architecture. Am J Respir Crit Care Med 156:881–885
3. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF, Redline S, Strohl KP, Davidson Ward SL, Tangredi MM (2012) Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the

Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 8:597–619
4. Staats BA, Bonekat HW, Harris CD, Offord KP (1984) Chest wall motion in sleep apnea. Am Rev Respir Dis 130:59–63
5. Boudewyns A, Willemen M, Wagemans M, De Cock W, Van de Heyning P, De Backer W (1997) Assessment of respiratory effort by means of strain gauges and esophageal pressure swings: a comparative study. Sleep 20:168–170
6. Luo YM, Tang J, Jolley C, Steier J, Zhong NS, Moxham J, Polkey MI (2009) Distinguishing obstructive from central sleep apnea events: diaphragm electromyogram and esophageal pressure compared. Chest 135:1133–1141
7. Pitson D, Stradling J (1998) Autonomic markers of arousal during sleep in patients undergoing investigation for obstructive sleep apnoea, their relationship to EEG arousals, respiratory events and subjective sleepiness. J Sleep Res 7:53–59
8. Pitson D, Sandell A, Van den Hout R, Stradling J (1995a) Use of pulse transit time as a measure of inspiratory effort in patients with obstructive sleep apnoea. Eur Respir J 81:669–674
9. Argod J, Pépin JL, Smith RP, Lévy P (2000) Comparison of esophageal pressure with pulse transit time as a measure of respiratory effort for scoring obstructive nonapneic respiratory events. Am J Respir Crit Care Med 162:87–93
10. Foo JYA, Wilson SJ, Bradley AP, Williams GR, Harris MA, Cooper DM (2005) Use of pulse transit time to distinguish respiratory events from tidal breathing in sleeping children. Chest 128:3013–3019
11. Geddes LA, Voelz M, James S, Reiner D (1981) Pulse arrival time as a method of obtaining systolic and diastolic blood pressure indirectly. Med Biol Eng Comput 19:671–762
12. Argod J, Pépin JL, Lévy P (1998) Differentiating obstructive and central sleep respiratory events through pulse transit time. Am J Respir Crit Care Med 158:1778–1783
13. Pitson DJ, Sandell A, van den Hout R, Stradling JR (1995b) Use of pulse transit time as a measure of inspiratory effort in patients with obstructive sleep apnoea. Eur Respir J 8:1668–1674
14. Katz ES, Lutz J, Black C, Marcus CL (2003) Pulse transit time as a measure of arousal and respiratory effort in children with sleep-disordered breathing. Pediatr Res 53:580–588
15. Pépin JL, Delavie N, Pin I, Deschaux C, Argod J, Bost M, Levy P (2005) Pulse transit time improves detection of sleep respiratory events and microarousals in children. Chest 127:722–730
16. Galland BC, Tan E, Taylor BJ (2007) Pulse transit time and blood pressure changes following auditory-evoked subcortical arousal and waking of infants. Sleep 30:891–897
17. Foo JYA, Wilson SJ, Williams GR, Harris MA, Cooper DM (2008) Investigation of pulse transit time characteristics during single and recurrent obstructive respiratory events. J Clin Monit Comput 22: 327–332
18. Smith RP, Argod J, Pépin JL, Lévy PA (1999) Pulse transit time: an appraisal of potential clinical applications. Thorax 54:452–457
19. Farré R, Montserrat JM, Navajas D (2004) Noninvasive monitoring of respiratory mechanics during sleep. Eur Respir J 24:1052–1060

Comment

This paper adds an important contribution for the clinical application of the PTT which can be used as an adjunct tool for the screening and evaluation of SDB.

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The results of this study demonstrated that PTT helps scoring a greater number of apneas as obstructive compared to standard RIP scoring. It is known that RIP may underestimate respiratory effort, because chest and abdominal wall movements may be influenced by lung volume and posture. Moreover, the sensor bands may be displaced during sleep, leading to an overestimation of central sleep apnea events. RIP may also be unreliable when the amplitude of the chest wall movements is small, as may be observed in very young children or in older children with obesity. This phenomenon has already been observed when RIP was compared to oesophageal pressure and to diaphragmatic EMG[309,310]. On the contrary, PTT correlated well with oesophageal pressure for the characterisation of sleep respiratory events[188,189]. All these considerations corroborate the hypothesis that PTT could be a useful additional tool for the scoring of central and obstructive apneas, since it appears more sensitive than RIP. The main drawbacks of this technique are artefacts that limit the interpretation of the signal. In the present study, only one third of the events were retained for analysis. Most of the artefacts derived from interference with the photoplethysmographic signal at the finger, or chest wall movements which disturb the ECG leads. For this reason, even if PTT appears to have a higher sensitivity than RIP, it may presently not be recommended as an alternative to RIP scoring but rather as a useful additional tool.

11. Noninvasive ventilation for the treatment of SDB in children

a. Continuous Positive Airway Pressure for Upper Airway Obstruction in Infants with Pierre Robin Sequence.

Upper airway obstruction is the hallmark of Pierre Robin sequence, as described by Robin in 1923[12]. Infants with Pierre Robin sequence present with a various degree of upper airway obstruction since birth with a management depending largely on the experience of centres[315]. Some of the infants may be managed via supine position, while others need additional measures according to the severity of the obstruction[316–320]. However, it has to be noted that invasive techniques such as tongue lip adhesion, mandibular distraction osteogenesis or tracheostomy are associated with complications such as infection, bone necrosis, displacement of the device or even death in some cases. Moreover, Pierre Robin sequence is a condition associated with a spontaneous improvement over time[319], who pleads for the use of noninvasive procedures.

In light of these considerations CPAP appears a promising alternative to more invasive surgical procedures[280,321]. After having previously published the feasibility and efficacy of nasal CPAP in children with Pierre Robin sequence and severe upper airway obstruction, we prospectively evaluated our standardised protocol that included CPAP as the first line treatment for infants with moderate to severe OSAS.

Continuous Positive Airway Pressure for Upper Airway Obstruction in Infants with Pierre Robin Sequence

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Summary: The aim of the study was to evaluate noninvasive continuous positive airway pressure as first-line treatment for upper airway obstruction in neonates with Pierre Robin sequence. Forty-four neonates were enrolled and classified in 4 groups: ventilator-dependent patients (severe upper airway obstruction group), patients with clinical upper airway obstruction, an abnormal (moderate upper airway obstruction group) or normal polygraphy (mild upper airway obstruction group), and those with no clinical upper airway obstruction (no upper airway obstruction group). Five neonates in the severe upper airway obstrction group (n = 9) were successfully managed by noninvasive continuous positive airway pressure and 4 required a tracheotomy. The moderate upper airway obstruction group (n = 4) was successfully managed by noninvasive continuous positive airway pressure and the other patients by prone positioning. Continuous positive airway pressure represents an effective treatment of upper airway obstruction in Pierre Robin sequence and may be recommended in selected patients. (*Plast. Reconstr. Surg.* 137: 609, 2016.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.

Upper airway obstruction is a hallmark in neonates with Pierre Robin sequence.[1–4] Noninvasive continuous positive airway pressure has been shown to be an effective treatment for severe upper airway obstruction in Pierre Robin sequence.[5] The aim of this study was to evaluate a standardized protocol using noninvasive continuous positive airway pressure as first-line treatment for upper airway obstruction in neonates with Pierre Robin sequence.

PATIENTS AND METHODS

The medical records of all neonates with Pierre Robin sequence evaluated between September of 2013 and September of 2014 were analyzed. Four groups were identified. The severe upper airway obstruction group comprised the neonates who were not able to breathe spontaneously without a tracheal tube or noninvasive continuous positive airway pressure without immediate desaturation (pulse oximetry <80 percent) and hypercapnia (transcutaneous carbon dioxide >60 mmHg). Neonates with less severe upper airway obstruction underwent daytime nap polygraphy, scored according to the American Academy of Sleep Medicine guidelines,[6] in the prone position and classified as those with abnormal (moderate upper airway obstruction group) or normal polygraphic (mild upper airway obstruction group) findings. The moderate upper airway obstruction group was started on noninvasive continuous positive

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airway pressure on the basis of the following criteria: apnea-hypopnea index greater than 10 per hour and/or oxygen desaturation index greater than 15 per hour and/or minimal pulse oximetry less than 90 percent and/or maximal transcutaneous carbon dioxide greater than 50 mmHg.

Continuous positive airway pressure was used continuously in the severe upper airway obstruction group with the aim of decreasing continuous positive airway pressure use to sleep periods only over a 1- to 2-week period.[7–9] The moderate upper airway obstruction group was treated with noninvasive continuous positive airway pressure during sleep periods only. Intensive care unit ventilators or home continuous positive airway pressure devices with industrial nasal masks were used. The initial noninvasive continuous positive airway pressure level was set at 6 cmH_2O and rapidly increased to the maximal tolerated continuous positive airway pressure level.[9] A tracheotomy was proposed in case of continuous ventilator-dependence or noninvasive continuous positive airway pressure failure. Patients admitted for nutritional problems only and those seen as outpatients comprised the no upper airway obstruction group.

The continuous positive airway pressure devices were either intensive care unit ventilators in the neonatal intensive care unit, or home continuous positive airway pressure devices on the neonatology ward: Infant Flow SiPAP system (CareFusion, Hoechberg, Germany), Trilogy 100 or BiPap A40 (Philips Respironics, Murrysville, Pa.), and S9 (ResMed, Saint Priest, France). Industrial nasal masks were used: Infant Flow (Fisher & Paykel, Auckland, New Zealand) in the neonatal intensive care unit, and Soft Baby (Air Liquide Medical Systems, Antony, France) or Nonny (AG Industries, St. Louis, Mo.) in the neonatology ward. The protocol was approved by the local ethical committee (Comité de Protection des Personnes Ile de France II, no. 2014-03-09 SC).

RESULTS

Forty-four patients were evaluated, 37 as inpatients (26 with isolated and 11 with associated/syndromic Pierre Robin sequence) and seven as outpatients (two patients with 22q11 and five

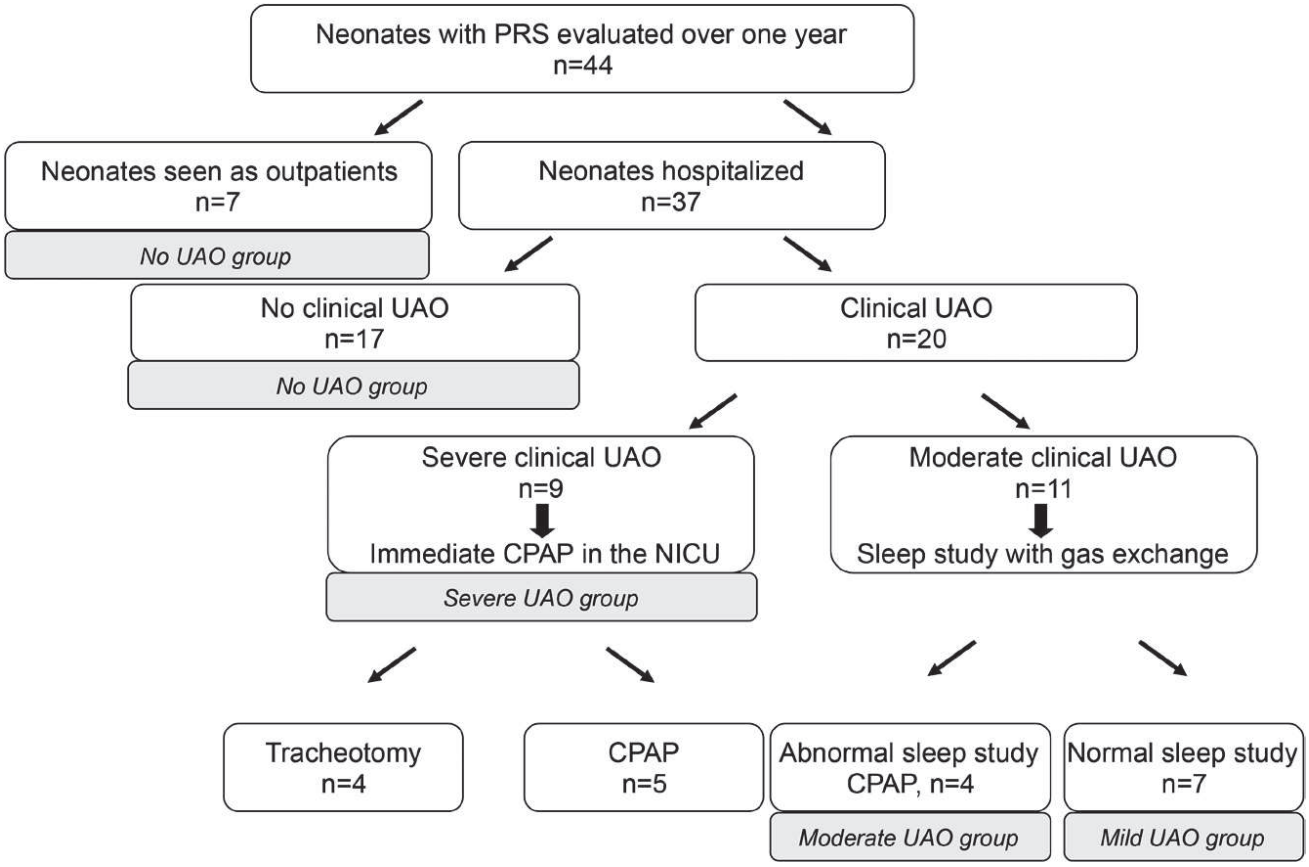

Fig. 1. Flowchart of the patients. *PRS*, Pierre Robin sequence; *UAO*, upper airway obstruction; *NICU*, neonatal intensive care unit; *CPAP*, continuous positive airway pressure.

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isolated Pierre Robin sequence) (Fig. 1). Five (four isolated and one associated/syndromic Pierre Robin sequence) of the nine patients of the severe upper airway obstruction group were successfully managed by noninvasive continuous positive airway pressure and four (three isolated and one Stickler syndrome) required a tracheotomy (Table 1).

Eleven neonates underwent polygraphy, which was normal in seven (mild upper airway obstruction group: five with isolated and two with associated/syndromic Pierre Robin sequence) and abnormal in four (moderate upper airway obstruction group: two with isolated and two with associated/syndromic Pierre Robin sequence) with an apnea-hypopnea index between 19 and 42 per hour, an oxygen desaturation index between 18 and 137 per hour, a minimal pulse oximetry value between 78 and 90 percent, and a maximal transcutaneous carbon dioxide value between 41 and 55 mmHg. These four patients were managed successfully by noninvasive continuous positive airway pressure (Table 1).

All nine noninvasive continuous positive airway pressure patients were successfully discharged to home after a median hospital stay of 1 month (range, 20 to 40 days). Objective compliance with noninvasive continuous positive airway pressure 1 month after discharge was greater than 8 hours per 24 hours. The four patients who were tracheotomized were discharged to home after a median hospital stay of 2 months (range, 6 weeks to 4 months).

The mild upper airway obstruction group comprised seven neonates having normal polygraphic findings in the prone position. The 17 hospitalized patients with no symptoms of upper airway obstruction and only feeding problems and the seven nonhospitalized patients comprised the no–upper airway obstruction group. These two groups experienced an uneventful course.

In conclusion, during a 1-year period, 44 neonates with Pierre Robin sequence were evaluated in our reference center before the age of 1 month; seven patients (16 percent) were seen as outpatients and 37 (84 percent) were seen as inpatients. Four patients (9 percent) required a tracheotomy and nine (20 percent) were successfully managed by noninvasive continuous positive airway pressure, with the remaining 31 patients (70 percent) having no significant upper airway obstruction and being managed by prone positioning.

DISCUSSION

This study shows that noninvasive continuous positive airway pressure is an effective treatment for moderate and severe upper airway obstruction,

Table 1. Patient Characteristics, Continuous Positive Airway Pressure Initiation Criteria, and Evolution of the Patients

Patient	Sex	Pierre Robin Sequence Form	Age at CPAP Initiation	Weight at CPAP Initiation (kg)	CPAP Indication	CPAP Pressure (cmH_2O)	CPAP Duration (mo)	Criteria of CPAP Withdrawal
1	F	Isolated	At birth	3.7	Weaning failure	7	1	Normal PG (AHI 4/hr) and gas exchange
2	M	Isolated	At birth	3.5	Weaning failure	6	2	Normal gas exchange
3	M	Associated	At birth	3.3	Weaning failure	6	2.5	Normal PG (AHI 3/hr) and gas exchange
4	F	Isolated	At birth	3.2	Weaning failure	7	5.5	Normal gas exchange
5	M	Isolated	At birth	4.0	Weaning failure	7	4	Still on CPAP
6	F	Isolated	7 days	2.6	AHI, 19/hr; ODI, 18/hr Spo_2 min, 90%; % time with Spo_2 <90%, 0%; $Ptcco_2$ max, 43 mmHg	7	1	Normal gas exchange
7	F	Isolated	10 days	3.5	AHI, 32/hr; ODI, 19/hr; Spo_2 min, 78%; % time with Spo_2 <90%, 0%; $Ptcco_2$ max, 52 mmHg	8	1.2	Normal gas exchange
8	F	Associated	15 days	3.0	AHI, 42/hr; ODI, 32/hr; Spo_2 min, 82%; % time with Spo_2 <90%, 16%; $Ptcco_2$ max, 55 mmHg	7	4	Still on CPAP
9	F	Associated	2 mo	4.2	AHI, 37/hr; ODI, 137/hr; Spo_2 min, 82%; % time with Spo_2 <90%, 4%; $Ptcco_2$ max, 41 mmHg	7	4	Still on CPAP

CPAP, continuous positive airway pressure; F, female; M, male; PG, polygraphy; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; Spo_2, pulse oximetry; $Ptcco_2$, transcutaneous carbon dioxide.

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assessed objectively by polygraphy, in neonates with Pierre Robin sequence.[5] As such, noninvasive continuous positive airway pressure may be recommended in selected neonates before more invasive procedures. Duration of noninvasive continuous positive airway pressure ranged from 4 weeks to more than 4 months, showing that noninvasive continuous positive airway pressure is necessary only during a critical window of a maximum of 6 months in most patients. This relatively short period restricts the potential side effects of long-term noninvasive continuous positive airway pressure such as facial flattening and maxillary retrusion.[10] However, the major advantage of noninvasive continuous positive airway pressure is that this treatment is noninvasive and can be applied on demand. Indeed, tracheotomy is associated with significant morbidity and mortality, with a mean duration in our center of 1 year.[11] Surgical procedures are associated with wound dehiscence, lip scar contracture for tongue-lip adhesion,[12] pin tract infection, or damage to the mandibular branch of the trigeminal or facial nerve for mandibular distraction.[13] These surgical treatments relieve only one obstacle, whereas some patients may have an upper airway obstruction at different levels.[12] Uncertainties exist also about long-term outcome. Moreover, these procedures do not respect the spontaneous improvement of the functional and anatomical anomalies of children with Pierre Robin sequence.[14] For that reason, we reserve neonatal mandibular distraction for only a selected group of patients with Pierre Robin sequence.

We have previously reported the physiologic and clinical benefit of noninvasive continuous positive airway pressure in seven infants with Pierre Robin sequence and severe upper airway obstruction.[5] The extension of noninvasive continuous positive airway pressure as routine care was possible because of the availability of well-adapted, well-tolerated industrial nasal masks for this age group, enabling this technique to be used on a larger scale.

CONCLUSIONS

Noninvasive continuous positive airway pressure represents an effective, safe, noninvasive treatment of moderate and severe upper airway obstruction in selected neonates with Pierre Robin sequence. Continuous positive airway pressure reduces the need for a tracheotomy and may represent an interesting alternative to other surgical procedures. Systematic sleep studies should be part of the respiratory management in Pierre Robin sequence.

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REFERENCES

1. Robin P. La chute de la base de la langue considérée comme une nouvelle cause de gène dans la respiration naso-pharyngienne. *Bull Acad Natl Med (Paris)* 1923;89:37–41.
2. Runyan CM, Tork S, Chen W, et al. Outcomes analysis of neonates treated for Pierre Robin sequence: An 18-year experience. *Plast Reconstr Surg.* 2014;134:7–8.
3. Meyer AC, Lidsky ME, Sampson DE, Lander TA, Liu M, Sidman JD. Airway interventions in children with Pierre Robin Sequence. *Otolaryngol Head Neck Surg.* 2008;138:782–787.
4. Tomaski SM, Zalzal GH, Saal HM. Airway obstruction in the Pierre Robin sequence. *Laryngoscope* 1995;105:111–114.
5. Leboulanger N, Picard A, Soupre V, et al. Physiologic and clinical benefits of noninvasive ventilation in infants with Pierre Robin sequence. *Pediatrics* 2010;126:e1056–e1063.
6. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: Update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med.* 2012;8:597–619.
7. Fauroux B, Pigeot J, Polkey MI, et al. Chronic stridor caused by laryngomalacia in children: Work of breathing and effects of noninvasive ventilatory assistance. *Am J Respir Crit Care Med.* 2001;164:1874–1878.
8. Essouri S, Nicot F, Clément A, et al. Noninvasive positive pressure ventilation in infants with upper airway obstruction: Comparison of continuous and bilevel positive pressure. *Intensive Care Med.* 2005;31:574–580.
9. Khirani S, Ramirez A, Aloui S, Leboulanger N, Picard A, Fauroux B. Continuous positive airway pressure titration in infants with severe upper airway obstruction or bronchopulmonary dysplasia. *Crit Care* 2013;17:R167.
10. Fauroux B, Lavis JF, Nicot F, et al. Facial side effects during noninvasive positive pressure ventilation in children. *Intensive Care Med.* 2005;31:965–969.
11. Carr MM, Poje CP, Kingston L, Kielma D, Heard C. Complications in pediatric tracheostomies. *Laryngoscope* 2001;111:1925–1928.
12. Murage KP, Tholpady SS, Friel M, Havlik RJ, Flores RL. Outcomes analysis of mandibular distraction osteogenesis for the treatment of Pierre Robin sequence. *Plast Reconstr Surg.* 2013;132:419–421.
13. Rachmiel A, Emodi O, Rachmiel D, Aizenbud D. Internal mandibular distraction to relieve airway obstruction in children with severe micrognathia. *Int J Oral Maxillofac Surg.* 2014;43:1176–1181.
14. Gosain AK. Discussion: The surgical correction of Pierre Robin sequence: Mandibular distraction osteogenesis versus tongue-lip adhesion. *Plast Reconstr Surg.* 2014;133:1440–1442.

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The present study showed that CPAP is an effective, safe, noninvasive treatment of moderate and severe upper airway obstruction in selected neonates with Pierre Robin sequence. A systematic evaluation with sleep studies helps to diagnose and objective quantify the severity of upper airway obstruction in infants with Pierre Robin sequence in order to choose the best and least invasive treatment approach.

b. Long term continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) in children: Initiation criteria in real life.

Long term CPAP and NIV are increasingly used in children worldwide[263,264,266,267,322,323]. However, there are no validated objective criteria to start long term respiratory support for children. This may be explained by the extreme heterogeneity of SDB regarding age and disease in children requiring CPAP or NIV. In children with neuromuscular disease a combination of clinical signs and abnormal gas exchange is recommended for the initiation of NIV[268]. For CPAP, the ERS taskforce recommends that CPAP should be started in children with a residual AHI of more than 5 events/h after adenotonsillectomy, or residual OSAS after adenotonsillectomy, or in presence of OSAS related to obesity, craniofacial abnormalities or neuromuscular disorders with no specification of residual AHI in this last group[1]. Even if these recommendations have the merit of introducing some objective and strict criteria, they do not take in account the clinical variability of heterogeneous diseases. The aim of our study was to describe our clinical practice by analysing the different objective criteria that lead to the initiation of CPAP or NIV in our center over a 1-year period.

Long Term Continuous Positive Airway Pressure (CPAP) and Noninvasive Ventilation (NIV) in Children: Initiation Criteria in Real Life

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Summary. Introduction: Long term noninvasive continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) are increasingly used in children but limited information is available on the criteria and conditions leading to the initiation of these treatments. The aim of the study is to describe the objective overnight respiratory parameters and clinical situations that led to the initiation of CPAP/NIV in a pediatric NIV unit. Material and Methods: Retrospective analysis of the data of all the children discharged on home CPAP/NIV over a 1 year period. Results: Seventy-six patients were started on CPAP (n = 64) or NIV (n = 12). CPAP/NIV was initiated because of CPAP/NIV weaning failure (*Acute group*) in 15 patients. None of these patients had an overnight gas exchange or sleep study before CPAP/NIV initiation. In 18 patients, CPAP/NIV was initiated on abnormal nocturnal gas exchange alone (*Subacute group*). These patients had a median of three of the following five overnight gas exchange abnormalities: minimal pulse oximetry (SpO_2) <90%, maximal transcutaneous carbon dioxide ($PtcCO_2$) >50 mmHg, time spent with SpO_2 <90% or $PtcCO_2$ >50 mmHg ≥2% of recording time, oxygen desaturation index >1.4/hr. In the last 43 patients, CPAP/NIV was initiated after an abnormal sleep study (*Chronic group*) on a mean of four of the aforementioned criteria and an apnea-hypopnea index >10/hr. Conclusion: In clinical practice, CPAP/NIV was initiated in an acute, subacute and chronic setting with most patients having an association of several abnormal gas exchange or sleep study parameters. Future studies should evaluate the effectiveness and benefits of CPAP/NIV according to the clinical situation and initiation criteria. **Pediatr Pulmonol.** © 2016 Wiley Periodicals, Inc.

Key words: noninvasive ventilation; continuous positive airway pressure; children; polygraphy; sleep apnea; gas exchange.

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BACKGROUND

Long term noninvasive ventilation (NIV) and continuous positive airway pressure (CPAP) are increasingly used in children.[1–8] NIV represents nowadays the first line treatment of chronic hypercapnic respiratory failure due to neuromuscular,[9,10] lung,[11] or chest wall disorders in children.[12] CPAP is an effective treatment for severe upper airway obstruction and in particular for persistent obstructive sleep apnea syndrome (OSAS) after adenotonsillectomy (AT)[13] or occurring in children with underlying disorders or conditions such as obesity,

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storage disorders or complex craniofacial malformations.[14–18] Although the spectrum of indications for NIV and CPAP in children is widening, few information is available on the criteria and conditions in which these treatments are initiated. In patients with Duchenne muscular dystrophy, NIV is recommended when a combination of signs and symptoms of hypoventilation and gas exchange abnormalities are met.[19] In the absence of stronger evidence from randomized trials, these parameters have been extended and adapted for the respiratory care of paediatric neuromuscular patients.[20] Moreover, these criteria are often extrapolated and applied to patients with chest wall or lung disease, without any evidence to support this assumption. Validated criteria to start CPAP are also lacking, since the degree of severity of OSAS at which a respiratory support treatment should be started has not been established. Clinicians must therefore deal with uncertainty when deciding when to start NIV or CPAP. In clinical practice, given the lack of definite cut-off values, a combination of clinical situations, gas exchange, and polysomnographic data are often used. In a recent study analyzing 68 children who were started on CPAP because of severe OSAS, CPAP was started "electively" in 62% of the patients and in an "acute" setting in 38%.[18] But the authors did not give any information on the objective parameters that led to the decision of CPAP. Finally, the heterogeneity of the pediatric population which may require CPAP/NIV, with regard to age and underlying disease, represents a supplemental challenge. Information on the objective criteria and clinical conditions, in terms of underlying diseases and sleep study results that justify the initiation of CPAP/NIV is important because this may potentially influence outcome, effectiveness, and adherence to treatment.

The aim of this retrospective study was to describe the sleep exams performed to assess the need for CPAP/NIV, the objective abnormalities found on these exams and to analyze the settings that led to the initiation of long term CPAP/NIV in a pediatric NIV unit at a tertiary care hospital over a 1-year period.

MATERIALS AND METHODS

We retrospectively reviewed the clinical charts of all the patients started on long term CPAP or NIV, defined as the need for CPAP or NIV for more than 2 months after hospital discharge, from October 2013 to September 2014 in the NIV and sleep unit at Necker Children's Hospital. This hospital is a tertiary pediatric university hospital, with a capacity of almost 500 beds comprising all the pediatric medical and surgical subspecialties. The NIV and sleep unit consists in a three beds unit exclusively dedicated to sleep studies with a mobile unit capable of performing sleep studies and NIV initiation in every unit of the hospital. Almost 450 polysomnography (PSG)/polygraphy (PG) and 900 gas exchange studies are performed per year.

For each patient, the spontaneous breathing overnight gas exchange and/or PG or PSG abnormalities, as well as the clinical situation at CPAP/NIV initiation was analyzed. The data were extracted from the electronic database of the NIV unit and there was no missing data.

PSG or PG were performed using CID 102* (Cidelec, Angers, France). For the patients younger than 6 months, a daytime (nap) sleep PG was performed as an alternative to overnight study if the patient slept for more than 1 hr during the study period. Due to equipment and staff limitation, in our center PSG is usually reserved to patients with non-respiratory sleep problems (such as insomnia or parasomnias) whilst the majority of patients with sleep disordered breathing (SDB) undergo a simple PG. The recorded data included airflow, body position, body movements, thoracic and abdominal movements assessed with inductance belts for the CID 102*, pulse oxymetry (SpO_2). For PSG, the electroencephalographic (EEG) recordings were based on the international 10–20 system, which includes the placement of electrodes in positions F1-A2, F2-A1, C3-A2, −C4-A1, −O1-A2, O2-A1, the recording of eye movements, the electromyography of the chin and the electrocardiogram. Sleep stages were obtained manually using standard criteria.[22,23] Respiratory events were scored according to the American Academy of Sleep Medicine (AASM) manual and following update[21,22] OSAS was considered as moderate when the apnea-hypopnea index (AHI) was between 5 and 10 events/hr and severe when the AHI was >10 events/hr. Oxygen desaturation was defined as a fall in peripheral oxygen saturation (SpO_2) of at least 3% and the oxygen desaturation index (ODI) was defined as the number of oxygen desaturation per hour of PSG/PG recording. Nocturnal hypoxia was defined as the presence of a SpO_2 $\leq$90% for at least 2% of night time[23] and the ODI was considered as abnormal when >1.4/hr.[24]

Overnight gas exchange study consists on combined SpO_2 and transcutaneous carbon dioxide ($PtcCO_2$) recordings, performed with the SenTec Digital Monitor (SenTec Inc, Therwil, Switzerland). Mean, maximal $PtcCO_2$, and the percentage of night-time spent with a $PtcCO_2$ greater than 50 mmHg were recorded.[25] Nocturnal hypercapnia was defined as a $PtcCO_2$ $\geq$50 mmHg for at least 2% of night time.[25]

The protocol was approved by the local ethical committee (CPP Ile de France II, n° 2014-03-09 SC).

Statistical Analysis

All the data are presented as median and range. The difference in median was evaluated with Mann–Whitney Rank Sum Test. A *P*-value less than 0.05 was considered statistically significant.

RESULTS

During the study period, 374 PSGs or PGs and 684 overnight gas exchange studies were performed. Subsequently, 76 patients were started on long term CPAP (n = 64) or NIV (n = 12). CPAP was initiated because of isolated OSAS, while NIV was initiated in patients presenting with alveolar hypoventilation alone or associated with OSAS. The majority of the patients were referred from the genetic, neurology, metabolic disease, and otolaryngology and maxillo-facial surgery departments of the hospital. The patients were subdivided into three groups according to clinical scenarios under which long term respiratory support were initiated:

- Fifteen (20%) patients were started on CPAP/NIV without any spontaneous breathing overnight gas exchange or PG/PSG recording. Indeed, the respiratory status of this group was too unstable and did not allow an overnight spontaneous breathing recording. All these patients were hospitalized in the intensive care unit (ICU) because of the inability to be weaned from noninvasive ventilatory support after an acute respiratory failure requiring an acute initiation of CPAP/NIV or an endotrachaeal intubation. All of these patients had arterial blood gases analysis as a part of their clinical follow up but no data were collected about these exams. This group was designated the *Acute group*. The median age of this group was 0.3 (0.1–13.5) years with a predominance of infants with Pierre Robin syndrome (6 patients out of 15, Table 1) due to the recruitment of our hospital.
- Eighteen (24%) patients were started on CPAP/NIV after a variable association of overnight gas exchange abnormalities alone. None of these patients had a PG/PSG. These patients were hospitalized for 1) an acute moderate respiratory exacerbation that did not require an ICU admission or 2) a scheduled hospitalization for their underlying disease during which the presence of SDB symptoms justified an overnight gas exchange recording. These patients had a mean of three of the five aforementioned overnight gas exchange abnormalities (Tables 1, 2, and 3, variables 1–5, and Figs. 1 and 2). This group was designated the *Subacute group*. The median age of these patients was 0.6 (0.2–18.2) years.
- In the last 43 (56%) patients, CPAP/NIV was initiated after an overnight PSG (n = 4) or PG (n = 28), or a nap study (n = 11). These patients were referred to the NIV

TABLE 1—Clinical and Demographics Characteristics of the Patients According to the Three Study Groups (total n = 76)

	Acute group $n = 15$		Subacute group $n = 18$		Chronic group $n = 43$	
Median age, years (interquartile range)	0.3 (0.1–13.5)		0.6 (0.2–18.2)		1.6 (0.1–19.5)	
Female to male ratio (F/M)	7/8		8/10		22/21	
Diagnosis	Pierre Robin syndrome	6	Laryngomalacia	4	Pierre Robin syndrome	5
	Laryngomalacia	3	Prader Willi syndrome	1	Down syndrome	5
	Polymalformative syndrome	2	Pierre Robin syndrome	1	Mucopolysaccharidosis type 1	3
	Kabuki syndrome	1	Bronchopulmonary dysplasia	1	Charge syndrome	3
	Cystic fibrosis	1	Crouzon syndrome	1	Laryngomalacia	3
	Bronchopulmonary dysplasia	1	Treacher Collins syndrome	1	Polymalformative syndrome	3
	Neuromuscular disorder	1	Vocal cord palsy	1	Treacher Collins syndrome	2
			Down syndrome	1	Achondroplasia	2
			Mucopolysaccharidosis type 2	1	Prader Willi syndrome	2
			Duchenne muscular dystrophy	1	Bronchopulmonary dysplasia	2
			Immunodeficiency with lymphoid tissue hyperplasia	1	Congenital myasthenia	1
			Craniofacial malformation	1	Nemaline myopathy	1
			Generalised dystonia	1	Mucopolysaccharidosis type 2	1
			Achondroplasia	1	Myhre syndrome	1
			Tracheomalacia	1	Spinal muscular atrophy	1
					Rett syndrome	1
					Goldenhar syndrome	1
					Hanhart syndrome	1
					Beckwith Wiedemann syndrome	1
					Loeys Dietz syndrome	1
					Ossificant fibrodysplasia	1
					Idiopathic OSAS	1

OSAS, obstructive sleep apnea syndrome.

TABLE 2—Respiratory Variables Used for Continuous Positive Pressure or Noninvasive Ventilation Initiation

1.	Minimum SpO_2 <90%
2.	Maximal $PtcCO_2$ >50 mmHg
3.	Time spent with a SpO_2 <90% ≥2% of recording time
4.	Time spent with a $PtcCO_2$ >50 mmHg ≥2% of recording time
5.	Oxygen desaturation index >1.4 events/hr
6.	AHI >10 events/hr

SpO_2, pulse oximetry; $PtcCO_2$, transcutaneous carbon dioxide; AHI, apnea-hypopnea index.

and sleep unit by the other medical and surgical departments of the hospital. CPAP/NIV was initiated after a scheduled PSG/PG that showed a mean of four out of six criteria (made up by the five overnight gas exchange abnormalities aforementioned and the addition of an AHI >10/hr) (Tables 2 and 3 and Figs. 1 and 2). These patients did not have overt symptoms of SDB, based on parents' reports. This group was designated as the *Chronic group*. A combination of several abnormal gas exchange or PSG/PG data was observed in most of the patients. In this group, the four patients with a normal AHI and SpO_2 had an ODI of 5, 12, 16, and 38/hr, respectively.

Clinical and demographic characteristics of the three groups are shown in Table 1. The median age of the patients in the *Acute group* was significantly lower as the other two groups ($P = 0.009$). The *Acute group* was characterized by the unavailability of any abnormal overnight gas exchange or PG/PSG criteria whereas the median number of criteria in the *Subacute* and *Chronic group* were three and four, respectively.

Figure 2 shows the number of patients with abnormal criteria for the *Subacute* and *Chronic group*. In the *Subacute group* the most common alterations were a minimal SpO_2 ≤90% and an abnormal ODI. The majority of patients in the *Chronic group* were hypoxemic (minimal SpO_2 ≤90% and abnormal ODI) and had a high AHI. On the other hand hypercapnia, defined as a $PtcCO_2$ ≥50 mmHg for at least 2% of night time and as a maximal $PtcCO_2$ ≥50 mmHg, was seen in almost half of our cohort.

Table 3 shows the overnight gas exchange and sleep study results in the *Subacute* and *Chronic group*. No

TABLE 3—Nocturnal Gas Exchange and Sleep Study Results in the *Subacute Group* and the *Chronic Group*

	Subacute group $n = 18$	Chronic group $n = 43$	P
Nocturnal gas exchange			
Minimal SpO_2 (%)	79 (68–90)	80 (57–92)	0.65
Time spent with SpO_2 <90% (%)	2 (0–13)	1 (0–89)	0.99
Oxygen desaturation index (number/hr)	16 (0–48)	21 (2–88)	0.22
Maximal $PtcCO_2$ (mmHg)	53 (41–83)	51 (38–70)	0.20
Time spent with $PtcCO_2$ >50 mmHg (%)	7 (0–100)	0 (0–93)	0.08
AHI (events/hr)	NA	23 (0–159)	

Data are given as median and range.
AHI, apnea hypopnea index; NA, not available; $PtcCO_2$, transcutaneous carbon dioxide; SpO_2, pulse oximetry.

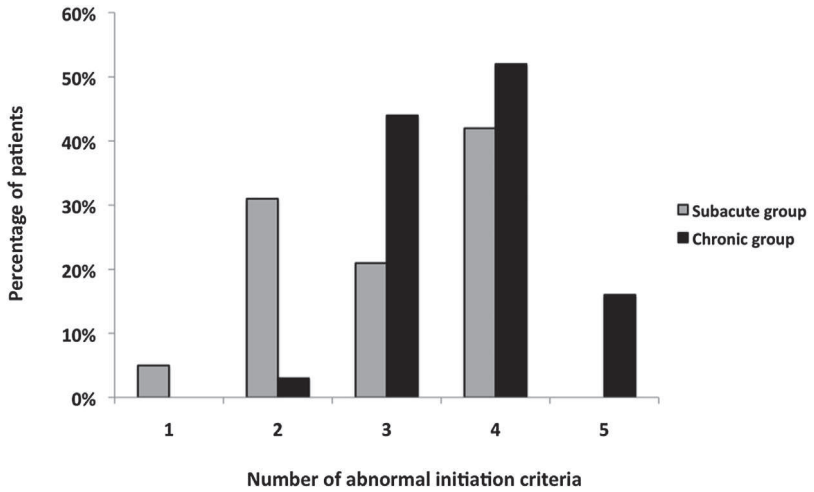

Fig. 1. Percentage of patients having one or more abnormal criteria that led to the initiation of CPAP or NIV in the *Subacute* (n = 18) and *Chronic group* (n = 43).

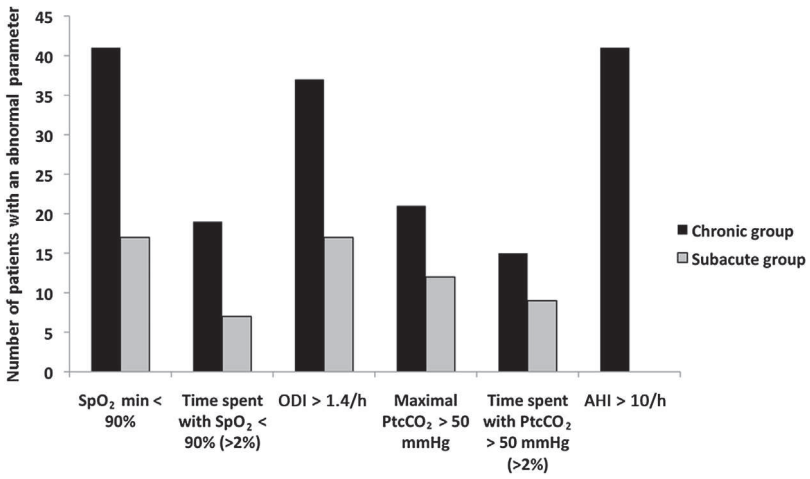

Fig. 2. Number of patients having an abnormal nocturnal parameter in the *Subacute* (n = 18) and *Chronic group* (n = 43). SpO_2, pulse oximetry; ODI, oxygen desaturation index; $PtcCO_2$, transcutaneous carbon dioxide; AHI, apnea-hypopnea index.

significant differences were observed between these two groups regarding overnight gas exchange. Median SpO_2 and $PtcCO_2$ were also comparable for the two groups with a median SpO_2 of 95% (89–97%) and 94% (86–100%) for the *Subacute* and *Chronic group*, respectively ($P = 0.97$), and a median $PtcCO_2$ of 46 mmHg (41–83 mmHg) and 51 (38–70 mmHg) for the *Subacute* and *Chronic group*, respectively ($P = 0.37$).

DISCUSSION

This study is the first to analyze the objective overnight respiratory parameters and the clinical situations that led to the initiation of CPAP or NIV in a large pediatric population. Our results show that CPAP or NIV was initiated in three different situations namely an acute, subacute, or chronic setting, with the majority of the patients in the two latter groups having an association of several abnormal objective respiratory parameters such as SpO_2, $PtcCO_2$, and/or AHI.

Long term CPAP/NIV was started in an acute setting after a respiratory exacerbation or as transition from invasive ventilation in 20% of our patients but also in 38% of the patients presenting severe complex OSAS in a Portuguese pediatric center.[18] In this *Acute group*, the clinical respiratory status of the patients was too unstable to allow any spontaneously breathing overnight gas exchange or PG/PSG recording. Due to the specific recruitment of our hospital, which concentrates numerous national reference centers, including the national reference center for Pierre Robin Sequence, the patients in this group were younger than those of the two other groups.[15]

The *Subacute group* comprised patients referred by a subspecialist during a hospital admission, either for a moderate acute respiratory exacerbation or a scheduled hospitalization for the follow up for their underlying disease. Since the number of PGs and PSGs that may be performed is strongly limited by the availability of sleep equipments, we usually apply a shortcut in order to overcome the inevitable delay for a sleep study in clinical practice. Such practice is also reported by other centers with only 49% of the patients being started on CPAP/NIV being evaluated by a PG.[18] Patients in whom the clinical presentation was considered severe enough based on clinical examination and age, usually underwent only an overnight gas exchange study. On the contrary, patients with a suspected SDB but in a stable condition underwent a PG or a PSG along with an overnight gas exchange study, in order to quantify the degree of severity of their SDB. The decision of performing either a gas exchange or a PSG/PG was taken by the medical staff of the NIV unit. Based on these premises, we expected to find a higher degree of severity in the *Subacute group* as compared to the *Chronic group*. But we did not observe any important difference between the two groups regarding the severity of gas exchange abnormalities or general characteristics such as age. Some patients with the same underlying disease (such as Prader Willi syndrome or achondroplasia) could belong to different groups. This may be explained by the presence of more overt SDB symptoms in patients in the *Subacute* as compared to the *Chronic group*. However, the poor correlation between symptoms and objective assessments of SDB is well known in children. In summary, as patients in the present *Subacute* and *Chronic group* had similar gas exchange abnormalities, it may seem justified to join these two groups for future studies.

It is known that nocturnal SpO_2, if evaluated by a skilled physician, could effectively identify children with OSAS[26] or with SDB due to neuromuscular disease.[27]

Moreover, the addition of overnight capnography enables the diagnosis of nocturnal hypoventilation.[28] One can therefore speculate that, since a gas exchange study may effectively identify which patient has severe SDB, a complete sleep study may be superfluous for some children requiring CPAP/NIV. On the contrary, PSG remains the gold standard for children with suspected SDB, as it allows to assess the severity of SDB and to identify subtle alterations that can not detected by a simple gas exchange monitoring or a PG, in particular for patients with mild to moderate abnormalities ($1<AHI<10$ events/hr).[29] However, the patients in our study had profound abnormalities on their PSG or PG with a median AHI of 23 (0–159) events/hr, which may suppose that the performance of a PSG instead of a PG would not have changed the decision of CPAP or NIV.

Another important finding of our study is that the initiation of CPAP or NIV was usually based on a combination of several severely abnormal physiological parameters, with very few patients having only one or two abnormalities. Obviously, some abnormalities are clearly related to each others, like minimal SpO_2 and the time spent with SpO_2 <90% or ODI and AHI, but this observation highlights the importance of identifying a "core" of objectives measurements that could coherently identify which child will benefit most from long term ventilatory support.

The most frequent gas exchange abnormality was hypoxia, in particular pathological minimal SpO_2% and ODI. This data could possibly reflect the high prevalence of patients with OSAS due to upper airway malformations in our cohort.

This study has several limitations. Our data come from a single specialized center in pediatric NIV and may not be applicable to other centers. Secondly, our recruitment may also differ from other centers with a majority of patients having complex genetic disorders. However, the pathologies presented by our patients are comparable to that of other pediatric centers in Europe.[18,30] Thirdly, we arbitrarily selected a core of major criteria routinely used to initiate CPAP/NIV at our center. We voluntary omit some criteria that may be taken into account when deciding to start CPAP/NIV such as clinical symptoms of SDB, sleep quality and quality of life,[31] lung function tests, and the rate of unscheduled hospital admissions[20] as for neuromuscular patients. Since these criteria are difficult to be standardized in order to create a univocal set of objective measures, we decided not to add them in the analysis of CPAP/NIV initiation criteria. However, these criteria may be taken into account on an individual basis when deciding for a PSG/PG. Besides these considerations it has to be said that every patient in our cohort had at least one pathological criterion.

In conclusion, our main results are that the initiation of CPAP/NIV in children occurred in three different settings; that is, an acute, subacute and chronic setting with the majority of the patients of the *Subacute* and *Chronic groups* presenting an association of severely abnormal gas exchange or PG parameters. Future studies evaluating the effectiveness and benefits of CPAP/NIV should take in account the clinical situation and initiation criteria.

AUTHORS' CONTRIBUTIONS

Drs. Amaddeo and Fauroux contributed to the conception, design, acquisition, analysis and interpretation of data, and the writing of the manuscript. Dr. Moreau and Felix, and Mrs Khirani contributed to the conception and design of the study and the interpretation of the data. Mrs. Frapin contributed to the CPAP/NIV treatment and contributed to the conception and design of the study and the interpretation of the data. Mrs. Fernandez-Bolanos contributed to the management of the patients, the interpretation of sleep studies, and the interpretation of the data. All the authors contributed to the redaction of the manuscript and approved the final version.

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REFERENCES

1. Racca F, Berta G, Sequi M, Bignamini E, Capello E, Cutrera R, Ottonello G, Ranieri VM, Salvo I, Testa R, et al., for the LTV Pediatric Italian Network. Long-term home ventilation of children in Italy: a national survey. Pediatr Pulmonol 2011;46: 566–572.
2. Rose L, McKim DA, Katz SL, Leasa D, Nonoyama M, Pedersen C, Goldstein RS, Road JD, on behalf of the CANuVENT Group. Home mechanical ventilation in Canada: a national survey. Respir Care 2015;60:695–704.
3. McDougall CM, Adderley RJ, Wensley DF, Seear MD. Long-term ventilation in children: longitudinal trends and outcomes. Arch Dis Child 2013;98:660–665.
4. Edwards EA, Hsiao K, Nixon GM. Paediatric home ventilatory support: the Auckland experience. J Paediatr Child Health 2005;41:652–658.
5. Amin R, Sayal P, Syed F, Chaves A, Moraes TJ, MacLusky I. Pediatric long-term home mechanical ventilation: twenty years of follow-up from one Canadian center. Pediatr Pulmonol 2014;49: 816–824.
6. Ottonello G, Ferrari I, Pirroddi IMG, Diana MC, Villa G, Nahum L, Tuo P, Moscatelli A, Silvestri G. Home mechanical ventilation in children: retrospective survey of a pediatric population. Pediatr Int 2007;49:801–805.
7. Goodwin S, Smith H, Langton Hewer S, Fleming P, Henderson AJ, Hilliard T, Fraser J. Increasing prevalence of domiciliary

ventilation: changes in service demand and provision in the South West of the UK. Eur J Pediatr 2011;170:1187–1192.
8. Fauroux B, Boffa C, Desguerre I, Estournet B, Trang H. Long-term noninvasive mechanical ventilation for children at home: a national survey. Pediatr Pulmonol 2003;35:119–125.
9. Simonds AK, Ward S, Heather S, Bush A, Muntoni F. Outcome of paediatric domiciliary mask ventilation in neuromuscular and skeletal disease. Eur Respir J 2000;16:476–481.
10. Ward S, Chatwin M, Heather S, Simonds AK. Randomised controlled trial of non-invasive ventilation (NIV) for nocturnal hypoventilation in neuromuscular and chest wall disease patients with daytime normocapnia. Thorax 2005;60:1019–1024.
11. Moran F, Bradley JM, Piper AJ. Non-invasive ventilation for cystic fibrosis. Cochrane Database Syst Rev 2013;4:CD002769.
12. Khirani S, Bersanini C, Aubertin G, Bachy M, Vialle R, Fauroux B. Non-invasive positive pressure ventilation to facilitate the post-operative respiratory outcome of spine surgery in neuromuscular children. Eur Spine J 2014;23:S406–S411.
13. Marcus CL, Brooks LJ, Draper KA, Gozal D, Halbower AC, Jones J, Schechter MS, Ward SD, Sheldon SH, Shiffman RN, et al., for the American Academy of Pediatrics. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2012;130:e714–e755.
14. Della Marca G, Scarano E, Leoni C, Dittoni S, Losurdo A, Testani E, Colicchio S, Gnoni V, Vollono C, Zampino G. Pycnodysostosis with extreme sleep apnea: a possible alternative to tracheotomy. Sleep Breath Schlaf Atm 2012;16:5–10.
15. Leboulanger N, Picard A, Soupre V, Aubertin G, Denoyelle F, Galliani E, Roger G, Garabedian E-N, Fauroux B. Physiologic and clinical benefits of noninvasive ventilation in infants with Pierre Robin sequence. Pediatrics 2010;126:e1056–e1063.
16. Miller SDW, Glynn SF, Kiely JL, McNicholas WT. The role of nasal CPAP in obstructive sleep apnoea syndrome due to mandibular hypoplasia. Respirol Carlton Vic 2010;15:377–379.
17. Essouri S, Nicot F, Clément A, Garabedian E-N, Roger G, Lofaso F, Fauroux B. Noninvasive positive pressure ventilation in infants with upper airway obstruction: comparison of continuous and bilevel positive pressure. Intensive Care Med 2005;31:574–580.
18. Girbal IC, Gonçalves C, Nunes T, Ferreira R, Pereira L, Saianda A, Bandeira T. Non-invasive ventilation in complex obstructive sleep apnea—a 15-year experience of a pediatric tertiary center. Rev Port Pneumol 2014;20:146–151.
19. Birnkrant DJ, Bushby KMD, Amin RS, Bach JR, Benditt JO, Eagle M, Finder JD, Kalra MS, Kissel JT, Koumbourlis AC, et al. The respiratory management of patients with Duchenne muscular dystrophy: a DMD care considerations working group specialty article. Pediatr Pulmonol 2010;45:739–748.
20. Hull J, Aniapravan R, Chan E, Chatwin M, Forton J, Gallagher J, Gibson N, Gordon J, Hughes I, McCulloch R, et al. British Thoracic Society guideline for respiratory management of children with neuromuscular weakness. Thorax 2012;67:i1–i40.
21. Iber C, Ancoli_Israel S, Chesson AL, Quan SF, for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specification. 1st ed Westchester, IL: American Academy of Sleep Medicine; 2007.
22. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF, et al., for the American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. J Clin Sleep Med 2012;8:597–619.
23. Hukins CA, Hillman DR. Daytime predictors of sleep hypoventilation in Duchenne muscular dystrophy. Am J Respir Crit Care Med 2000;161:166–170.
24. Marcus CL, Omlin KJ, Basinki DJ, Bailey SL. Normal polysomnographic values for children. Am Rev Respir Dis 1992;146:1235–1239.
25. Paiva R, Krivec U, Aubertin G, Cohen E, Clément A, Fauroux B. Carbon dioxide monitoring during long-term noninvasive respiratory support in children. Intensive Care Med 2009;35: 1068–1074.
26. Brouillette RT, Morielli A, Leimanis A, Waters KA, Luciano R, Ducharme FM. Nocturnal pulse oximetry as an abbreviated testing modality for pediatric obstructive sleep apnea. Pediatrics 2000;105:405–412.
27. Phillips MF, Smith PE, Carroll N, Edwards RH, Calverley PM. Nocturnal oxygenation and prognosis in Duchenne muscular dystrophy. Am J Respir Crit Care Med 1999;160:198–202.
28. Kotterba S, Patzold T, Malin J-P, Orth M, Rasche K. Respiratory monitoring in neuromuscular disease—capnography as an additional tool? Clin Neurol Neurosurg 2001;103:87–91.
29. Tan H-L, Gozal D, Ramirez HM, Bandla HPR, Kheirandish-Gozal L. Overnight Polysomnography versus respiratory polygraphy in the diagnosis of pediatric obstructive sleep apnea. Sleep 2014;37:255–260.
30. Pavone M, Verrillo E, Caldarelli V, Ullmann N, Cutrera R. Non-invasive positive pressure ventilation in children. Early Hum Dev 2013;89:S25–S31.
31. Marcus CL, Radcliffe J, Konstantinopoulou S, Beck SE, Cornaglia MA, Traylor J, DiFeo N, Karamessinis LR, Gallagher PR, Meltzer LJ. Effects of positive airway pressure therapy on neurobehavioral outcomes in children with obstructive sleep apnea. Am J Respir Crit Care Med 2012;185:998–1003.

This study identified three clinical situations that lead to CPAP or NIV initiation in children. Twenty percent of children were initiated to noninvasive respiratory support in an acute setting after an acute respiratory exacerbation because of weaning failure or for transition from the ICU to the home. These children, who were included in the "acute group", were too unstable to have a sleep study and therefore where initiated to CPAP or NIV solely because of their clinical condition. Twenty-four percent of patients were initiated after an overnight gas exchange study. These patients were either explored during a hospitalisation for an acute respiratory exacerbation or because of a clinically suspected severe SDB. This "subacute group" should ideally undergo a full sleep study, but given the limited availability of equipment and the severity of their suspected SDB, a simple overnight gas exchange study was sufficient to identify a core of parameters that justified by itself the initiation of NIV or CPAP. The last 56% of patients were in a stable clinical condition and had a full sleep study ("chronic group"). This group comprised children in a stable clinical state who were referred for a sleep study because of suspected SDB due to their underlying disease.

In conclusion, our main results are that the initiation of CPAP/NIV in children occurred in three different settings; namely an acute, subacute and chronic setting with the majority of the patients of the subacute and chronic groups presenting an association of severely abnormal gas exchange or PG parameters. Future studies evaluating the effectiveness and benefits of CPAP/NIV should take in account the clinical situation and initiation criteria.

c. Outpatient initiation of long-term continuous positive airway pressure in children

Current guidelines recommend that the initiation of CPAP for OSAS in children should be started with a supervised titration study[296]. These recommendations highlight the importance of a complete resolution of sleep apnea during CPAP treatment but do not take into account the shortage of hospital beds, the limited access to PSG and economic constraints. Moreover, most of the children requiring CPAP belong to type 3 OSAS and have chronic diseases with complex comorbidities. For these patients, who spent already a large amount of time in hospital, repeated hospitalizations may be stressful. Moreover, hospitalizations are associated with school and parent's work loss, and a risk of nosocomial infection, particularly during the winter season. In addition, with regard to comfort and quality of life, subjects and families inevitably prefer outpatient versus inpatient care. With the increased improvements of CPAP devices' performances, a large amount of detailed data regarding adherence and effectiveness are now available via the in-built software of the devices and allow a strict follow up of these patients without the need of repeated hospitalisations. These factors prompted us to set up an outpatient initiation program for CPAP. This study presents our results and is submitted at the Journal of Clinical Sleep Medicine.

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Outpatient initiation of long-term continuous positive airway pressure in children

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Conflict of interest

All the authors declare that they have no conflict of interest with this manuscript.

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Abstract

Introduction

Current guidelines recommend initiating continuous positive airway pressure (CPAP) in children during an overnight in-hospital titration study. Due to a shortage of hospital beds and economic constraints, we started an outpatient initiation of CPAP in selected children with obstructive sleep apnea (OSA).

Methods

Objective CPAP compliance and efficacy were evaluated in consecutive children enrolled in an outpatient CPAP program when they fulfilled the following criteria: persistent OSA, age > 6 months, stable condition, family living in the Parisian area and agreeing with a regular follow-up.

Results

Thirty-one children, median (range) age 8.9 years (0.8-17.5), were included in the program. The most common diagnoses were Down syndrome (n=7), achondroplasia (n=3) and obesity (n=3). Median baseline obstructive apnea-hypopnea index (OAHI) was 12.5 events/h (5-100). Median duration of follow-up was 12.3 months (2.2-25.2). Four subjects (3 adolescents with Down syndrome) were not compliant at 2-month follow-up with a compliance <4 h/night. In the other 27 subjects, median compliance was 08:21 h:min/night (05:45-12:20), with a median number of night use per month of 25 (18-30). CPAP efficacy at the end of follow-up was excellent in the compliant subjects with a median AHI of 2 events/h (0-4) and normal gas exchange with CPAP therapy. Three subjects were successfully weaned from CPAP treatment during the study period.

Conclusion

Initiating CPAP in an outpatient setting in children is feasible and effective in selected subjects. A high rate of compliance can be achieved as well as a correction of OSA.

Key words

Children, Obstructice sleep apnea OSA, Continuous positive airway pressure (CPAP), Outpatient

Abbreviation list

Continuous positive airway pressure (CPAP)

Obstructive sleep apnea (OSA)

Obstructive apnea-hypopnea index (OAHI)

Polysomnography (PSG)

Polygraphy (PG)

Pulse oximetry (SpO2)

Transcutaneous carbon dioxide (PtcCO2)

Brief summary

Study rationale

- Current guidelines recommend that continuous positive airway pressure (CPAP) should be initiated in a hospital setting during a titration overnight polysomnography (PSG).
- Due to the shortage of hospital beds and the increasing number of children who need CPAP an outpatient initiation program should be preferred.

Study impact

- Initiation of CPAP in an outpatient setting is feasible and effective in selected pediatric subjects.
- A high rate of compliance can be achieved as well as a correction of obstructive sleep apnea syndrome (OSAS).

Introduction

Continuous positive airway pressure (CPAP) is increasingly used in children with persistent obstructive sleep apnea (OSA) despite optimal medical and/or surgical management [1–3]. CPAP has proven its efficacy for treating OSA in children with various underlying disorders such as Down syndrome, congenital bone diseases, metabolic diseases, Prader Willi syndrome, and craniofacial malformations [1,4–8].

Current guidelines recommend a CPAP initiation in an hospital setting with an overnight supervised polysomnography (PSG) titration study [9]. However, this approach is not always feasible in real life because of shortage of hospital beds, limited access to PSG, and economic constraints. Moreover, repeated hospitalizations may be stressful for children with chronic conditions who spent already a large amount of time in hospital. Hospitalizations are associated with school and parent's work loss, and a risk of nosocomial infection, particularly during the winter season. In addition, with regard to comfort and quality of life, subjects and families inevitably prefer outpatient versus in patient care [10]. Moreover, there have been dramatic improvements in the technology of home CPAP devices over last decade. The in-built software of CPAP devices can now provide a large amount of data regarding treatment compliance and efficacy, even in young children [11]. For all these reasons, initiation of CPAP in an outpatient setting within a strict protocol may constitute an alternative to an inpatient initiation. Some experience has been reported on the initiation of mechanical ventilation in an outpatient or home setting in adult subjects, but experience in children is scarce [12,13].

The aim of the present study was to evaluate the objective compliance and efficacy of CPAP initiated through an outpatient CPAP program in selected children with OSA.

Methods

Selection and description of participants

The study was conducted between Mars 2015 and January 2017 at the noninvasive ventilation (NIV) and sleep unit of Necker Children's Hospital. All consecutive children who underwent an

overnight polysomnography (PSG) or polygraphy (PG) in our sleep laboratory and who presented persistent OSA defined as an obstructive apnea-hypopnea index (OAHI) > 5 events/hour despite optimal surgical and/or medical treatment, were included in an outpatient CPAP initiation program if they fulfilled the following inclusion criteria: 1) stable medical condition, 2) age > 6 month of age, 3) French-speaking family living in the Parisian area and agreeing with regular follow-up visits.

The protocol was approved by the local ethical committee (CPP Ile de France II, n° 2014-03-09 SC).

Outpatient initiation program

The program consisted of an individual approximately 2-hours outpatient visit. During the first 30 minutes, the results of the sleep study and the principles of CPAP treatment were explained to the patient (if age > 2 – 3 years) and the parents by a paediatric pulmonologist and a nurse specialized in NIV and educational intervention, by means of specific age-adapted educational tools. These tools associated educational boards and cartoons, a booklet explaining CPAP, and a teddy bear breathing with a CPAP device (online Figures 1 and 2).

The choice of the ventilator was made according to manufacturers' recommendations, i.e. based on a minimal weight [14–17]. This choice was made in order to avoid an underestimation of objective compliance due to a too low flow rate in young children, as previously reported by our group [18]. Heated humidification was systematically proposed. The most appropriate and comfortable interface according to patient's age, facial morphology and preference was chosen.

The interface was then tried first without the CPAP device. The parents (and the patient if possible) were trained to put on and off the interface. CPAP was then started at a minimal pressure of 4 cmH_2O, which was progressively increased to the highest tolerated pressure level, while the patient was lying down calmly. The patient was then asked to keep the CPAP with the chosen pressure for at least 30 minutes. According to manufacturers' indications, auto-titrating CPAP was only used in subjects weighting more than 30 kg [16,17]. During that period, relaxation or distraction was obtained

with the patient's favourite nursery rhymes, music, or calm videos, according to the age and preference of the patient.

Afterwards, the nurse reviewed the use and maintenance of the interface and CPAP device with the parents. An information and follow-up booklet on CPAP was explained and given to the parents. The parents were asked to contact the NIV unit by phone or email after one week and earlier if they encountered any problem at home.

A home care provider trained in paediatric NIV performed a first scheduled visit at home within the 3 days following the CPAP initiation and then on a weekly basis during the first month. During these visits, objective compliance, efficacy and comfort were assessed as well as the correct use and maintenance of the equipment. The data recorded on the in-built software of the CPAP device was systematically downloaded and transmitted to the hospital team. An overnight recording of pulse oximetry (SpO_2) and transcutaneous carbon dioxide ($PtcCO_2$) was performed (SenTec Digital Monitor, Therwil, Switzerland) at home when the CPAP use reached > 6 hours/night or at least once within the first two months. CPAP and/or interface adjustments were eventually performed at home according to the results.

A follow-up outpatient consultation with the paediatrician and the NIV nurse was scheduled 1 month after CPAP initiation. Objective compliance and recorded data were reviewed via the respective in-built software (Encore Basic Version 2.2 and DirectView 2.2, Philips Herrsching, Germany, for Philips devices and ResScan Data Management software 5.0 and further versions, ResMed, NSW, Australia for ResMed devices). Potential problems or difficulties with CPAP were analyzed and the interface and/or CPAP settings were changed if necessary. Follow-up outpatient visits were then performed monthly during the first two months and then every three months. Subjects and their families were contacted by phone or via email (when preferred) every two weeks in the first two months. CPAP compliance and efficacy was checked via in-built software data at each visit. In-hospital polygraphy (PG) or PSG with CPAP was only performed in case of persistent symptoms of

OSA despite an objective compliance > 6 hours/night or when the gas exchange and in-built software data were not conclusive or not interpretable.

Objective compliance was calculated as the median number of hours of CPAP use per night and the percentage of nights with a CPAP use > 4 hours/night. Non-compliance CPAP was arbitrarily defined as an objective CPAP use of less than 4 hours per night after the first two months. CPAP efficacy was evaluated using the OAHI on a PG/PSG or the AHI recorded by in-built software data of the CPAP device that was checked for accuracy, and the overnight gas exchange with CPAP. Data are presented as median and range or mean and standard deviation.

Results

Thirty-one subjects were included in the outpatient program, which represented 35% of the subjects started on long term CPAP during the study period (Table 1). Fifty-seven subjects were not included because of an age ≤ 6 month (n=16), an unstable clinical state with an initiation in the intensive care unit (n=8), non-French-speaking family or a family living outside the Parisian area (n=33). The median age of the population at CPAP initiation was 8.9 years (range 0.8-17.5) with a predominance of male gender (n=19). The median BMI centile was 87.3 (range 5.7-99.6). The most common diagnosis was Down syndrome (n=7), followed by achondroplasia (n=3) and obesity (n=3). Median baseline OAHI was 12.5 events/h (range 4-100).

Twenty seven (87%) subjects achieved an excellent compliance after the first two months, with a median use of 08:21 h:min (range 05:45-12:20) per night (Table 2) at the follow-up visit. CPAP was used a median of 25 (range 18-30) nights per month and for more than 4 h/night during a median of 83 ± 17% of nights. The majority of subjects (81%) used a nasal mask. Fifteen subjects (55%) used a constant CPAP with a mean pressure of 8.5 ± 1.0 cmH_2O. Auto-titrating CPAP was used in the 12 (45%) oldest subjects. The most common auto-titrating CPAP pressure ranges were 8-12 cmH_2O in 8 (67%) of the 12 patients.

Four subjects never achieved a CPAP use of more than 4 hours per night. Three of these subjects were adolescents with Down syndrome (a boy of 16.2 years and two girls of 16.6 and 10.2 years respectively) and the last patient was an 8-year-old girl with an arteriovenous cervico-facial malformation. All these subjects combined variable degrees of developmental delay, behaviour problems and a deficient family structure that never adhered to the CPAP treatment.

Efficacy of CPAP was assessed after 2 months by nocturnal gas exchange in all the subjects, and by the AHI given by the in-built software of the CPAP device in 17 (63%) subjects and on a PSG/PG in 4 (15%) subjects (Table 3). None of the subjects spent ≥ 2% of night time with a SpO_2 < 90% or a $PtcCO_2$ > 50 mmHg. The OAHI on the PSG/PG, as well as the AHI given by the in-built software data on the CPAP device, improved dramatically (Figure 1). One child developed central sleep apneas with a central apnea index of 7 events/h that resolved with the decrease of CPAP pressure. With the exception of this patient, none other patients required several overnight assessments with CPAP in order to achieve the correction of OSA.

Three subjects were weaned from CPAP treatment after 21.5, 16.9 and 13.6 months of follow-up respectively. One patient with mucopolysaccaridosis improved after mandibular distraction osteogenesis while the other two subjects, one with 22q11 deletion and the other with a polymalformative syndrome, improved spontaneously with age. Concerning the non-compliant children, the boy with Down syndrome had a second adenoidectomy that resolved his OSA. The two girls with Down syndrome were switched to high flow air by nasal cannula but did neither comply with this type of respiratory support. The oldest girl had persistent OSA with an OAHI of 9 events/h and the mother decided to stop the follow-up at the last visit. The youngest girl, whose OAHI remains high at 45 events/h at the last PG control, will have an orthodontic treatment with surgical palatal enlargement. The girl with the arteriovenous cervico-facial malformation had a laser reduction of the mass with a control sleep study planned in the next months.

Discussion

Our study shows that an outpatient CPAP initiation program is feasible and efficacious in selected children with OSA with an excellent compliance in the majority of subjects and a correction of OSA. Indeed, 87% of the subjects achieved an excellent compliance with a median objective use of CPAP of about 8 hours per night and the correction of OSA.

One of the main concerns about CPAP is compliance to treatment. Most studies reported a suboptimal compliance with CPAP uses ranging from 4.7 to 5.3 h/night despite a behavioural program and a close follow-up [19,20]. Possible explanations for the excellent compliance observed in the present study may include the use of a CPAP educational program with age-adapted tools. Different types of intervention such as supportive interventions during follow-up, educational interventions and behavioural therapy have proven their efficacy to improve CPAP usage in adult subjects [21]. To our knowledge, only one study has evaluated the effect of educational interventions on CPAP compliance in children, showing that 3 out of 4 preschool children maintain the benefit of education intervention over time[22]. We have developed this type of intervention since several years, which may explain the excellent compliance (over 8 hours/night) reported in a previous study from our group [18]. Importantly, especially for children, it is crucial to choose the age- and developmental-adjusted interventions that best match individual patient needs in order to reach the most successful and cost-effective therapy (online Figures 1 and 2) [21]. Second, few children in our study were initiated to CPAP due to obesity (n=3), which has been recognized as a risk factor for poor adherence [20,23]. Finally, the close collaboration with home care providers trained in pediatric CPAP may have contributed to the excellent compliance. These home care providers perform regular home visits and transmit to the hospital team the objective CPAP compliance data which allows prompt adjustments during the first weeks of treatment. Indeed, the first weeks of CPAP treatment are crucial for CPAP success [24] . The close follow-up visits during the first weeks with overnight recording of nocturnal gas exchange during CPAP allows immediate and efficacious adjustment of the interface and the CPAP settings [25].

However, 4 (13%) subjects never accepted CPAP despite repeated visits and treatment adjustments. Three of these subjects had Down syndrome and all these subjects had some degree of developmental delay, behavioural problems and most importantly, a deficient family structure. CPAP failure was particularly high in a recent study where 5 out of 10 children with Down syndrome and OSA did not accept CPAP [26]. All these children were deficient in tests of adaptive behaviour, visual-motor integration, and achievement. Importantly, investment and motivation of the family is absolutely mandatory for the success of long term CPAP. In our experience, a supportive family is probably one of the greatest predictor of CPAP success[27].

The efficacy of the outpatient CPAP program with regard to the correction of OSA was excellent and comparable to previous work from our group. CPAP was associated with a normalization of nocturnal gas exchange [18,28] and a dramatic decrease of the OAHI and AHI [28]. Moreover, at the present time, we observed no long-term failure among the compliant subjects and none of the subjects required a tracheotomy.

Our study has some limitation. First, the subjects included in the outpatient initiation program were not compared to a control group. We did not take this option because of the selection criteria of the outpatient population. Indeed, in clinical practice, because of medical and practical constraints, only around 35% of the total population started on long term CPAP was eligible for this program. Finally, in a previous study from our group, during which CPAP was initiated in the hospital for all the subjects, the mean objective CPAP compliance was found to be as high as 8:17 ± 2:30 h/min per night [18]. Another limitation of our study is that the correction of OSA was not always controlled by a PSG/PG. However, we have shown that when CPAP is performed by a skilled and experienced team, residual respiratory events during CPAP are rare [28]. Concerning the use of the in-built software data of the CPAP devices, studies in adult subjects have shown the reliability of the AHI given by the devices [29–31]. Our group has very recently shown that automatic AHI given by the CPAP may overestimate the polygraphic AHI [32]. We therefore checked the flow tracings on the CPAP software to ascertain the accuracy of reported AHI.

In conclusion, the present study confirms that the initiation of CPAP in an outpatient setting is feasible and effective in selected pediatric subjects. A high rate of compliance can be achieved as well as a correction of OSAS. We strongly believe that our results highlight the importance of a dedicated pediatric CPAP/NIV unit working in close collaboration with trained pediatric homecare providers for the initiation and the follow-up of these subjects.

References

1. Kureshi SA, Gallagher PR, McDonough JM, et al. Pilot Study of Nasal Expiratory Positive Airway Pressure Devices for the Treatment of Childhood Obstructive Sleep Apnea Syndrome. *J Clin Sleep Med*. June 2014.

2. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. 2012;130(3):e714-755.

3. Amaddeo A, Moreau J, Frapin A, et al. Long term continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) in children: Initiation criteria in real life: Long Term CPAP and NIV in Children. *Pediatr Pulmonol*. 2016;51(9):968-974.

4. Leboulanger N, Fauroux B. Non-invasive positive-pressure ventilation in children in otolaryngology. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2013;130(2):73-77.

5. Della Marca G, Scarano E, Leoni C, et al. Pycnodysostosis with extreme sleep apnea: a possible alternative to tracheotomy. *Sleep Breath Schlaf Atm*. 2012;16(1):5-10.

6. Girbal IC, Gonçalves C, Nunes T, et al. Non-invasive ventilation in complex obstructive sleep apnea – A 15-year experience of a pediatric tertiary center. *Rev Port Pneumol*. 2014;20(3):146-151.

7. Miller SDW, Glynn SF, Kiely JL, McNicholas WT. The role of nasal CPAP in obstructive sleep apnoea syndrome due to mandibular hypoplasia. *Respirol Carlton Vic*. 2010;15(2):377-379.

8. Leboulanger N, Picard A, Soupre V, et al. Physiologic and clinical benefits of noninvasive ventilation in infants with Pierre Robin sequence. *Pediatrics*. 2010;126(5):e1056-1063.

9. Force PAPTT, Medicine AA of S, others. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med*. 2008;4(2):157.

10. Markström A, Sundell K, Lysdahl M, Andersson G, Schedin U, Klang B. Quality-of-life evaluation of patients with neuromuscular and skeletal diseases treated with noninvasive and invasive home mechanical ventilation. *Chest*. 2002;122(5):1695-1700.

11. Pasquina P, Adler D, Farr P, Bourqui P, Bridevaux PO, Janssens J-P. What Does Built-In Software of Home Ventilators Tell Us? An Observational Study of 150 Patients on Home Ventilation. *Respiration*. 2012;83(4):293-299.

12. Chatwin M, Nickol AH, Morrell MJ, Polkey MI, Simonds AK. Randomised trial of inpatient versus outpatient initiation of home mechanical ventilation in patients with nocturnal hypoventilation. *Respir Med*. 2008;102(11):1528-1535.

13. Hazenberg A, Kerstjens H a. M, Prins SCL, Vermeulen KM, Wijkstra PJ. Initiation of home mechanical ventilation at home: a randomised controlled trial of efficacy, feasibility and costs. *Respir Med*. 2014;108(9):1387-1395.

14. https://www.usa.philips.com/healthcare/product/HC1054260/trilogy100ventilator

15. http://ontvep.ca/wp-content/uploads/2014/05/Stellar-150-Clinical-Guide.pdf

16. https://www.respshop.com/manuals/ResMed-AirSense-10-for%20her.pdf

17. https://www.philips.co.uk/b-dam/b2bhc/gb/SleepApnoea/pdf/REMstar%20Pro%20User%20Manual.pdf

18. Ramirez A, Khirani S, Aloui S, et al. Continuous positive airway pressure and noninvasive ventilation adherence in children. *Sleep Med*. 2013;14(12):1290-1294.

19. O'Donnell AR, Bjornson CL, Bohn SG, Kirk VG. Compliance rates in children using noninvasive continuous positive airway pressure. *Sleep*. 2006;29(5):651-658.

20. Marcus CL. Adherence to and Effectiveness of Positive Airway Pressure Therapy in Children With Obstructive Sleep Apnea. *PEDIATRICS*. 2006;117(3):e442-e451.

21. Wozniak DR, Lasserson TJ, Smith I. Educational, supportive and behavioural interventions to improve usage of continuous positive airway pressure machines in adults with obstructive sleep apnoea. *Cochrane Database Syst Rev*. 2014;(1):CD007736.

22. Slifer KJ, Kruglak D, Benore E, et al. Behavioral training for increasing preschool children's adherence with positive airway pressure: a preliminary study. *Behav Sleep Med*. 2007;5(2):147-175.

23. Banis HT, Varni JW, Wallander JL, et al. Psychological and social adjustment of obese children and their families. *Child Care Health Dev*. 1988;14(3):157-173.

24. Damjanovic D, Fluck A, Bremer H, Muller-Quernheim J, Idzko M, Sorichter S. Compliance in sleep apnoea therapy: influence of home care support and pressure mode. *Eur Respir J*. 2009;33(4):804-811.

25. Felemban O, Leroux K, Aubertin G, et al. Value of gas exchange recording at home in children receiving non-invasive ventilation. *Pediatr Pulmonol*. 2011;46(8):802-808.

26. Brooks LJ, Olsen MN, Bacevice AM, Beebe A, Konstantinopoulou S, Taylor HG. Relationship between sleep, sleep apnea, and neuropsychological function in children with Down syndrome. *Sleep Breath Schlaf Atm*. 2015;19(1):197-204.

27. DiFeo N, Meltzer LJ, Beck SE, et al. Predictors of positive airway pressure therapy adherence in children: a prospective study. *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med*. 2012;8(3):279-286.

28. Amaddeo A, Caldarelli V, Fernandez-Bolanos M, et al. Polygraphic respiratory events during sleep in children treated with home continuous positive airway pressure: description and clinical consequences. *Sleep Med*. 2015;16(1):107-112.

29. Cilli A, Uzun R, Bilge U. The accuracy of autotitrating CPAP-determined residual apnea-hypopnea index. *Sleep Breath Schlaf Atm*. 2013;17(1):189-193.

30. Desai H, Patel A, Patel P, Grant BJB, Mador MJ. Accuracy of autotitrating CPAP to estimate the residual Apnea-Hypopnea Index in patients with obstructive sleep apnea on treatment with autotitrating CPAP. *Sleep Breath Schlaf Atm*. 2009;13(4):383-390.

31. Ueno K, Kasai T, Brewer G, et al. Evaluation of the apnea-hypopnea index determined by the S8 auto-CPAP, a continuous positive airway pressure device, in patients with obstructive sleep apnea-hypopnea syndrome. *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med*. 2010;6(2):146-151.

32. Khirani S, Delord V, Olmo Arroyo J, et al. Can the analysis of built-in software of CPAP devices replace polygraphy in children? *Sleep Med*. 2017;37:46-53.

Figure Legends

Figure 1.

AHI before and after treatment

Abbreviations: Apnea Hypopnea Index = AHI (events/h)

Online Figure 1.

Booklet for educational intervention.

Online Figure 2.

Teddy bear breathing with a CPAP device.

Table 1: Demographic data and characteristics of the subjects (n=31).

Female to male ratio	12/19	
Age, years (median, range)	8.9 (0.8-17.5)	
BMI, centile (median, range)	87.3 (5.7-99.6)	
Predisposing conditions	Down syndrome	7
	Achondroplasia	3
	Obesity	3
	22q11 deletion	2
	Prader Willi syndrome	2
	Pycnodysostosis	2
	Mucolipidosis type 1	2
	Mucopolysaccaridosis type 2	1
	Crouzon syndrome	1
	Chiari malformation type 2	1
	Pierre Robin sequence	1
	Polymalformative syndrome	1
	Cervicofacial venous malformation	1
	Idiopathic OSA	1
	Immunodeficiency with lymphoid tissue hyperplasia	1
OAHI, events/h (median, range)	12.5 (4-100)	

Abbreviations: BMI: body mass index, OSA: obstructive sleep apnea, OAHI: obstructive apnea-hypopnea index

Table 2: Continuous positive airway pressure (CPAP) compliance and equipment (n=27).

Duration of follow-up, months (median, range)	12.3 (2.2 – 25.2)
Objective CPAP compliance over the last month (n=27)	
• Average use per night, h:min (median, range)	08:21 (05:45-12:20)
• Percentage of nights with CPAP use > 4 hours, % (mean ± standard deviation)	83 ± 17
Average nights use per month, nights (median, range)	25 (18-30)
Constant CPAP pressure, cmH_2O (mean ± SD) (n=15)	8.5 ± 1.0
Interface (n=27)	
- Nasal mask	22
- Facial mask	3
- Nasal prongs	2

Table 3. Continuous positive airway pressure efficacy data of the 27 compliant subjects.

Poly(somno)graphy apnea-hypopnea index (events/h), n= 4	2 (0-2)
In-built software apnea-hypopnea index (events/h), n =17	2 (0-4)
Nocturnal gas exchange, n= 27	
Mean SpO_2 (%)	97 (93-100)
Minimal SpO_2 (%)	91 (84-96)
Time spent with $SpO_2 < 90\%$ (%)	0 (0-1)
Oxygen Desaturation Index (events/h)	1 (0-9)
Mean $PtcCO_2$ (mmHg)	41 (35-48)
Maximal $PtcCO_2$ (mmHg)	46 (42-52)
Time spent with $PtcCO_2 > 50$ mmHg (%)	0

Abbreviations: SpO_2: pulse oximetry, $PtcCO_2$: transcutaneous carbon dioxide.

Data are presented as median (range).

Figure 1

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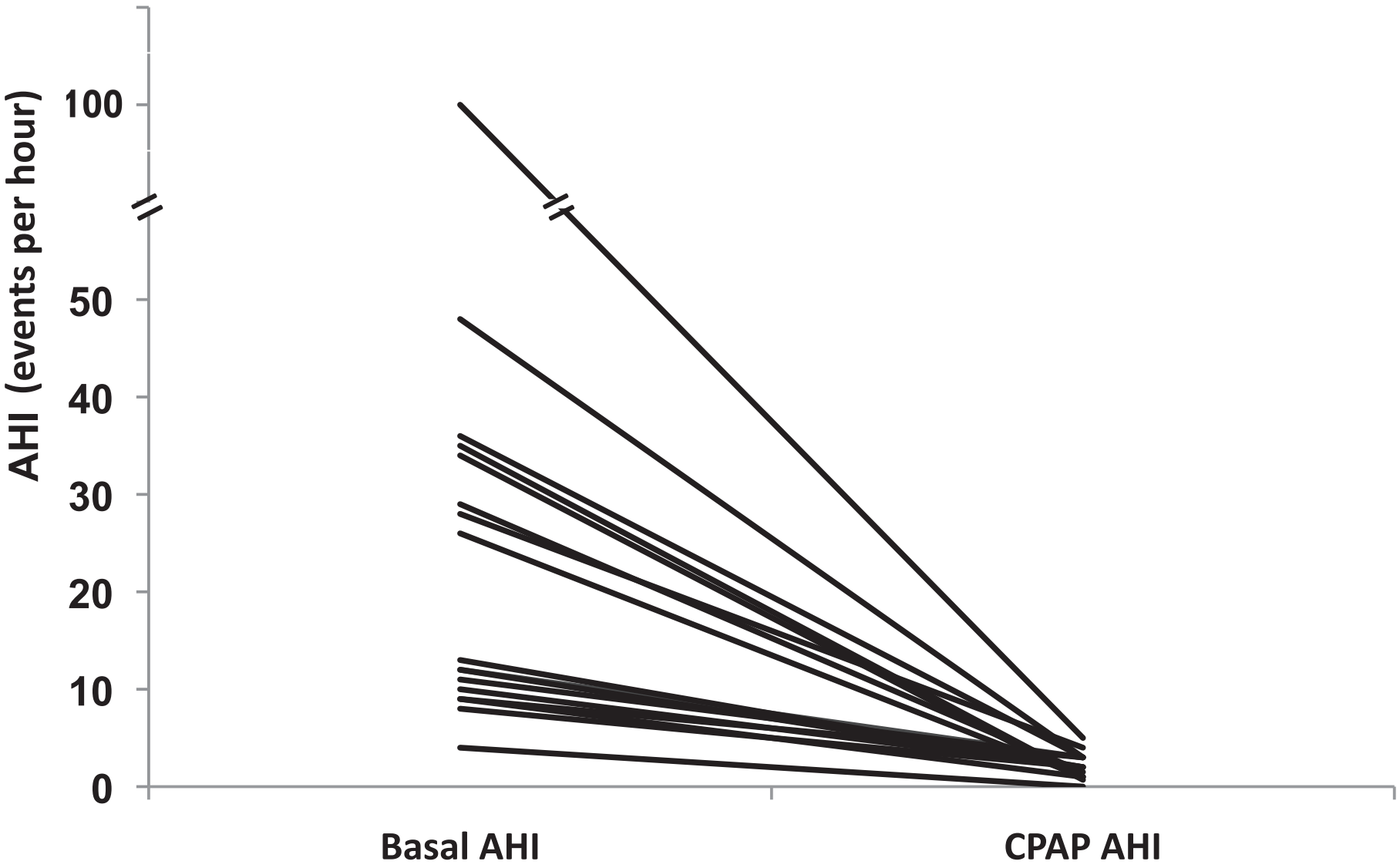

Online Figure 1

Click here to download Figure Fig 2 .pdf

Online Figure 2

This study demonstrated that a dedicated outpatient program for CPAP initiation in a selected group of 31 children was able to provide good results in terms of OSAS control and adherence to treatment. A high rate of compliance was achieved as well as the correction of OSAS. We strongly believe that our results highlight the importance of a dedicated pediatric CPAP/NIV unit working in close collaboration with trained pediatric homecare providers for the initiation and the follow-up of these children. Our study only concerned patients who were initiated to CPAP since this technique is believed to be easier to set and to tolerate. Future studies should validate this approach in patients requiring NIV.

12. Conclusions and perspectives

During my PhD thesis, I had the opportunity to develop two main axes of clinical research. The development of new diagnostic tools, able to simplify and increase the accuracy of sleep studies in children is one of the main challenges of the future of sleep medicine. This is particularly important for two main raisons. First, the increased awareness regarding SDB in children has led to a dramatic growth of the demand of sleep studies in the pediatric population. However, due to the lack of dedicated pediatric sleep centres, most of these children can't have a PSG or a PG or are referred to adult sleep centres that in many cases lack the expertise for interpreting pediatric sleep studies. This is prejudicial in children with type 1 and 2 OSAS, but may represent a dramatic disadvantage for children with type 3 OSAS. Moreover, children are often difficult to explore, since they do not always tolerate the large number of sensors that is required for a full PSG. So, even if in most of the pediatric centres there is a continuous effort in creating a child-friendly environment, a lot of sleep studies are difficult to interpret because of the presence of artefacts and the loss of signals (in particular those of the nasal cannula and the oronasal thermal sensor). The development and validation of new techniques that may substitute standard recommended signals is thus of major importance. We demonstrated that the suprasternal pressure sensor (PneaVox®) may be a useful tool for characterising sleep apnea in children. An ongoing study concerns the use of PneaVox® as a substitute of nasal cannula and oronasal thermal sensor for the detection of apneas and hypopneas, in order to provide an alternative detection of respiratory flow.

We have started a collaborative study between the NIV and sleep unit of Necker Children hospital and Jerome Lejeune Institute in Paris. The study concerns the screening and early diagnosis of SDB in infants with Down syndrome. Forty children of six months of age will be enrolled in the study group. These children will undergo a level 2 PSG (non-attended domiciliary PSG with a Cidelec polysomnograph) every 6 months from the age of 6 months to 3 years of age. In case of SDB, an appropriate treatment will be proposed. The neurocognitive development, behaviour and language at 3 years of age will be compared to those of a standard group of patients explored only at the age of 3 years. Besides the main results of this study, one of the consequences will be the availability of a huge database of PSG in a homogeneous population. This database may be used for the validation of PneaVox sensor in a large population of infants and also for the analysis of other integrated signals.

We investigated the use of PWA as a surrogate tool for the detection of cortical arousals. The principal aim of this study was to demonstrate that PWA variations could effectively replace

EEG cortical arousal for the scoring of hypopneas in children. However, the results of the study did not show a sufficient sensitivity and specificity of this tools compared to standard EEG. These negative results should be interpreted with caution since in our study, PWA variations led to the scoring of a larger number of events compared to standard EEG. This is probably due to the higher sensitivity of PWA in detecting non-cortical (autonomic) arousals that are integrated into the brainstem but not processed to the cortex. One could speculate that, since this type of autonomic activation is not taken into account by the AASM scoring, it should be not considered. However, there is increasing evidence of a role of this type of events on the cardiovascular comorbidity of SDB. One of the main fields of application of this tool may be the detection of sleep fragmentation and respiratory-related arousals during NIV or CPAP in order to increase the effectiveness and tolerance of these treatments.
Finally, I collaborated in the data analysis and preparation of the manuscript concerning the validation of an automated integrated software for the detection of PTT in children. This study demonstrated the importance of this tool as an additional integrated signal for the characterisation of apneas in children. Further studies will be performed to validate this tool as a surrogate signal of cortical and autonomic arousals.

The second part of my PhD program concerned the treatment of SDB in children. The study about the use of CPAP in Pierre Robin syndrome demonstrated that this type of ventilator support may be used beyond neonatal intensive care in this group of infants and may avoid the use of more invasive surgical techniques. Moreover, it demonstrated that sleep studies are crucial in the care of these children since an objective classification of SDB allows a more efficient treatment.
I also collaborated to tow studies on the treatment of children with achondroplasia and Down syndrome. These studies are of major importance since they highlight the importance of a tailored treatment strategy for these children, involving a multidisciplinary team of pediatric pulmonologist, nutritionists, ENT surgeons, neurosurgeons and maxillo-facial surgeons. Other studies, concerning different subgroups of patients (with mucolipidosis, pycnodysostosis, Morquio disease and Chiari syndrome) are in preparation.
The study about the initiation criteria of NIV and CPAP in children provided, via the analysis of a retrospective cohort, a core of objective criteria that lead to the initiation of long term ventilatory support in children. The decision of when to start NIV or CPAP in children is highly dependent on the clinical practice of each centre. The proposal of these criteria will help harmonising practice and comparing different treatment strategies.

Finally, the study concerning the outpatient CPAP initiation reflects a mandatory change in clinical practice that is in line with the need of reducing hospitalisations. The creation of this outpatient initiation program required the set-up of a dedicated program that includes a nurse trained in therapeutic education and NIV/CPAP and an efficient collaboration with home care providers. The good compliance of the patients is a marker of the efficacy of the program. Moreover, the initiation and follow up of CPAP during outpatient visits precludes in-hospital titration studies. The improvements of the in-built software technology of modern ventilators allow now the control of the efficacy of the treatment. More studies will be performed in the future to validate these new tools for the follow up of children under NIV/CPAP.

13. Annexes

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Original Article

Central sleep apnea in children: experience at a single center

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ABSTRACT

Objective: Central sleep apnea (CSA) syndromes are rare in children and data in children over one year of age are scarce. The aim of the study was to describe the sleep characteristics, underlying disorders, management, and outcome of children with CSA.
Patients/Methods: A retrospective chart review of all children >1 year of age, diagnosed with CSA on a laboratory sleep study during a 20-month period, was performed. CSA was defined by a central apnea index (CAI) >5 events/h. The clinical management and the patient's outcome were analyzed.
Results: Eighteen of 441 (4.1%) patients recorded during the study period had CSA. The median CAI, pulse oximetry, and oxygen desaturation index were 13/h (range 6–146), 96% (93–98%), and 18/h (6–98), respectively. Neurosurgical pathologies represented the most common underlying disorders with Arnold–Chiari malformation in four and ganglioglioma in three patients. Other underlying disorders were Prader–Willi syndrome ($N = 3$), achondroplasia ($N = 2$), and Down syndrome, with one patient having an achondroplasia and a Down syndrome. The remaining six patients had other genetic diseases. The most common investigation was brain magnetic resonance imaging (MRI). Individualized management with neurosurgery and/or chemotherapy, continuous positive airway pressure (in two patients having associated obstructive events), or noninvasive ventilation resulted in an improvement in CSA and the clinical presentation in 11 patients.
Conclusion: CSA is rare in children >1 year of age. Underlying disorders are dominated by neurosurgical disorders. Individualized management is able to improve CSA and the clinical condition in most patients.
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1. Introduction

Central sleep apnea (CSA) is a rare but serious condition that may be associated with arterial oxygen desaturation, increase in carbon dioxide, arousals, and a hyperadrenergic state [1]. CSA is defined as the absence of chest and abdominal movements associated with a cessation of airflow for more than 20 s, or lasting more than two baseline respiratory cycles if associated with an arousal, an awakening or an oxygen desaturation of at least 3% [2]. The central apnea index (CAI) is defined as the number of central apneas per hour of sleep. Central apneas (CAs) are physiological in newborns and infants, whose index of up to five events per hour is considered within the normal range [3,4]. Although a CAI >1/h is by convention diagnostic of CSA, a CAI up to 5/h has been reported in healthy children [4–8]. Therefore, a CAI >5/h is considered by some authors to be outside the normal range [9].

CSA is the hallmark of congenital central hypoventilation syndrome (CCHS), which is a rare genetic disease associated with a *PHOX2B* mutation [10]. CSA is rare outside of this situation and only limited data have been reported in the literature about children over one year of age. Most observations are case reports and few series on children have been reported [9]. Brainstem lesions, such as Arnold–Chiari malformation, or brainstem compression, as observed in patients with mucopolysaccharidosis or achondroplasia, may also be responsible for CSA [11–14]. CSA has also been observed in association with Prader–Willi syndrome and hypothyroidism [15–17].

The aim of the study was to describe the sleep characteristics, underlying disorders, management, and outcome of children over one year of age diagnosed with CSA at a single pediatric sleep center.

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2. Methods

2.1. Patients

All the patients between the ages of one and 18 years who underwent an overnight level 3 polysomnography (PSG) or polygraphy (PG) in our sleep laboratory between September 2013 and April 2015 were considered for inclusion. Patients were referred to the sleep laboratory either for symptoms of sleep-disordered breathing or because of an underlying disease that is associated with an increased risk of sleep-disordered breathing. Only patients with a CAI >5/h were identified for further analysis. Patients with CCHS were excluded. The medical records of all the patients were systematically reviewed and data were collected on the patient's medical history and demographics. Interventions after the baseline sleep study, subsequent sleep studies, and outcomes were analyzed for every patient. The study was conducted in agreement with the French regulations and received appropriate legal and ethical approval from the Ethical Committee of Necker University Hospital (CPP Ile de France II).

2.2. Overnight sleep studies

All sleep studies were performed in the sleep laboratory of Necker hospital. All patients were accompanied by one parent throughout the night. Neither sedation nor sleep deprivation was used on any patient.

The following standardized measurements were simultaneously recorded during every level 3 PSG or PG: nasal flow through a nasal pressure transducer, pulse oximetry by a pulse oximeter (SpO_2), oximeter pulse wave form, thoracic and abdominal respiratory inductance plethysmography, digital synchronized infrared video monitoring (Cidelec, St Gemmes sur Loire, France or Alice 6, Philips Respironics, St Priest, France), and transcutaneous carbon dioxide pressure ($PtcCO_2$, SenTec, Therwil, Switzerland). For PSG, the following data were also recorded: electroencephalogram (C_3A_2, C_4A_1, O_1A_2, and O_2A_1), right and left electro-oculogram, submental, anterior tibialis electromyogram, and electrocardiography.

Scoring of sleep stages and respiratory events were performed according to the actualized 2012 scoring rules of the American Academy of Sleep Medicine [2]. The following definitions for respiratory events were used for scoring purposes [2]. CA was defined as the absence of airflow with the cessation of respiratory effort, lasting more than 20 s or of shorter duration and associated with an arousal and/or a 3% oxygen desaturation. CA occurring after gross body movements or after sighs was not included in the analysis. Obstructive apnea (OA) was defined as the absence of nasal airflow with continued chest wall and abdominal movements for at least two breaths. Mixed apnea was defined as an apnea that usually begins as central and ends as obstructive according to changes in the chest, abdominal, and flow traces. Hypopnea was defined as a decrease in nasal airflow of at least 30% with a corresponding decrease in pulse oximetry (SpO_2) of at least 3% and/or an arousal. The apnea–hypopnea index (AHI) was calculated as the sum of apneas and hypopneas per hour of total sleep time. An obstructive AHI (OAHI) <1.5/h and CAI <5/h were considered as normal. All the PSGs/PGs were scored by two experienced pediatric sleep specialists.

Mean, minimal SpO_2 values, and the percentage of total sleep time spent with SpO_2 <90% were calculated. The oxygen desaturation index (ODI) was defined as the number of SpO_2 drops of at least 3% per hour of total sleep time. Mean, maximal values of $PtcCO_2$ and the percentage of total sleep time spent with a $PtcCO_2$ >50 mmHg were calculated.

Repeat sleep studies were performed or planned for all 18 patients. As there are no recommendations or guidelines, we chose to define an improvement by a >50% reduction in the CAI in the repeat sleep studies as it was thought to represent a true change rather than intra-individual variability.

3. Results

3.1. Patients

Four-hundred and forty-one children over the age of one year underwent an overnight sleep study in our laboratory during the study period. Eighteen patients (4.1%) had a CAI >5/h (Table 1).

Apneas during sleep and wakefulness were reported only by the parents of patient #7 who suffered from a ganglioglioma; all the other patients had no symptoms of sleep-disordered breathing and were referred to the sleep laboratory for a systematic sleep study.

Neurosurgical pathologies represented the most common underlying disorders with four patients (patients #1 to #4) having an Arnold–Chiari malformation and three patients (patients #5 to #7) having a ganglioglioma. Other underlying disorders were Prader–Willi syndrome ($N = 3$, patients #8 to #10), achondroplasia ($N = 2$, patients #11 and #12), and Down syndrome (patient #13), with patient #12 having both an achondroplasia and a Down syndrome. The remaining five patients had various other genetic diseases (patients #14 to #18).

3.2. Polygraphic data

A level 3 PSG was performed in two patients (patients #6 and #10) whereas a PG was performed in all the other patients. The CAI was highly variable with five patients having a CAI between 5/h and 6/h (patients #3, #4, #13, #16, and #17), the other patients having a CAI between 11/h and 146/h, with the highest value being observed in a patient with a ganglioglioma (patient #5). Four patients had exclusively CSA (patient #2 and patients #16 to #18) whereas two other patients (patients #13 and #15) also had some obstructive events. Mean SpO_2 was ≥94% in all the patients except in patient #2 who had an Arnold–Chiari malformation. Minimal SpO_2 was below 90% except in one patient with Prader–Willi syndrome (patient #2) but only two patients spent more than 1% of the recording time with a SpO_2 <90% (patients #1 and #13). The ODI was very high with a median value of 18/h. Only two patients had a maximal $PtcCO_2$ >50 mmHg (patients #7 and #13).

3.3. Interventions and outcome of the patients

Table 2 shows intervention and outcome of the patients.

A brain magnetic resonance imaging (MRI) was performed in all the patients. This MRI revealed a cervico-medullary compression in six patients, in the four patients with an Arnold–Chiari malformation, in one patient with a ganglioglioma (patient #7), and another patient with achondroplasia (patient #12). A cervico-medullary decompression was performed in five patients (patients #1, #2, #3, #4, and #7) and could not be performed in patient #12 (achondroplasia with Down syndrome). Patient #1 was successfully managed by noninvasive ventilation (NIV) due to persistence of the CSA after the cervico-medullary decompression. Patient #3 required a tracheostomy after the cervico-medullary decompression because of an increase in CSA. A modification of the chemotherapy was associated with an improvement in CSA in patient #6 who suffered from a ganglioglioma. The other patient with a ganglioglioma (patient #7) was successfully managed with servo-assisted ventilation after the persistence of CSA despite a cervicomedullary decompression. A spontaneous resolution of the CSA was observed in one patient with Prader–Willi syndrome (patient #9) and one patient with achondroplasia (patient #11). Acetazolamide was tried in the two patients with Prader–Willi syndrome (patients #8 and #10). A 50% reduction in CAI was

Table 1
Characteristics of the patients and baseline sleep data.

Patient	Gender	Age (years)	Underlying disease	CAI (events/h)	AHI (events/h)	Mean SpO_2 (%)	Minimal SpO_2 (%)	ODI (events/h)	% time with SpO_2<90%	Mean $PtcCO_2$ (mmHg)	Maximal $PtcCO_2$ (mmHg)
1	M	2.3	Medullary malformation	34	36	93	80	38	5	37	38
2	M	5.2	Arnold–Chiari malformation	12	12	98	87	6	0	38	42
3	F	5.3	Arnold–Chiari malformation + Sensenbrenner syndrome	6	9	95	87	14	0	NA	NA
4	M	3.1	Arnold–Chiari malformation	6	7	96	89	12	0	35	38
5	M	5.0	Ganglioglioma + SDB	146	160	97	85	79	0	37	40
6	F	6.5	Ganglioglioma + SDB	11	24	96	84	23	0	44	47
7	M	11.0	Ganglioglioma + SDB	50	104	96	84	98	0	48	53
8	F	3.6	Prader–Willi syndrome + OSAS PG after CPAP withdrawal	43	44	96	91	11	0	39	44
9	F	4.0	Prader–Willi syndrome + GH, OSAS PG after CPAP withdrawal	19	20	97	87	20	0	NA	NA
10	F	11.4	Prader–Willi syndrome + GH	44	46	96	87	18	0	38	42
11	F	4.2	Achondroplasia + SDB	11	14	96	80	8	0	37	42
12	F	6.0	Achondroplasia + Down syndrome	11	13	96	83	17	0	NA	NA
13	M	15.6	Down syndrome + SDB	5	27	94	80	22	1	53	62
14	M	1.6	Arthrogryposis + hypothyroidism PG after CPAP withdrawal	13	17	94	84	27	0	43	49
15	M	1.4	Polymalformation	21	33	97	82	31	0	39	41
16	M	4.3	Spondyloepiphyseal dysplasia congenita	6	6	97	83	6	0	41	45
17	M	4.8	Pierre Robin + Cornelia de Lange syndrome	6	8	96	81	14	0	44	48
18	M	2.4	Potocki–Lupski syndrome	22	22	98	80	27	0	33	37
Median		4.5		13	21	96	84	18	0	39	43

Abbreviations: AHI, apnea–hypopnea index; CAI, central apnea index; CPAP, continuous positive airway pressure; GH, growth hormone; NA, not available; ODI, oxygen desaturation index; OSAS, obstructive sleep apnea syndrome; PG, polygraphy; $PtcCO_2$, transcutaneous carbon dioxide pressure; SDB, sleep disordered breathing; SpO_2, pulse oximetry.

observed in patient #8, who later improved spontaneously. Noninvasive continuous positive airway pressure (CPAP) was initiated in two patients who had associated obstructive events (patients #13 and #15). CPAP was associated with an improvement in minimal SpO_2, ODI, and hypercapnia in patient #1 and with an improvement in the ODI in patient #15. Three patients moved abroad and were lost to follow-up (patient #5, #12, and #14). Clinical follow-up continues in all the other 15 patients, with repeat sleep studies being planned in the three patients who had no intervention after initial diagnosis (patients #16 to #18). These patients had a normal MRI.

In summary, an improvement in CSA was observed in 11 patients, one patient required a tracheostomy, follow-up is continued for three patients, and three patients were lost for follow-up.

4. Discussion

To our knowledge, this study is the largest series of CSA in children older than one year of age published to date. The main findings are that the prevalence of CSA reaches almost 5% (4.1%), but this number may be underestimated due to a lack of clinical symptoms in the vast majority of patients. Causes are dominated by neurosurgical disorders such as Arnold–Chiari malformations, cerebral tumors, and occipito-cervical compression. Finally, an individualized, multidisciplinary management approach, based on the clinical presentation, may result in an improvement of CSA in majority of patients. This may include neurosurgery, chemotherapy, and noninvasive respiratory support.

The prevalence of CSA in our population was similar to a recent study by Kritzinger et al. [9]. They included children under the age of one year, finding a prevalence of 5.4% as compared to a prevalence of 4.1% in the present study. This moderate difference may be explained by a recruitment bias, the fact that CSA was diagnosed by a PSG in the study by Kritzinger et al. and a PG in the present study, and the inclusion of children younger than one year of age by Kritzinger et al. Both reports could underestimate the real prevalence of CSA as patients are generally asymptomatic, as opposed to patients with obstructive sleep apnea. In the present series, only one patient with a ganglioglioma complained of apneas which were witnessed by his parents during sleep. This underlines the importance of a systematic sleep study in all children having any disorder or risk factor for CSA. As the prevalence, prognosis, and outcome of CSA are largely unknown, it is unknown at which intervals these children need to be assessed.

Brain MRI had a highest diagnostic yield of the investigations performed with 40% (six out of 15 patients) of the patients having a cervicomedullary compression requiring a neurosurgical intervention. None of the patients had *PHOXB2* genetic testing because all the patients were older than one year of age and none presented with alveolar hypoventilation and diffuse autonomic nervous system dysregulation [10]. Moreover, all the patients had an underlying disorder that may be associated with or cause CSA. Neurosurgical disorders were the leading cause of CSA in the present series, representing 39% (seven of 18) of the patients. One patient with achondroplasia and Down syndrome had a stenosis of the foramen magnum on brain MRI (patient #12). These two diseases are known to be associated with brainstem compression, which underlines the importance of a systematic screening with MRI and a sleep study in children with achondroplasia or Down syndrome [14,18,19]. Patients with Down syndrome may effectively present OA but CSA may also be observed [19]. Cervicomedullary decompression is generally effective in correcting the CSA in patients with Arnold–Chiari malformation, as observed in patient #2 [20]. Patient #1 had an unexplained medullary malformation with no improvement after a cervicomedullary decompression.

Table 2
Interventions and evolution of the patients.

Patient	Underlying disease	Intervention	Delay between PG (months)	CAI	AHI	Mean SpO_2 (%)	Minimal SpO_2 (%)	ODI (events/h)	% time with SpO_2<90%	Mean $PtcCO_2$ (mmHg)	Maximal $PtcCO_2$ (mmHg)	Follow-up
1	Medullary malformation	CMD	2	81	82	94	83	80	4	NA	NA	
			3	80	92	96	78	63	4	37	40	Brain MRI: persistence of the ptosis of the cerebellar tonsils
		NIV	12	2	2	96	92	0	0	38	41	Follow-up of NIV
2	Arnold–Chiari malformation	CMD	2	0	0	98	92	0	0	38	41	Not necessary
3	Arnold–Chiari malformation	CMD										Tracheostomy after CMD
4	Arnold–Chiari malformation	CMD										Uneventful CMD
5	Ganglioglioma	None										Lost for follow-up (abroad)
6	Ganglioglioma	Chemotherapy continued	9	4	12	95	87	49	0	50	54	Brain MRI: stability of the lesions, modification of chemotherapy
7	Ganglioglioma	CMD	13	32	111	95	85	98	0.3	41	47	
		Servo-assisted ventilation	14	0	0	95	92	1	0	48	50	Servo-assisted ventilation continued
8	Prader–Willi syndrome	Acetazolamide 125 mg/j	8	20	20	97	91	7	0	39	44	Acetazolamide withdrawal
9	Prader–Willi syndrome	None	7	1	2	98	91	1	0	41	44	Normal brain MRI
10	Prader–Willi syndrome	Acetazolamide since 15 days	4	3	8	96	87	7	0	38	39	Normal brain MRI
		After acetazolamide withdrawal	10	4	4	94	86	3	0	NA	NA	
11	Achondroplasia		2	7	7	97	85	2	0	40	45	Normal brain MRI
		None	12	1.9	4	97	86	3.5	0	42	46	
12	Achondroplasia + Down syndrome	None										Stenosis of the foramen magnum on brain MRI Lost for follow-up (abroad)
13	Down syndrome	CPAP	4	NA	NA	99	92	2	0	NA	NA	
		CPAP	8	NA	NA	95	92	1	0	49	56	CPAP continued
14	Arthrogryposis + hypothyroidism	None	12	4	24	96	78	36	1	NA	NA	Lost for follow-up (abroad)
15	Polymalformation	CPAP	2	NA	N/A	98	85	3	0	35	38	
		Autotitrated CPAP	4	25	32	NA	NA	23	NA	37	38	
		Palatal cleft repair + CPAP	6	NA	N/A	95	90	11	0	44	45	
		CPAP	11	0	31	96	82	13	0	36	39	CPAP continued
16	Spondyloepiphyseal dysplasia congenita	None										Normal brain MRI
17	Cornelia de Lange + Pierre Robin syndrome	None										Normal brain MRI
18	Potocki–Lupski syndrome	None										Normal brain MRI PG planned

Abbreviations: AHI, apnea–hypopnea index; CAI, central apnea index; CMD, cervico-medullary decompression; CPAP, continuous positive airway pressure; MRI, magnetic resonance imaging; NA, not available; NIV, noninvasive ventilation; ODI, oxygen desaturation index; PG, polygraphy; $PtcCO_2$, transcutaneous carbon dioxide pressure; SpO_2, pulse oximetry.

CSA of this patient was thereafter completely corrected by noninvasive ventilation set in a controlled mode. In another neurosurgical patient with a ganglioglioma, CSA was corrected with servo-assisted ventilation [21]. CSA has been observed in children with Prader–Willi syndrome [16,22]. The management of CSA associated with Prader–Willi syndrome is challenging in the absence of any therapeutic evidence or recommendation. Acetazolamide was not tolerated in one patient and the effect was moderate in another patient. Spontaneous improvement was observed in the third patient with Prader–Willi syndrome. However, in these three patients, central apneas were generally of short duration and not associated with severe hypoxemia, desaturation, or hypoventilation. Noninvasive CPAP was initiated with success in two patients who had associated obstructive apneas, one patient with Down syndrome, and another patient with a polymalformative syndrome and cleft palate. The treatment of these obstructive events was associated with an improvement in nocturnal gas exchange in both patients. The three last patients had rare genetic diseases, namely spondyloepiphyseal dysplasia congenita, Pierre Robin syndrome with Cornelia de Lange syndrome, and Potocki–Lupski syndrome, all of which have been reported to be associated with CSA [23–25].

Our study has several limitations. This was a single-center study with an unavoidable recruitment bias. Due to poor cooperation and neurocognitive impairment in some patients, a full PSG could not be performed. PG is not able to identify post-arousal central or sleep–wake transition central events from true central events that lead to arousals. Therefore, it is possible that the real prevalence and severity of CSA were underestimated.

In conclusion, asymptomatic children with underlying disorders or known risk factors for CSA should be referred for a sleep study in a timely manner in order to detect CSA or other sleep disorders. Similarly, any child with CSA should undergo a brain MRI. An individualized management strategy can therefore improve CSA and the clinical presentation in most patients.

Conflict of interest

All the authors certify that they have no conflict of interest with the data presented in this work. The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2016.07.016.

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References

[1] Javaheri S, Parker TJ, Liming JD, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. Circulation 1998;97(21):2154–9.
[2] Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 2012;8:597–619.
[3] Ng DK, Chan CH. A review of normal values of infant sleep polysomnography. Pediatr Neonatol 2013;54:82–7.
[4] Marcus CL, Omlin KJ, Basinki DJ, et al. Normal polysomnographic values for children and adolescents. Am Rev Respir Dis 1992;146:1235–9.
[5] Uliel S, Tauman R, Greenfeld M, et al. Normal polysomnographic respiratory values in children and adolescents. Chest 2004;125:872–8.
[6] Traeger N, Schultz B, Pollock AN, et al. Polysomnographic values in children 2–9 years old: additional data and review of the literature. Pediatr Pulmonol 2005;40:22–30.
[7] Montgomery-Downs HE, O'Brien LM, Gulliver TE, et al. Polysomnographic characteristics in normal preschool and early school-aged children. Pediatrics 2006;117:741–53.
[8] Verhulst SL, Schrauwen N, Haentjens D, et al. Reference values for sleep-related respiratory variables in asymptomatic European children and adolescents. Pediatr Pulmonol 2007;42:159–67.
[9] Kritzinger FE, Al-Saleh S, Narang I. Descriptive analysis of central sleep apnea in childhood at a single center. Pediatr Pulmonol 2011;46:1023–30.
[10] Rand CM, Carroll MS, Weese-Mayer DE. Congenital central hypoventilation syndrome: a neurocristopathy with disordered respiratory control and autonomic regulation. Clin Chest Med 2014;35:535–45.
[11] Losurdo A, Dittoni S, Testani E, et al. Sleep disordered breathing in children and adolescents with Chiari malformation type I. J Clin Sleep Med 2013;9:371–7.
[12] Valayannopoulos V, Nicely H, Harmatz P, et al. Mucopolysaccharidosis VI. Orphanet J Rare Dis 2010;5:5.
[13] Lin HY, Chen MR, Lin CC, et al. Polysomnographic characteristics in patients with mucopolysaccharidoses. Pediatr Pulmonol 2010;45:1205–12.
[14] Reina V, Baujat G, Fauroux B, et al. Craniovertebral junction anomalies in achondroplastic children. Adv Tech Stand Neurosurg 2014;40:295–312.
[15] Lin HY, Lin SP, Lin CC, et al. Polysomnographic characteristics in patients with Prader–Willi syndrome. Pediatr Pulmonol 2007;42:881–7.
[16] Pavone M, Caldarelli V, Khirani S, et al. Sleep disordered breathing in patients with Prader–Willi syndrome: a multicenter study. Pediatr Pulmonol 2015;50:1354–9.
[17] Terán-Pérez G, Arana-Lechuga Y, González-Robles RO, et al. Polysomnographic features in infants with early diagnosis of congenital hypothyroidism. Brain Dev 2010;32:332–7.
[18] Julliand S, Boulé M, Baujat G, et al. Lung function, diagnosis and treatment of sleep-disordered breathing and in children with achondroplasia. Am J Med Genet A 2012;158A(8):1987–93.
[19] Ferri R, Curzi-Dascalova L, Del Gracco S, et al. Respiratory patterns during sleep in Down's syndrome: importance of central apnoeas. J Sleep Res 1997;6:134–41.
[20] Arnautovic A, Splavski B, Boop FA, et al. Pediatric and adult Chiari malformation Type I surgical series 1965–2013: a review of demographics, operative treatment, and outcomes. J Neurosurg Pediatr 2015;15:161–77.
[21] Ramar K, Desrues B, Ramar P, et al. Analysis of cardiopulmonary coupling to assess adaptive servo-ventilation success in complex sleep apnea management. Sleep Breath 2013;17:861–6.
[22] Cohen M, Hamilton J, Narang I. Clinically important age-related differences in sleep related disordered breathing in infants and children with Prader–Willi Syndrome. PLoS ONE 2014;9:e101012.
[23] Veeravagu A, Lad SP, Camara-Quintana JQ, et al. Neurosurgical interventions for spondyloepiphyseal dysplasia congenita: clinical presentation and assessment of the literature. World Neurosurg 2013;80:437.
[24] Pinheiro Neto CD, Alonso N, Sennes LU, et al. Polysomnography evaluation and swallowing endoscopy of patients with Pierre Robin sequence. Braz J Otorhinolaryngol 2009;65:852–6.
[25] Lee CG, Park SJ, Yim SY, et al. Clinical and cytogenetic features of a Potocki-Lupski syndrome with the shortest 0.25 Mb microduplication in 17p11.2 including RAI1. Brain Dev 2013;35:681–5.

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ORIGINAL ARTICLE

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Sleep-disordered breathing and its management in children with achondroplasia

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Sleep-disordered breathing is a common feature in children with achondroplasia. The aim of our study was to review the poly(somno)graphic (P(S)G) findings and consequent treatments in children with achondroplasia followed in the national reference center for skeletal dysplasia. A retrospective review of the clinical charts and P(S)G of 43 consecutive children (mean age 3.9 ± 3.5 years) with achondroplasia seen over a period of 2 years was performed. Twenty four (59%) children had obstructive sleep apnea (OSA). Thirteen children had an obstructive apnea-hypopnea index (OAHI) < 5/hr, four had an OAHI between 5 and 10/hr, and seven had an OAHI ≥ 10/hr. Ten of the 15 children who had previous upper airway surgery still had an abnormal P(S)G. All the patients with an AHI ≥ 10/hr were under 7 years of age and none had a prior tonsillectomy. The children who underwent adeno-tonsillectomy, coupled in most cases with turbinectomy, were significantly older (mean age 7.5 ± 3.5 vs. 3.5 ± 1.7 years old, $P = 0.015$) and had significantly better P(S)G results than those who underwent only adeno-turbinectomy. No correlation was observed between the mean AHI value at the baseline P(S)G and the type of academic course (standard, supported or specialized). In conclusion, OSA is common in children with achondroplasia. The observation of a reduced prevalence of OSA after (adeno-) tonsillectomy is in favor of this type of surgery when possible.

KEYWORDS

achondroplasia, neurosurgery, polysomnography, sleep apnea, tonsillectomy

1 | INTRODUCTION

Achondroplasia is the most frequent form of short-limb dwarfism. Its incidence is between 1 in 10,000 and 1 in 30,000 affecting more than 250,000 individuals worldwide (Baujat, Legeai-Mallet, Finidori, Cormier-Daire, & Le Merrer, 2008; Horton, Hall, & Hecht, 2007). The genetic defect has been identified as an arginine for glycine substitution of the aminoacid residue at position 380 in the gene encoding for *fibroblast growth factor receptor 3* (*FGFR3*) (Shiang et al., 1994). Most of the clinical features of achondroplasia are either direct or indirect consequences of increased *FGFR3* signaling on endochondral bone growth. Affected individuals exhibit short stature with predominant rhizomelic shortening of the limbs, characteristic facies with frontal bossing and midface hypoplasia, exaggerated lumbar lordosis, limitation of elbow extension, genu varum, and trident hand (Bellus et al., 1995). Natural history studies identified a higher mortality among children compared with the general population with a causative association with foramen magnum stenosis and sudden death (Simmons, Hashmi, Scheuerle, Canfield, & Hecht, 2014; Wynn, King, Gambello, Waller, & Hecht, 2007).

Sleep-disordered breathing is a common finding in patients with achondroplasia. The combination of midface hypoplasia, micrognathia, and depressed nasal bridge causing narrow nasal passages or choanal stenosis, relative adenoids, and tonsils hypertrophy, relative macroglossia, a high palate and decreased temporo–mandibular joint mobility and airway muscles hypotonia predisposes these patients

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to upper airway obstruction and obstructive sleep apnea (OSA) (Holzman, Mancuso, & Polaner, 2008). Cervical cord compression at the cervical medullary junction may cause central sleep apneas (CSA) and may require surgical decompression in infancy or early childhood (Baujat et al., 2008).

The American Academy of Pediatrics (AAP) recommends performing neuroimaging and polysomnography (PSG) at the time of diagnosis and in case of suggestive symptoms of sleep-disordered breathing (Trotter & Hall, 2005). Still, few studies have analyzed serial polygraphies (PG) and therapeutic interventions in children with achondroplasia. Mogayzel et al. reviewed the data of 88 children (Mogayzel, Carroll, Loughlin, Hurko, Francomano, & Marcus, 1998). Despite prior upper airway surgery or neurosurgery, 42 children had an abnormal overnight PSG, with 18 children having severe anomalies. Similar findings were observed in another cohort of 46 children (Afsharpaiman, Sillence, Sheikhvatan, Ault, & Waters, 2011).

The aim of our study was to analyze the P(S)G findings with the prior and subsequent therapeutic interventions in a large cohort of consecutive children with achondroplasia followed in a national reference center.

2 | MATERIALS AND METHODS

2.1 | Patients

We conducted a retrospective review of the sleep studies and management of all consecutive children with achondroplasia who were followed at our national reference centre for skeletal dysplasia between September 2013 and September 2015. All the children carried the Gly380Arg (G380R) mutation on the *FGFR3* gene. Sleep studies are performed once a year, with the first study being performed between the age of 6 and 12 months of age in infants diagnosed or referred to the reference centre for skeletal dysplasia before the age of 1 year. Clinical data including coexisting medical conditions, surgical history, use of non invasive ventilation (NIV), and academic level were obtained from the patients' files. The study was approved by the ethical committee and informed consent was obtained from parents and/or children.

2.2 | Sleep study

Overnight PG (Cidelec, Saint Gemme sur Loire, France or Alice 6, Respironics, Carquefou, France) with the recording of nasal flow, respiratory movements (by respiratory inductance plethysmography), tracheal sound, body position, heart rate, pulse oximetry (SpO_2) and transcutaneous carbon dioxide (SenTec Digital Monitor, SenTec^{Inc}, Therwil, Switzerland) were performed in room air (Berry et al., 2012). Overnight PSG monitoring included in addition to the PG study: electrocardiogram, central and occipital electroencephalogram (O1A2, O2A1, C4A1, C3A2), right and left electrooculogram (ROC/A1, LOC/A2), and submental and leg electromyograms (EMG). The choice of a PS or a PSG was let to the attending sleep specialist: a PSG was performed when abnormalities of sleep architecture or non-respiratory sleep disorders were suspected, a PG was performed in the other cases. The sleep study was recorded on videotape with an infrared video camera.

Obstructive apnea was defined as a drop in nasal flow amplitude by 90% of baseline for at least two respiratory cycles, with continued or increased inspiratory effort. Central apnea was defined as a drop in nasal flow amplitude by 90% of baseline without inspiratory effort, of a duration of at least two breaths and associated with an arousal, an awakening, or a 3% oxygen desaturation (OD), or of a duration of at least 20 sec. Mixed apnea was defined as a drop in nasal flow amplitude by 90% of baseline for at least two respiratory cycles with the absence of inspiratory effort during one portion of the event and the presence of inspiratory effort during another portion, regardless of which portion comes first. Hypopnea was defined as a drop in nasal flow amplitude by 30% of baseline of a duration of at least two breaths, associated with an arousal, an awakening, or a 3% OD (Berry et al., 2012).

Apnea-hypopnea index (AHI) was calculated as the sum of the apnea and hypopnea events per hour of total sleep. Sleep study was considered normal in case of an apnea index < 1 event/hr and AHI < 1.5 events/hr (Uliel, Tauman, Greenfeld, & Sivan, 2004). Mild sleep apnea was defined as an AHI between 1.5 and 5 events/hr, moderate sleep apnea as an AHI between 5 and 10 events/hr, and severe sleep apnea as an AHI ≥ 10 events/hr. The oxygen desaturation index (ODI) was considered abnormal when >5 events/hr.

2.3 | Therapeutic interventions

All the patients were seen every 6 months during the first 2 years of life and then once a year by pediatrician, medical geneticist, pediatric ENT surgeon, and neurosurgeon. Indications for ENT surgery were large with upper airway surgery being performed in case of clinical upper airway obstruction, such as hypertrophy of the adenoids, tonsils, and/or turbinates, *a fortiori* but not obligatory, associated with obstructive sleep apnea (OSA). When there was no surgically accessible airway obstruction or when ENT surgery was not able to reduce the IAH < 10 events/hr, noninvasive continuous positive airway pressure (CPAP) or bilevel ventilation (BiPAP) in case of associated nocturnal alveolar hypoventilation was initiated (Simmons et al., 2014).

Cervical decompression was performed after a multidisciplinary evaluation based on a neurological examination, a cerebral and cervico-medullar MRI and a sleep study (Julliand et al., 2012; Wynn et al., 2007).

2.4 | Statistical analysis

All continuous variables were expressed as mean ± standard deviation, or as median and interquartiles. Comparisons between two quantitative variables were done using the Student t-test in case of normally distributed population or the Mann–Whitney Rank test, otherwise. Comparisons between three quantitative variables were done using the One Way Analysis of Variance (ANOVA) in case of normally distributed population or the Kruskal–Wallis One Way ANOVA on ranks test, otherwise. Comparisons between qualitative variables were done using the Chi-square test. Correlation between two variables was

done using the Pearson correlation test in case of normally distributed population or the Spearman correlation test otherwise. A P value < 0.05 was considered as statistically significant.

3 | RESULTS

3.1 | Patients

Forty-seven consecutive children with achondroplasia were evaluated at our center during the study period. Three patients were excluded from the analysis because they were already treated with BiPAP at the time of the baseline P(S)G and one patient was excluded because of a concomitant Down syndrome.Forty-three patients were therefore included in the analysis (Table 1). The mean age at the baseline P(S)G was 3.9 ± 3.5 years (range 0.3–13.3 years). Most of the patients were young, with 10 (23%) patients being younger than 1 year of age and 9 (21%) patients being between 1 and 2 years old. Seventeen (39%) patients had a previous sleep study in other medical centers. Two patients had a PSG and 41 patients had a PG. Before the baseline P(S)G, 11 patients (26%) had a prior ENT surgery, 2 patients had prior neurosurgery, and 4 patients had both surgeries (Table 1).

3.2 | Sleep-disordered breathing

Twenty four (56%) patients had an abnormal P(S)G presenting OSA.. Table 2 shows patients characteristics according to severity of OSA. Thirteen (29%) patients had mild OSA, four (9%) had a moderate OSA, and seven (16%) had a severe OSA (Table 2). Two patients (5%) were treated prior to the baseline P(S)G study with NIV for severe OSA and had a PG in spontaneous breathing in order to know if NIV could be withdrawn. Moderate to severe OSA was still present in these two patients (with an IAH of 5/hr and 18/hr). Table 2 compares the surgical history and nocturnal gas exchange of the patients without and with OSA. Patients without and with OSA did not differ with regard to age or a history of prior ENT surgery or neurosurgery. Minimal SpO_2 was lower and the ODI was significantly higher in patients with severe OSA as compared to patients without OSA. All the patients with mild or severe OSA were younger than 8 years old (Figure 1). As expected, a significant positive correlation ($r = 0.676$, P–< 0.001) was observed between the AHI and the ODI (Figure 2).

TABLE 1 Patients' characteristics and previous surgical interventions

Characteristics of patients ($n = 43$)	
Age at the P(S)G (years)	3.9 ± 3.5
Sex (M/F)	22/21
Number of patients who had previous surgical interventions	16
ENT surgery	15
Adeno-turbinectomy[a]	9
Adeno-tonsillectomy	2
Adeno-tonsillectomy+ turbinectomy	4
Neurosurgery[a]	6

P(S)G, poly(somno)graphy; M, male; F, female; ENT surgery, otorhinolaryngology surgery. Data are presented as mean ± standard deviation.
[a]Four patients had both adeno-turbinectomy and neurosurgery.

3.3 | Prior ENT surgery

Fifteen (35%) patients had upper airway surgery prior to the baseline P(S)G, associated or not with other therapeutic interventions (Table 1). Time elapsed between the surgical intervention and the baseline P(S)G ranged from 2 months to 4 years (mean 23 ± 14 months). Among these 15 patients, 10 (67%) patients had still an abnormal P(S)G (Table 2).

The six children who underwent prior adeno-tonsillectomy (associated with turbinectomy in four children) were significantly older (mean age 7.5 ± 3.5 vs. 3.5 ± 1.7 years old, $P = 0.015$) and had significantly better P(S)G and nocturnal gas exchange parameters than those who had an adeno-turbinectomy (Table 3). All the patients an AHI ≥ 10/hr were under 7 years of age (Figure 3A and B). None of these patients had a prior tonsillectomy.

3.4 | Neurosurgery

Cervical and cerebral MRI reports were available for 32 of the 43 patients (74%). Radiological abnormalities were reported in 24/32 patients but only six patients (14% of total population) had a prior neurosurgery. Cervical decompression was required in five patients because of severe stenosis of the foramen magnum associated with radiological and/or clinical signs of medullar injury. Three of the six patients with prior neurosurgery had moderate or severe OSA (Table 2).

3.5 | Academic level or learning skills

Nineteen (44%) of the 43 patients were preschoolers and at the time of the baseline P(S)G: 15 patients had a normal neuro-cognitive development while generalized hypotonia and/or speech delay was observed in four patients. Among the 24 school-aged patients, 15 (62%) followed a standard academic course, 4 (17%) needed individualized teaching support, and 4 (17%) attended a specialized school for children with developmental delay and/or learning disabilities. Academic level was not available in one patient. No correlation was observed between the mean AHI value at the baseline P(S)G and the type of academic course (standard, supported or specialized).

3.6 | Management after the baseline P(S)G

Figure 4 shows the follow up of the patients after the baseline P(S)G.

3.6.1 | Upper airway surgery

All the seven patients with severe OSAS were evaluated by a pediatric ENT specialist. Five of these patients underwent ENT surgery (adeno-turbinectomy, $n = 2$, adeno-tonsillectomy, $n = 1$, adeno-tonsillectomy with turbinectomy, $n = 1$, tonsillectomy with turbinectomy, $n = 1$) even if three of these patients had already prior ENT surgery 2–4 years before the baseline P(S)G. In one of these patients, adeno-turbinectomy was

TABLE 2 Patients' characteristics and distribution according to the severity of obstructive sleep apnea

	OAHI < 1.5 events/hr (*n* = 19)	OAHI 1.5–5 events/hr (*n* = 13)	OAHI 5-10 events/hr (*n* = 4)	OAHI ≥ 10 events/hr (*n* = 7)	*P* value
Age (years)	4.4 ± 3.7 (range 0.3–12.4)	3.4 ± 3.9 (range 0.3–13.3)	4.2 ± 3.6 (range 0.3–7.8)	3.3 ± 2.2 (range 0.5–6.2)	0.728
Sex (M/F)	9/10	6/7	4/0	3/4	
Previous interventions					
ENT surgery[a]	5	3	2	5	0.403
Adeno-turbinectomy	2	1	1	5	
Adeno-tonsillectomy	1	1	0	0	
Adeno tonsillectomy+ Turbinectomy	2	1	1	0	
Neurosurgery[a]	3	0	1	2	
No intervention	13	10	1	2	
Nocturnal gas exchanges					
Minimal SpO_2 (%)	91 ± 4	87 ± 7	86 ± 6	75 ± 14	0.007°
3% Oxygen desaturation index (events/hr)	2 ± 3	6 ± 6	4 ± 3	38 ± 34	<0.001°
Maximal $PtcCO_2$ (mmHg)	43 ± 3	43 ± 2	44 ± 8	50 ± 9	0.341

OAHI, obstructive apnea-hypopnea index; M, male; F, female; ENT surgery, upper airway surgery; $PtcCO_2$, transcutaneous carbon dioxide pressure; SpO_2, pulse oximetry. Data are presented as mean ± standard deviation.
[a]Four patients had both adeno-turbinectomy and neurosurgery. ° Statistically significant between OAHI < 1.5 and ≥10 events/hr.

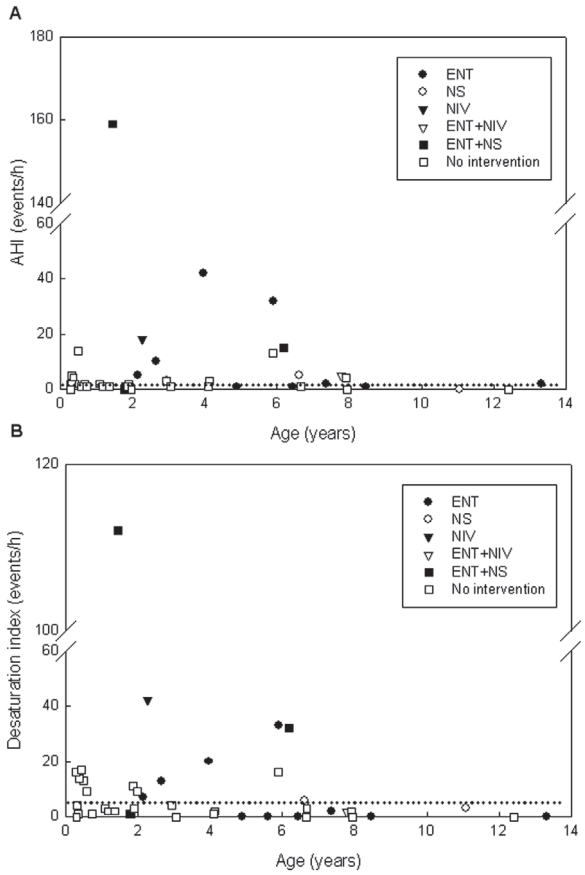

FIGURE 1 Relationship between patients' age and AHI (A) and desaturation index (B) according to the previous treatments. AHI, apnea-hypopnea index; ENT, upper airway surgery; NS, neurosurgery; NIV, noninvasive ventilation

coupled with immediate CPAP initiation because of extremely severe OSA with an AHI 159 events/hr. CPAP was also started in a second patient because of an AHI of 10/hr despite an adeno-tonsillectomy with turbinectomy 9 months before his baseline P(S)G. P(S)G was repeated 5 months later in a last patient who had no symptoms and neither clinical airway obstruction at the time of his baseline P(S)G; this second P(S)G showed an AHI of 2 events/hr. A complete normalization of nocturnal transcutaneous gas exchanges and the AHI on the in-built software of the CPAP device was observed in the two patients treated with nocturnal CPAP.

In the group with mild to moderate OSAS; one patient had a cervico-medullary decompression and an adeno-turbinectomy because of rare but profound oxygen desaturations and hypercapnia; one patient

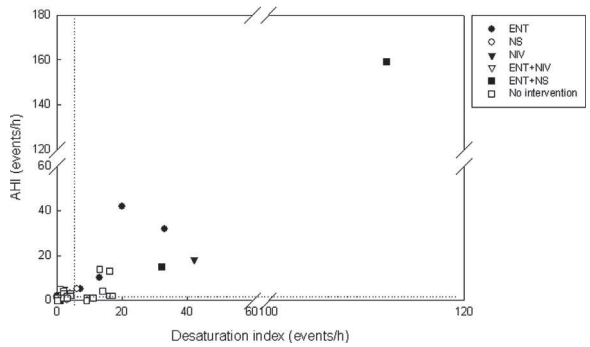

FIGURE 2 Relationship between AHI and desaturation index according to the previous treatment patients have undergone. AHI, apnea-hypopnea index; ENT, upper airway surgery; NS, neurosurgery; NIV,noninvasive ventilation

TABLE 3 Patients' characteristics according to ENT surgery

	Adenoidectomy + Turbinectomy (*n* = 9)	Adenoidectomy + Tonsillectomy (± Turbinectomy) (*n* = 6)	P value
Age (years)	3.5 ± 1.7	7.5 ± 3.7	0.015
AHI (events/hr)	10 (2.5–34.5)	1.5 (1–2)	0.045
3% ODI (events/hr)	13 (3.3–32)	0.5 (0–2)	0.021
$PtcCO_2$ max (mmHg)	48 ± 7.6	44 ± 1.6	0.025
SpO_2 min (%)	85 (66–91)	93 (91–93)	0.039

AHI, apnea-hypopnea index; 3% ODI, 3% oxygen desaturation index; $PtcCO_2$ max, maximal transcutaneous carbon dioxide pressure; SpO_2 min, minimal pulse oximetry. Data are presented as mean ± standard deviation or median [interquartiles].

previously treated with CPAP had to restart his treatment because of the resumption of his OSAS; one patient had an adenoidectomy because of recurrent middle ear infection with speech delay; and one patient was started on NIV because of a persistent lobar atelectasis.

In the group of patients without sleep apneas, one patient was successfully treated by CPAP because of an alveolar hypoventilation due to a restrictive syndrome.

3.6.2 | Neurosurgery

One patient had a cervical decompression with adeno-turbinectomy because of the presence of a foramen magnum re-ossification and a moderate OSAS. This patient had already required neurosurgery for a cervical decompression 7 years before.

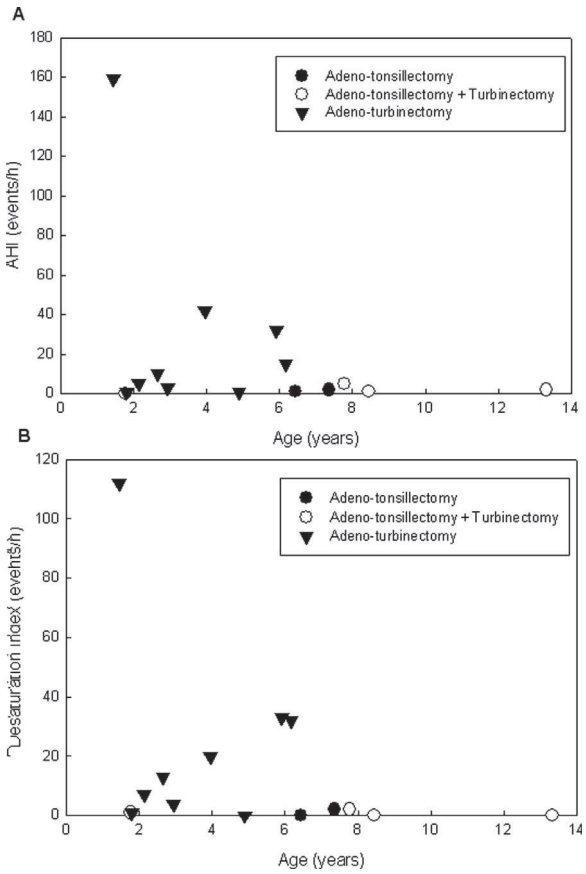

FIGURE 3 Relationship between patients'age and AHI (A) or desaturation index (B) according to the type of ENTsurgery; AHI, apnea-hypopnea index

4 | DISCUSSION

The main results of our study are that OSA was observed in 24 (56%) of 43 children with achondroplasia followed at a national reference center for skeletal dysplasia. Importantly, all the patients with severe OSA were younger than the age of 7 years and none of the patients with a history of tonsillectomy had severe OSA.

The prevalence of OSA in achondroplasia varies from 10% to 87%, according to the definition of OSA (Julliand et al., 2012; Mador and Tobin, 1990; Nelson et al., 1988; Stokes et al., 1983; Waters, Everett, Sillence, Fagan, & Sullivan, 1993; Waters, Everett, Sillence, Fagan, & Sullivan, 1995) (Table 4). In the present study, the prevalence of OSA remained high despite prior, and sometimes repeated, upper airway surgery in more than 1/3 of the patients. The number of children who had prior ENT surgery before the baseline P(S)G evaluation was comparable to those reported in other studies (Julliand et al., 2012; Schlüter, De Sousa, Trowitzsch, & Andler, 2011; Sisk, Heatley, Borowski, Leverson, & Pauli, 1999; Tasker et al., 1998). Persistent OSA after ENT surgery has been reported by several authors. Six of 10 children (60%, and 14% of the global series) who had adeno-tonsillectomy for OSA required CPAP treatment for persistent OSA (Waters et al., 1995). More recently, two patients (mean age 2.6 years) out of five had a persistent OSA despite clinical improvement after upper airway surgery (Collins and Choi, 2007). An improvement in OSA was observed in five patients with OSA treated by various surgical procedures after a median delay of 6.5 months (range 3–13 months) but three patients did not normalize their AHI and ODI and two required NIV (Julliand et al., 2012).

Importantly, in the present study, incomplete correction of OSA was observed in all the patients in whom tonsillectomy was not possible or not performed. Similar findings were observed in another cohort of 95 children with achondroplasia (Sisk et al., 1999). Indeed, the recurrence of OSA in their population was significantly lower (20%) in the 24 children who had a tonsillectomy than in the 10 children who had an adenoidectomy (90%). Of note, OSA was defined on clinical evidence of OSA without systematic P(S)G. These observations are in agreement with studies in healthy children with OSA, which showed that a tonsillectomy with adenoidectomy translated into a greater

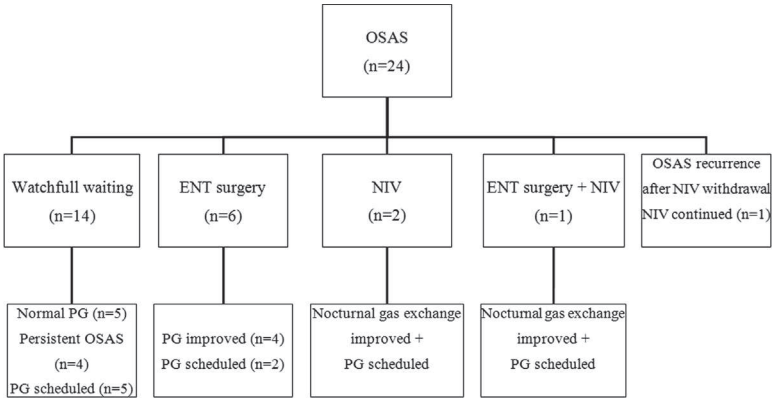

FIGURE 4 Treatments and outcomes of patients after the sleep study. OSAS, obstructive sleep apnea syndrome; n, number of patients in each category; ENT surgery, upper airway surgery; NIV, non invasive ventilation

improvement of OSA than either procedure alone (Guilleminault, Li, Khramtsov, Pelayo, & Martinez, 2004; Guilleminault, Li, Quo, & Inouye, 2004). However, in the present study, the type of ENT surgery was determined by the ENT surgeon on the clinical examination of the child. In infants, it are essentially the adenoids that may be enlarged, whereas hypertrophy of the tonsils is observed at an older age. This explains why the mean age of the children who underwent tonsillectomy was significantly older than those who had adenoidectomy without tonsillectomy (Table 3). Turbinectomy can be performed at any age but again only when the size of the turbinates is sufficient. To conclude, this observation justifies 1) a regular and systematic sleep evaluation in all children until the age of possible potential tonsillectomy (i.e., 6–8years) and 2) an "aggressive" attitude with regard to upper airway surgery. The high incidence of persistent OSA justifies a systematic P(S)G control 2–4 months after the upper airway surgery.

As reported by our group in a previous study on 30 children with achondroplasia, none of the patients had isolated CSA (Julliand et al., 2012). CSA may increase the risk of sudden unexpected death in infants (Pauli et al., 1984), and as children with achondroplasia are still at a much higher risk of death compared with the general population (Simmons et al., 2014), CSA detection should be one of the criteria to be taken into account in favor of neurosurgical intervention. Neurosurgery was performed in six of our patients on the basis of abnormal cervical and cerebral MRI, sometimes associated with clinical symptoms, but not on the presence of CSA on a P(S)G. Unfortunately, P(S)G was not performed before neurosurgery in these six patients. Several studies have tried to identify non-radiological predictors of brain stem compression in infants with achondroplasia. (Waters et al., 1995) did not find any correlation between somesthetic potentials, CSA and brainstem compression in a group of 30 children with achondroplasia. Similar findings were observed by White *et al.* (White, Parnell, Kifle, Blackledge, & Bompadre, 2015) in a group of 17 achondroplastic children (mean age 2.4 years). These authors found that T2 cord signal abnormalities or clinical findings of clonus were the most predictive factors of the need of subsequent cord decompression, however these observations were weakened by the fact that five of the six patients with a CSAI > 5 events/hr were younger than 6 months old, as it is known that a CSAI up to10–20 events/hr may be observed in healthy infants during the first year of life (Ng and Chan, 2013). However, even if CSA is rare and insufficient as the only screening tool for foramen magnum stenosis, systematic overnight sleep studies with neuroimaging are recommended during infancy as stated by a recent international consensus agreement on evaluation and treatment of foramen magnum stenosis in achondroplasia during infancy (Trotter and Hall, 2005; White et al., 2016).

Although achondroplasia is associated with normal intelligence capacity, mild developmental delay or learning difficulties may be observed as a consequence of undertreated chronic upper airway obstruction, middle ear dysfunction, craniocervical junction stenosis, thoracolumbar kyphosis, bowing of the lower legs and psychological problems (Trotter and Hall, 2005). Neurocognitive dysfunction and abnormal behavior are the most common and severe consequences of OSA in children without underlying diseases (Marcus et al., 2012). Few studies have assessed the impact of sleep-disordered breathing in children with achondroplasia. A relationship has been observed between severe respiratory dysfunction with abnormal PSG and a lower intellectual potential in 13 achondroplastic infants (Hecht, Thompson, Weir, Patchell, & Horton, 1991) but very little is known about academic level of achondroplastic children in relation to the presence of sleep apneas. In our study, 62% of the school-aged children followed a standard academic course and only 17% attended a specialized school. We did not observe a correlation between the academic level and P(S)G results but many other factors may be involved in the development retardation and learning difficulties of achondroplastic children such as hypoacousia due to chronic serous otitis media (Ireland et al., 2011).

Our study has several limitations, such as its retrospective single centre design and the frequent use of PG instead of PSG. Our study population was not homogenous with regard to previous history and treatments and age distribution. P(S)G was not systematically performed before every surgical procedure in all the patients. However, compared to our previous experience, this study highlights how a more radical surgical approach to airway obstruction could

TABLE 4 Obstructive sleep apnea in children with achondroplasia: summary of the literature

Study, Year	Design	No. of patients	Age (years)	Previous treatments for sleep apnea	Diagnostic criteria for OSAS	OSAS prevalence	Treatments	Conclusion drown
Waters et al. (1995)	Prospective. PSG and somatosensory evoked potentials (SEPs) recorded before and after OSA treatment.	30	Median 6.6 (range 1–48)	Not reported	RDI (respiratory disturbance index) >5/hr	60%	Adeno-tonsillectomy (*n* = 4), Adeno-tonsillectomy + CPAP (*n* = 6), CPAP (*n* = 7), weight loss (*n* = 1)	High proportion of children had persisting OSA despite adeno-tonsillectomy. Improvement of sleep architecture and SEPs scores associated with RDI reduction after treatment.
Tasker et al. (1998)	Prospective. Clinical, cardiorespiratory, upper airway and neurological assessment of symptomatic children.	17	Mean 1.3 (range 0.3–3.5)	Not reported	4% SpO_2 dip rate >3/hr	100%	Adeno-tonsillectomy (*n* = 9), ventriculo-peritoneal shunt (*n* = 5), foramen magnum decompression (*n* = 2)	Identification of 3 distinct phenotypes of patients with sleep disordered breathing due to distinct anatomical aetiologies. Adeno-tonsillectomy is effective only in the least symptomatic group of patients.
Mogayzel et al. (1998)	Prospective. PSG performed before and after treatments.	88	Median 1.2 (range 0.1–12.6) at first PSG	Tracheostomy (*n* = 5), foramen magnum decompression (*n* = 9), ventriculo-peritoneal shunt (*n* = 6), tonsillectomy and/or adenoidectomy (*n* = 11), supplemental oxygen (*n* = 7)	AI (apnea index) >1/hr	19% (respiratory abnormalities in 48% of patients)	Adeno-tonsillectomy (*n* = 6), adeno-tonsillectomy + CPAP (*n* = 2), tracheostomy (*n* = 3), foramen magnum decompression (*n* = 6), foramen magnum decompression + ventriculo-peritoneal shunt (*n* = 3)	Hypoxemia is the most frequent sleep-related respiratory disturbance. A minority of patients have severe central or obstructive apnea, adeno-tonsillectomy is effective in reducing obstruction but not in all the cases. Restrictive syndrome can be present at a young age.

(Continues)

TABLE 4 (Continued)

Study, Year	Design	No. of patients	Age (years)	Previous treatments for sleep apnea	Diagnostic criteria for OSAS	OSAS prevalence	Treatments	Conclusion drown
Sisk et al. (1999)	Retrospective. PSG or clinical diagnosis of OSA before and after ENT surgery to evaluate the effectiveness of different approaches.	95	Mean 1.6 (range 0.7–14) at first clinical evaluation	Not reported	Desaturations>90% associated with hypopnea and obstruction or anamnestic recognition of apnea episodes	38%	Adeno-tonsillectomy (n = 22), adenoidectomy (n = 10), tonsillectomy (n = 2)	Surgery is effective but recurrent symptoms are common, particularly when initial procedure is adenoidectomy (90% requiring further surgery).
Collins and Choi (2007)	Retrospective. Descriptive statistics of common otolaryngological diagnoses.	22	Range 0.5–22	Not reported	Not reported. PSG performed only in symptomatic patients (n = 9)	27%	Adeno-tonsillectomy (n = 5), adenoidectomy (n = 2), foramen magnum decompression (n = 11)	Clinical improvement in all patients after adeno-tonsillectomy but high rate of OSA recidivism after ENT surgery.
Afsharpaiman et al. (2011)	Retrospective.	46	Mean 3.9 (range 0.3–14)	Not reported	AHI (apnea-hypopnea index) >5/hr	54%	Adeno-tonsillectomy (n = 11), CPAP (n = 9)	OSA was more frequent and more severe in children aged <2 years but frequent use of CPAP avoided tracheostomy. Positive neurological association between OSA and hydrocephalus.

(Continues)

TABLE 4 (Continued)

Study, Year	Design	No. of patients	Age (years)	Previous treatments for sleep apnea	Diagnostic criteria for OSAS	OSAS prevalence	Treatments	Conclusion drown
Schlüter et al. (2011)	Prospective. PSG performed before and after treatments.	22 + 2 hypocondroplasia	Median 3 (range 0.01–15)	Adenoidectomy (*n* = 11), tonsillectomy (*n* = 1), adeno-tonsillectomy (*n* = 2), ventriculo-peritoneal shunt (*n* = 3), foramen magnum decompression (*n* = 6).	Not reported in the abstract (full paper not available)	33% (respiratory abnormalities in 79% of patients)	Adenoidectomy (*n* = 1), tonsillectomy (*n* = 2), adeno-tonsillectomy (*n* = 2), CPAP (*n* = 3)	All achondroplastic children should be evaluated by PSG. Achondroplastic children with OSA, who do not benefit from adenoidectomy and/or adeno-tonsillectomy, should be treated with CPAP therapy.
Julliand et al. (2012)	Prospective. Evaluation of lung function and sleep disordered breathing performing polygraphic sleep study.	30	Median 3.0 (range 0.3–17)	Adenoidectomy (*n* = 5), adenoidectomy + turbinectomy (*n* = 3), turbinectomy (*n* = 1), tonsillectomy (*n* = 1)	AHI (apnea-hypopnea index) >5/hr	87% (respiratory abnormalities in 93% of patients)	Adeno-tonsillectomy + turbinectomy (*n* = 2), adenoidectomy + turbinectomy (*n* = 1), tonsillectomy (*n* = 1), NIV (*n* = 5)	Systematic sleep studies are recommended because of the high prevalence of sleep disordered breathing. Upper airway surgery and CPAP/NIV are effective treatments.

lower incidence of OSA in children with achondroplasia managed according to a protocolized respiratory management at a national reference center (Julliand et al., 2012).

In conclusion, our data confirm that OSA is common in children with achondroplasia. Children with achondroplasia should have systematic ENT and P(S)G evaluation until at least the age of 8 years. The observation of a reduced prevalence of OSA after (adeno-) tonsillectomy is in favor of this type of surgery when possible. However, correction of OSA should be checked by a P(S)G after every therapeutic intervention.

CONFLICT OF INTEREST

None.

REFERENCES

Afsharpaiman, S., Sillence, D. O., Sheikhvatan, M., Ault, J. E., & Waters, K. (2011). Respiratory events and obstructive sleep apnea in children with achondroplasia: Investigation and treatment outcomes. *Sleep and Breathing*, *15*, 755–761.

Baujat, G., Legeai-Mallet, L., Finidori, G., Cormier-Daire, V., & Le Merrer, M. (2008). Achondroplasia. *Best Practice and Research Clinical Rheumatology*, *22*, 3–18.

Bellus, G. A., Hefferon, T. W., Ortiz de Luna, R. I., Hecht, J. T., Horton, W. A., Machado, M., . . . Francomano, C. A. (1995). Achondroplasia is defined by recurrent G380R mutations of FGFR3. *American Journal of Human Genetics*, *56*, 368–373.

Berry, R. B., Budhiraja, R., Gottlieb, D. J., Gozal, D., Iber, C., Kapur, V. K., . . . Tangredi, M. M. American Academy of Sleep Medicine(2012). Rules for scoring respiratory events in sleep: Update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *Journal of Clinical Sleep Medicine*, *8*, 597–619.

Collins, W. O., & Choi, S. S. (2007). Otolaryngologic manifestations of achondroplasia. *Archives of Otolaryngology-Head and Neck Surgery*, *133*, 237–244.

Guilleminault, C., Li, K. K., Khramtsov, A., Pelayo, R., & Martinez, S. (2004). Sleep disordered breathing: Surgical outcomes in prepuberal children. *Laryngoscope*, *114*, 132–137.

Guilleminault, C., Li, K. K., Quo, S., & Inouye, R. (2004). A retrospective study of surgical outcomes of children with sleep disordered breathing. *Sleep*, *27*, 95–100.

Hecht, J. T., Thompson, N. M., Weir, T., Patchell, L., & Horton, W. A. (1991). Cognitive and motor skills in achondroplastic infants: Neurologic and respiratory correlates. *American Journal of Medical Genetics*, *41*, 208–211.

Holzman, R. S., Mancuso, T. J., & Polaner, D. M. (2008). *A Practical Approach to Pediatric Anesthesia*. 1st Edition. Philadelphia, USA: Lippincott Williams and Wilkins.

Horton, W. A., Hall, J. G., & Hecht, J. T. (2007). Achondroplasia. *The Lancet*, *370*, 162–167.

Ireland, P. J., McGill, J., Zankl, A., Ware, R. S., Pacey, V., Ault, J. E., . . . Johnston, L. M. (2011). Functional performance in young Australian children with achondroplasia. *Developmental Medicine and Child Neurology*, *53*, 944–950.

Julliand, S., Boulé, M., Baujat, G., Ramirez, A., Couloigner, V., Beydon, N., . . . Fauroux, B. (2012). Lung function, diagnosis, and treatment of sleep-disordered breathing in children with achondroplasia. *American Journal of Medical Genetics Part A*, *158A*, 1987–1993.

Mador, M. J., & Tobin, M. J. (1990). Apneustic breathing: A characteristic feature of brainstem compression in achondroplasia? *Chest*, *97*, 877–883.

Marcus, C. L., Brooks, L. J, Ward, S. D., Draper, K. A., Gozal, D., Halbower, A. C., . . . Spruyt, K. (2012). Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*, *130*, e714–e755.

Mogayzel, P. J., Jr., Carroll, J. L., Loughlin, G. M., Hurko, O., Francomano, C. A., & Marcus, C. L. (1998). Sleep-disordered breathing in children with achondroplasia. *Jornal de Pediatria*, *132*, 667–671.

Nelson, F. W., Hecht, J. T., Horton, W. A., Butler, I. J., Goldie, W. D., & Miner, M. (1988). Neurological basis of respiratory complications in achondroplasia. *Annals of Neurology*, *24*, 89–93.

Ng, D. K., & Chan, C. H. (2013). A review of normal values of infant sleep polysomnography. *Pediatrics & Neonatology*, *54*, 82–87.

Pauli, R. M., Scott, C. I., Wassman, E. R., Jr., Gilbert, E. F., Leavitt, L. A., Ver Hoeve, J., . . . Sommer, A. (1984). Apnea and sudden unexpected death in infants with achondroplasia. *Jornal de Pediatria*, *104*, 342–348.

Schlüter, B., De Sousa, G., Trowitzsch, E., & Andler, W. (2011). Diagnostics and management of sleep-related respiratory disturbances in children with skeletal dysplasia caused by FGFR3 mutations (achondroplasia and hypochondroplasia). *Georgian Medical News*, *196–197*, 63–72.

Shiang, R., Thompson, L. M., Zhu, Y. Z., Church, D. M., Fielder, T. J., Bocian, M., . . . Wasmuth, J. J. (1994). Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. *Cell*, *78*, 335–342.

Simmons, K., Hashmi, S. S., Scheuerle, A., Canfield, M., & Hecht, J. T. (2014). Mortality in babies with achondroplasia: Revisited. *Birth Defects Research Part A, Clinical and Molecular Teratology*, *100*, 247–249.

Sisk, E. A., Heatley, D. G., Borowski, B. J., Leverson, G. E., & Pauli, R. M. (1999). Obstructive sleep apnea in children with achondroplasia: Surgical and anesthetic considerations. *Otolaryngology Head and Neck Surgery*, *120*, 248–254.

Stokes, D. C., Phillips, J. A., Leonard, C. O., Dorst, J. P., Kopits, S. E., Trojak, J. E., . . . Brown, D. L. (1983). Respiratory complications of achondroplasia. *Jornal de Pediatria*, *102*, 534–541.

Tasker, R. C., Dundas, I., Laverty, A., Fletcher, M., Lane, R., & Stocks, J. (1998). Distinct patterns of respiratory difficulty in young children with achondroplasia: A clinical, sleep, and lung function study. *Archives of Disease in Childhood*, *79*, 99–108.

Trotter, T. L., & Hall, J. G. American Academy of Pediatrics Committee on Genetics(2005). Health supervision for children with achondroplasia. *Pediatrics*, *116*, 771–783.

Uliel, S., Tauman, R., Greenfeld, M., & Sivan, Y. (2004). Normal polysomnographic respiratory values in children and adolescents. *Chest*, *125*, 872–878.

Waters, K. A., Everett, F., Sillence, D., Fagan, E. R., & Sullivan, C. E. (1993). Breathing abnormalities in sleep in achondroplasia. *Archives of Disease in Childhood*, *69*, 191–196.

Waters, K. A., Everett, F., Sillence, D. O., Fagan, E. R., & Sullivan, C. E. (1995). Treatment of obstructive sleep apnea in achondroplasia. Evaluation of sleep, breathing, and somatosensory-evoked potentials. *American Journal of Medical Genetics*, *59*, 460–466.

White, K. K., Bompadre, V., Goldberg, M. J., Bober, M. B., Campbell, J. W., Cho, T. J., . . . Savarirayan, R. (2016). Best practices in the evaluation and treatment of foramen magnum stenosis in

achondroplasia during infancy. *American Journal of Medical Genetics Part A*, *170*, 42–51.

White, K. K., Parnell, S. E., Kifle, Y., Blackledge, M., & Bompadre, V. (2015). Is there a correlation between sleep disorderd breathing ad formanen magnum stenosis in children with achondroplasia? *American Journal of Medical Genetics Part A*, *9999A*, 1–10.

Wynn J., King T. M., Gambello M. J., Waller D. K., & Hecht J. T. 2007. Mortality in Achondroplasia Study: A 42-Year follow-up. *American Journal of Medical Genetics Part A 143A*: 2502–2511.

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ORIGINAL ARTICLE

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Obstructive sleep apnea in Down syndrome: Benefits of surgery and noninvasive respiratory support

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Children with Down syndrome are at increased risk of obstructive sleep apnea (OSA). The aim of the study was to describe the management of OSA in a large cohort of children with Down syndrome. A retrospective analysis of sleep studies and consequent management was performed for all consecutive Down syndrome patients evaluated between September 2013 and April 2016. The data of 57 patients were analyzed: 51/53 had an interpretable overnight polygraphy and 4 the recording of nocturnal gas exchange. Mean age at baseline sleep study was 6.2 ± 5.9 years. Eighteen patients (32%) had prior upper airway surgery. Mean apnea-hypopnea index (AHI) was 14 ± 16 events/hr with 41 of the 51 (80%) patients having OSA with an AHI >1 event/hr and 20 patients (39%) having an AHI ≥10 events/hr. Consequently, eight patients (14%) had upper airway surgery. OSA improved in all patients except two who needed noninvasive respiratory support. Nineteen (33%) patients required noninvasive respiratory support. Mean age at noninvasive respiratory support initiation was 7 ± 7 years. On 11 patients with objective adherence data available, mean compliance at 2 ± 1 years of treatment was excellent with an average use per night of 8 hr46 ± 3 hr59 and 9 patients using the noninvasive respiratory support >4 hr/night. Noninvasive respiratory support was associated with an improvement of nocturnal gas exchange. The prevalence of OSA is high in Down syndrome. Upper airway surgery is not always able to correct OSA. Noninvasive respiratory support represents then an effective treatment for OSA and good compliance may be achieved in a majority of patients.

KEYWORDS
continuous positive airway pressure, Down syndrome, noninvasive ventilation, sleep apnea, treatment adherence, upper airway surgery

1 | INTRODUCTION

Down syndrome (DS), defined by an extra copy of chromosome 21, is the commonest chromosomal disorder (Parker et al., 2010), with an estimated prevalence in the United States from 9.0 to 11.8 per 10,000 live births (Shin et al., 2009). Patients with DS are predisposed to upper airway obstruction and obstructive sleep apnea (OSA) due to altered craniofacial anatomy with midfacial and mandibular hypoplasia, glossoptosis with relative macroglossia, frequent adenotonsillar hypertrophy, muscle hypotonia with an increased prevalence of pharyngo-laryngomalacia and subglottic and/or tracheal stenosis (Lal, White, Joseph, van Bakergem, & LaRosa, 2015). These anatomical predisposing factors for OSA are aggravated by obesity, hypothyroidism, and gastroesophageal reflux disease (Lal et al., 2015). Sleep-disordered breathing is common in patients with DS with a prevalence of OSA between 30% and 66% (Alexander et al., 2016; Bassell, Phan, Leu, Kronk, & Visootsak, 2015; Lal et al., 2015). Moreover, patients with DS tend to have severe OSA (Goffinski et al., 2015) which adversely affects language, neurocognitive development, behavior, functional outcome, and quality of life (Breslin et al., 2014; Brooks et al., 2015; Churchill, Kieckhefer, Bjornson, & Herting, 2015; Edgin et al., 2015).

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Adeno-tonsillectomy represents the first line surgical treatment for severe OSA (Lal et al., 2015). However, adeno-tonsillectomy is significantly less effective in children with DS as compared to non-DS children (Shete, Stocks, Sebelik, & Schoumacher, 2010). In the case of persistent OSA, noninvasive continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV) in the case of associated alveolar hypoventilation, is recommended (Amaddeo, Moreau et al., 2016; Kaditis et al., 2016). However, the implementation of CPAP/NIV may be more difficult and therapeutic compliance may be reduced in patients with DS as compared to non-DS patients (Brooks et al., 2015).

The aim of the study was first, to describe the sleep respiratory parameters of a large cohort of DS patients and second, the management of OSA with a particular emphasis on upper airway surgery and CPAP/NIV.

2 | MATERIALS AND METHODS

2.1 | Patients

Clinical and sleep study data of all consecutive DS patients followed at the sleep unit of Necker Children hospital (Paris, France), between September 2013 and April 2016 were retrospectively analyzed. Follow-up data were collected for patients who underwent upper airway surgery and/or who were treated with CPAP/NIV.

2.2 | Sleep data

All sleep studies were performed in the sleep laboratory of Necker hospital. All patients were accompanied by one parent throughout the night. Neither sedation nor sleep deprivation were used on any patient.

The following standardized measurements were simultaneously recorded during every polygraphy: nasal flow through a nasal pressure transducer, pulse oximetry by a pulse oximeter (SpO_2), thoracic and abdominal respiratory inductance plethysmography, synchronized infrared video monitoring (Cidelec, St. Gemme sur Loire, France or Alice 6, Philips Respironics, St. Priest, France), and transcutaneous carbon dioxide pressure ($PtcCO_2$, SenTec, Thurnwill, Switzerland).

Scoring of respiratory events was performed according to the 2012 scoring rules of the American Academy of Sleep Medicine (Berry et al., 2012). The following definitions for respiratory events were used for scoring purposes (Berry et al., 2012). Obstructive apnea (OA) was defined as the absence of nasal airflow with continued chest wall and abdominal movements for at least two breaths. Central apnea (CA) was defined as the absence of airflow with the cessation of respiratory effort, lasting more than 20 s or of shorter duration and associated with an arousal and/or a 3% oxygen desaturation. CA occurring after gross body movements or after sighs were not included in the analysis. Mixed apnea was defined as an apnea that usually begins as central and ends as obstructive according to changes in the chest, abdominal, and flow traces. Hypopnea was defined as a decrease in nasal airflow of at least 30% with a corresponding decrease in SpO_2 of at least 3% and/or an arousal. The apnea-hypopnea index (AHI) was calculated as the sum of apneas and hypopneas per hour of time on bed. The obstructive AHI was defined as the number of obstructive apneas-hypopneas per hour of time in bed with an obstructive AHI (OAHI) < 2 events/hr being considered as normal (Marcus et al., 1992; Montgomery-Downs, O'Brien, Gulliver, & Gozal, 2006; Uliel, Tauman, Greenfeld, & Sivan, 2004). Central apnea index (CAI) was defined as the number of central apneas per hour of time in bed, with a CAI < 5 events/hr being considered as normal (Kritzinger, Al-Saleh, & Narang, 2011).

Mean and minimum SpO_2 values were calculated. The oxygen desaturation index (ODI) was defined as the number of SpO_2 drops of at least 3% per hour of total time in bed. Mean and maximal values of $PtcCO_2$ were gathered and the percentage of total time in bed spent with a $PtcCO_2$ > 50 mmHg were calculated. All the SpO_2/$PtcCO_2$ data that were not interpretable (probe detachment, outlier data, artifacts) were discarded from the analysis.

2.3 | Upper airway surgery

All patients were evaluated by a pediatric ear, nose, and throat (ENT) surgeon. Upper airway surgery with adenoidectomy ± tonsillectomy ± turbinectomy were variably performed according to the clinical ENT examination in case of an AHI > 5 events/hr (Kaditis et al., 2016).

2.4 | CPAP/NIV

Continuous positive airway pressure was initiated in case of an AHI > 10 events/hr, despite upper airway surgery or when upper airway surgery was not indicated, by a pediatrician and a nurse with expertise in CPAP/NIV and therapeutic education (Amaddeo, Frapin, & Fauroux, 2016; Amaddeo, Moreau et al., 2016). CPAP/NIV was started in an out-patient setting in selected patients, or during a short hospitalization of two to three nights in patients with severe behavioral problems or neurocognitive impairment. CPAP titration was performed during a daytime nap study in the outpatient setting and during the night in the inpatient setting (Kushida et al., 2008). CPAP was changed for NIV in case of persistent desaturations and/or hypercapnia despite the highest tolerated CPAP pressure (Kushida et al., 2008). Continuous positive airway pressure/NIV initiation was performed within a specific therapeutic education program adjusted on mental age, cognition, and cooperation. The therapeutic education tools integrated booklets, a teddy bear breathing with NIV, and playful evaluation tools (see http://vnietsommeil.aphp.fr and Online Supplement). Patients were discharged after a therapeutic education session. Home visits with overnight gas exchange recording were performed every 2 weeks during the first 2 months and then every 1–3 months by technicians trained in pediatric CPAP/NIV. Patient adherence data were downloaded from the in-built software of the device during the routine hospital and home care provider visits (Ramirez et al., 2013). The mean daily adherence, the mean number of nights with CPAP/NIV use, and the number of nights the patient used CPAP/NIV for more than 4 hr were analyzed. The duration of home CPAP/NIV use also was reported.

2.5 | Statistical analysis

Data are expressed as mean ± standard deviation, median (range). The comparison of the characteristics of the patients was performed using the Student's *t*-test in case of normal distribution or Mann–Whitney rank sum test otherwise. Comparisons between qualitative variables were done using the χ^2 test. The comparison of the nocturnal gas exchanges before and after the initiation of the CPAP/NIV was done using the paired *t*-test in case of normal distribution or the Wilcoxon signed rank test otherwise. A *p*-value ≤ 0.05 was considered as statistically significant.

3 | RESULTS

3.1 | Patients and sleep data

Fifty-seven patients were included in the study (Table 1). Mean age at baseline sleep study was 6.2 ± 5.9 years. Associated disorders were common with 58% of the patients having an associated cardiopathy, 30% being treated for hypothyroidism and/or asthma, and 23% being treated for gastro-oesophageal reflux. Eighteen (32%) patients had prior upper airway surgery at a mean age of 5.1 ± 3.4 years before the baseline sleep study, with a majority of patients having adenoidectomy and/or tonsillectomy.

The results of the baseline sleep study are shown in Table 2. Fifty-three patients had a polygraphy with recording of nocturnal gas exchange and four had only a recording of nocturnal gas exchange.

TABLE 1 Characteristics of the patients

	Total population, *n* = 57
Age at first study (years), mean ± SD, median [min;max]	6.2 ± 5.9, 4.0 [0.2;24.7]
Male/female (number)	31/26
Body mass index, mean ± SD (Kg/m^2)	19.0 ± 4.9
Body mass index *z*-score, mean ± SD	1.7 ± 4.0
Associated disorders	
Cardiopathy (*n*, %)	33 (58)
Ventricular septal defect (*n*)	8
Atrial septal defect (*n*)	9
Ventricular atrial communication (*n*)	8
Other (*n*)	14
Arterial pulmonary hypertension (*n*, %)	11 (19)
Hypothyroidism (*n*, %)	17 (30)
Asthma (*n*, %)	17 (30)
Gastro-oesophageal reflux (*n*, %)	13 (23)
Prior upper airway surgery (*n*, %)	18 (32)
Adenoidectomy (*n*)	15
Tonsillectomy (*n*)	17
Turbinoplasty (*n*)	2
Other (*n*)	2

Two polygraphies were not interpretable. Mean AHI was 14 ± 16 events/hr, with 20 of the 51 patients (39%) having severe OSA defined by an AHI ≥ 10 events/hr (Table 2 and Figure 1). OSA was observed at any age (Figure 1). Of the 26 patients younger than the age of 4 years, 22 (85%) had an AHI > 1 event/hr, 16 (62%) had an AHI > 5 events/hr, and 11 (42%) had an AHI ≥ 10 events/hr.

Of the 18 patients who had upper airway surgery before the baseline sleep study, 6 had an AHI between 1 and 5 events/hr, 2 an AHI between 5 and 10 events/hr, and 4 an AHI ≥ 10 events/hr (Supplementary Online Table S1). The mean age of the patients who had prior upper airway surgery was higher than the age of patients who did not have prior upper airway surgery (Supplementary Online Table S1). There was a trend for mean AHI to be higher in patients without prior surgery (16 ± 18 events/hr) as compared to those with

TABLE 2 Baseline sleep data of the 57 patients

Respiratory events (*n* = 51)	
Mean AHI (events/hours), mean ± SD, median [min;max]	14 ± 16, 7 [0;62]
AHI ≤ 1 events/hr, *n* (%)	10 (19)
AHI > 1 and ≤5 events/hr, *n* (%)	12 (24)
AHI > 5 and <10 events/hr, *n* (%)	9 (18)
AHI ≥ 10 events/hr, *n* (%)	20 (39)
Mean central AI (events/hours), mean ± SD, median [min;max]	1 ± 2, 0 [0;10]
Central AI > 5 events/hr, *n* (%)	4 (8)
Mean obstructive AI (events/hours), mean ± SD, median [min;max]	8 ± 11, 3 [0;45]
Obstructive AI > 5 events/hr, *n* (%)	16 (31)
Obstructive AI > 10 events/hr, *n* (%)	10 (19)
Nocturnal gas exchange (*n* = 57)[a]	
Mean SpO_2 (%), mean ± SD, median [min;max]	95 ± 3, 96 [82;99]
Minimal SpO_2 (%), mean ± SD, median [min;max]	83 ± 14, 86 [61;98]
% of time with SpO_2 < 90% (%)	13 ± 29, 0 [0; 100]
Patients with >10% of time with a SpO_2 < 90%, *n* (%)	9 (18)
Mean 3% ODI (events/hours), mean ± SD, median [min;max]	17 ± 21, 10 [2;86]
ODI > 10 events/hr, *n* (%)	24 (47)
Mean $PtcCO_2$ (mmHg), mean ± SD, median [min; max]	43 ± 5, 43 [34;53]
Maximal $PtcCO_2$ (mmHg), mean ± SD, median [min;max]	48 ± 6, 47 [36;68]
% of time with $PtcCO_2$ > 50 mmHg (%), mean ± SD, median [min;max]	4 ± 17, 0 [0;95]
Patients with >10% of time with a $PtcCO_2$ > 50 mmHg, *n* (%)	3 (6)

AHI, apnea-hypopnea index; AI, apnea index; ODI, oxygen desaturation index; SpO_2, pulse oximetry; $PtcCO_2$, transcutaneous carbon dioxide.
[a]Four patients had only nocturnal gas exchange without a polygraphy, the nocturnal gas exchange data of these patients are included in the gas exchange data.

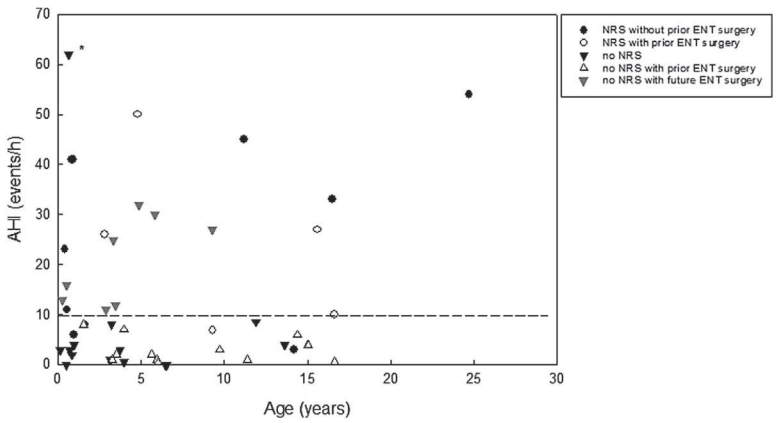

FIGURE 1 Apnea-hypopnea index (AHI) according to the age of the patient and his medical history. NRS, noninvasive respiratory support (including continuous positive airway pressure or noninvasive ventilation); ENT, ear, nose, and throat

prior surgery (9 ± 13 events/hr) but this was not statically significant ($p = 0.054$) (Supplementary Online Table S1). Similar results were observed for the mean obstructive AI. Only the ODI and the minimal SpO_2 differed between the two groups. Indeed, the ODI was higher and minimal SpO_2 was lower in patients without prior upper airway surgery as compared to those with prior surgery (20 ± 22/hr vs. 11 ± 18/hr, $p = 0.033$ for the ODI and 82 ± 8% vs. 89 ± 6%, $p = 0.003$ for minimal SpO_2).

Four patients had severe symptoms of sleep disordered breathing with witnessed apneas and arousals, snoring, and sweating which justified prompt overnight gas exchange assessment. The abnormalities of gas exchange in room air required immediate CPAP, which was initiated in the intensive care unit for two patients (Figure 2). These patients did not have a polygraphy but their baseline nocturnal gas exchange data are included in Table 2.

3.2 | Therapeutic management of OSA

Eight patients with severe OSA (AHI ≥ 10 events/hr) had upper airway surgery after the baseline sleep study with seven children having adenoidectomy and tonsillectomy and one adenoidectomy only (Table 3 and Figure 2). Patients treated with ENT surgery had a higher AHI than those not treated with ENT surgery (mean AHI 26 ± 11 vs. 13 ± 19 events/hr, $p = 0.045$). In the five patients who had a control sleep study after surgery, mean AHI decreased from 26 ± 11 events/hr before surgery to 13 ± 19 events/hr after surgery. A control sleep study is planned in the three remaining patients. Two patients subsequently required CPAP (Figure 2) because of persistent OSA (AHI of 47 and 11 events/hr) despite ENT surgery (Figure 2).

Nineteen (33%) patients required CPAP ($n = 15$) or NIV ($n = 4$) after the baseline sleep study (Table 4). The four patients treated with NIV had persistent alveolar hypoventilation despite CPAP. Patients who required CPAP/NIV did not differ from those who did not require CPAP/NIV with regard to age (5.9 ± 4.9 years vs. 6.9 ± 7.7, $p = 0.839$) and to mean BMI *z*-score (p = NS) (Supplementary Online Table S2) but they had a higher mean AHI (26 ± 18/hr) than those not requiring this treatment (9 ± 13/hr, $p < 0.001$) (Supplementary Online Table S3). Similarly, mean OAI and ODI were also higher in the patients requiring CPAP/NIV than those who did not (Supplementary Online Table S3).

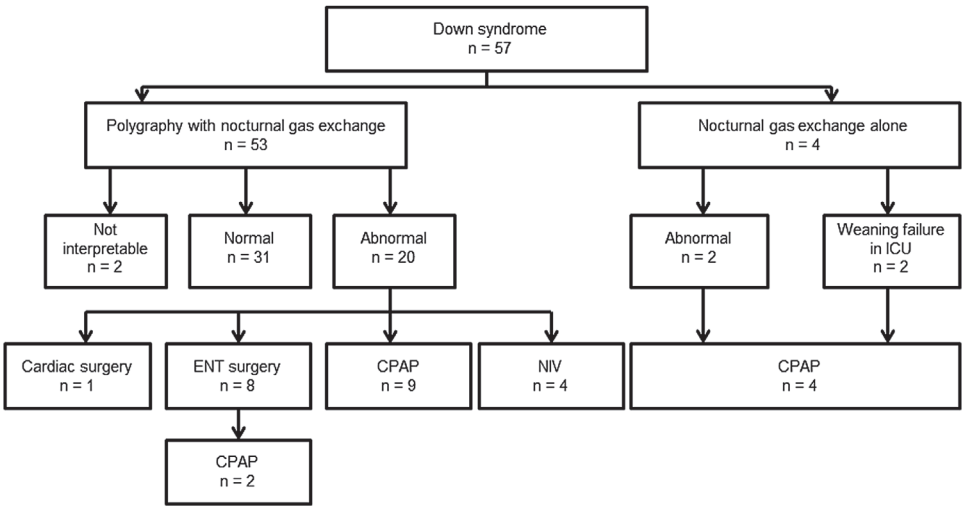

FIGURE 2 Flow chart of the patients. ICU, intensive care unit; CPAP, continuous positive airway pressure; NIV, noninvasive ventilation; ENT, ear, nose, and throat

TABLE 3 Efficacy of upper airway surgery and CPAP/NIV on nocturnal gas exchange

	Upper airway surgery			CPAP/NIV		
	Before surgery (n = 8)	After surgery (n = 5)[a]	p-value	Before CPAP/NIV (n = 19)	With CPAP/NIV (n = 16)	p-value
Mean delay (years)	Not applicable	0.5 ± 0.1,		Not applicable	0.8 ± 0.7,	
		0.5 [0.4;0.7]			0.6 [0;1.9]	
Mean SpO_2 (%)	94 ± 3,	96 ± 1,	0.269	94 ± 4,	96 ± 2,	0.142
	94 [89;97]	97 [94;97]		94 [86;99]	96 [92;99]	
Minimal SpO_2 (%)	77 ± 9,	84 ± 7,	0.063	82 ± 7,	88 ± 6,	0.02
	81 [61;85]	88 [73;88]		82 [71;93]	90 [73;95]	
% of time with SpO_2 < 90% (%)	8 ± 17,	0 ± 0,	0.205	21 ± 34,	1 ± 3,	0.01
	1 [0;49]	0 [0;0]		1 [0;100]	0 [0;11]	
ODI (events/hr)	26 ± 14,	18 ± 22,	0.267	30 ± 26,	5 ± 5,	0.003
	25 [11;48]	[8;57]		23 [2;76]	3 [92;99]	
Mean $PtcCO_2$ (mmHg)	44 ± 5,	45 ± 3,	0.624	43 ± 5,	42 ± 5,	0.131
	46 [37;49]	45 [42;48]		43 [36;53]	42 [31;48]	
Maximal $PtcCO_2$ (mmHg)	52 ± 5,	49 ± 4,	0.501	50 ± 7,	47 ± 3,	0.137
	52 [46;58]	49 [47;54]		48 [40;68]	48 [42;52]	
% of time with $PtcCO_2$ > 50 mmHg (%)	6 ± 13,	6 ± 13,	0.500	0 ± 1,	0 ± 0,	1
	0 [0;30]	0 [0;25]		0 [0;2]	0 [0;0]	

CPAP, continuous positive airway pressure; NIV, noninvasive ventilation; SpO_2, pulse oximetry; ODI, oxygen desturation index, $PtcCO_2$, transcutaneous carbon dioxide pressure.
Data are presented as mean ± SD and median [range].
[a]n = 5 because three patients are scheduled for a sleep study.

Upper airway surgery and CPAP/NIV were associated with an improvement of nocturnal gas exchange (Table 3). All the parameters improved but this was significant only for minimal SpO_2, the percentage of time with SpO_2 < 90%, and the ODI.

The data concerning CPAP/NIV are shown in Table 4. The mean age at CPAP/NIV initiation was 7 ± 7 years with a wide range (0.4–23 years). Mean duration of treatment at the time of the study was 2 ± 1 years. CPAP/NIV adherence was available only in 11 patients, mainly because of a too young age in 4 patients which did not allow an accurate interpretation of actual ventilator use (Caldarelli et al., 2013). Compliance was good with an average use per night of 8 hr46 ± 3 hr59 and 9/11 patients using CPAP/NIV > 4 hr/night. Three patients could be successfully weaned from CPAP/NIV. Finally, no complications were observed with surgery or CPAP/NIV.

4 | DISCUSSION

This study confirms the high prevalence and severity of OSAS in children with DS and the limited efficacy of upper airway surgery to prevent or cure OSA. CPAP/NIV was necessary in 33% of the patients and highly efficient on nocturnal gas exchange. Importantly, a good compliance could be obtained in the majority of patients.

The high prevalence and increased severity of OSA in patients with DS has been observed in all age groups. Sleep apnea was increased three- to fourfold in children and adults in a large epidemiological study performed in Australia which compared the prevalence of acquired cardiovascular diseases in 4,081 patients with DS and 16,324 controls over a period of 17 years (Sobey et al., 2015). Another large epidemiological study analyzed the global morbidity associated with DS in a cohort of 6,430 patients with DS and 19,176 controls in the United Kingdom over a period of 9 years (Alexander et al., 2016). The global incidence rate ratio for OSA in the patients with DS versus controls was 5.3. The risk of OSA has been shown to be even more important in young children. Indeed, in a group of 59 infants <6 months of age, referred to a DS clinic at a tertiary hospital because of symptoms of sleep-disordered breathing, 95% had an AHI ≥ 2/hr and 71% met the criteria for severe OSA with an AHI ≥ 10/hr (Goffinski et al., 2015). The diagnosis and effective treatment of OSA in infants and children with DS is of paramount importance as poor sleep quality and OSAS have been shown to be associated with poor cognitive function, and in particular verbal intelligence quotient and cognitive flexibility (Breslin et al., 2014; Brooks et al., 2015), language development (Edgin et al., 2015), and functional outcomes in daily life (Churchill et al., 2015). The present study confirms the high prevalence and severity of OSA in children with DS with 29 patients (57%) having an abnormal AHI and 20 (39%) severe OSA with an AHI ≥ 10/hr.

Adeno-tonsillectomy has a limited efficacy on OSA in DS. In a small study that evaluated 11 children with DS, mean AHI decreased from 15.3 ± 12.6 events/hr before adeno-tonsillectomy to 9.1 ± 10.5 after surgery with 6 of the 11 patients requiring CPAP or NIV for persistent OSA (Shete et al., 2010). Our study confirms the limited

TABLE 4 Continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) and adherence (n = 19)

Age at initiation (years)	7 ± 7, 4 [0.4;23]
Duration of CPAP/NIV treatment (years)	2 ± 1, 2 [0.2;4.8]
CPAP (n = 15)	
CPAP level (cmH_2O)	8 ± 1, 8 [6;9]
NIV (n = 4)	
Inspiratory pressure level (cmH_2O)	13 ± 2, 12 [12;17]
Expiratory pressure level (cmH_2O)	7 ± 1, 8 [5;8]
Interfaces	
Nasal mask (n)	17
Nasobuccal mask (n)	2
CPAP/NIV adherence (from the in-built software)	
Average use per night (hr:min)	8 hr46 ± 3 hr59, 10 hr33 [1 hr00;13 hr00]
Number of patient using CPAP/NIV>4 hr/night (n)[a]	9/11 (82%)[a]
Failure of long term CPAP/NIV (n)	5
Successful weaning of CPAP/NIV (n)	3

Data are presented as mean ± SD and median [range].
[a]CPAP/NIV adherence was available only in 11 patients.

benefit of upper airway surgery in children with DS. Indeed, even if adeno-tonsillectomy was associated with a significant improvement of OSA, almost half of the children had persistent OSA, which was not correlated to age, gender, or BMI z-score (Maris, Verhulst, Wojciechowski, Van de Heyning, & Boudewyns, 2017). These results may be explained by the multifactorial nature of the upper airway obstruction associating anatomical and functional factors such as midfacial and mandibular hypoplasia, glossoptosis with relative macroglossia, and muscle hypotonia (Lal et al., 2015). A systematic sleep study is thus recommended before and after each upper airway surgery in patients with DS.

Continuous positive airway pressure or NIV in case of alveolar hypoventilation, is indicated if OSA persists after upper airway surgery (Amaddeo, Moreau et al., 2016; Kaditis et al., 2016). One-third (33%) of the patients in the present study required CPAP/NIV, which underlines the severity of OSA in this population. The AHI threshold for CPAP/NIV initiation has not been validated in children but levels AHI > 5 or 10 events/hr are usual (Amaddeo, Moreau et al., 2016; Kaditis et al., 2016). However, in clinical practice, the initiation of CPAP/NIV is based on an association of clinical symptoms and sleep parameters, taking in account not only the AHI but also the SpO_2 and $PtcCO_2$ levels, as well as sleep quality (Amaddeo, Frapin et al., 2016). CPAP and NIV are very effective to treat OSA ± alveolar hypoventilation, as shown by the significant improvement of nocturnal gas exchange in the present study (Table 3). Of note, four patients had such severely abnormal gas exchange that a polygraphy was not necessary for the initiation of CPAP or NIV which was started immediately (and in the intensive care unit for two patients).

The major problem of CPAP/NIV in children with DS is compliance with treatment. Poor compliance or refusal of CPAP/NIV is significantly more common in these patients as compared to patients without DS, mainly because of behavioral disorders and neurocognitive impairment. In a recent study, the patients who did not comply with CPAP were deficient in tests of adaptive behavior, visual-motor integration, and achievement (Brooks et al., 2015). However, good compliance may be achieved, as observed in the present study, with a pediatric CPAP/NIV team, having an expertise in therapeutic education and CPAP/NIV (Amaddeo et al., 2015; Caldarelli et al., 2013). Indeed, the objective compliance in our patients was excellent with an average use of CPAP/NIV per night of 8 hr46 ± 3 hr59 and 9/11 patients using CPAP/NIV>4 hr/night (Table 4). Five patients did not tolerate CPAP/NIV treatment because of major behavioral disorders and family dysfunction.

We are aware of the limitations of our study. First, it was a single-center, retrospective study explaining that adherence data were incomplete. Second, the patients had a polygraphy and not a polysomnography which does not give information on sleep architecture and sleep quality and may underestimate the numbers of hypopneas (Tan, Gozal, Ramirez, Bandla, & Kheirandish-Gozal, 2014). Finally, poly(somno)graphy was not systematically performed before all upper airway surgery.

In conclusion, the present study confirms the high prevalence and increased severity of OSA in children with DS. Upper airway surgery represents a first line treatment but has a limited efficacy. CPAP or NIV represent a very effective therapeutic option in case of persistent OSA after upper airway surgery. The major problem of CPAP/NIV is compliance but good results may be achieved by an experienced pediatric CPAP/NIV team.

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CONFLICT OF INTEREST

All the authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

Alexander, M., Petri, H., Ding, Y., Wandel, C., Khwaja, O., & Foskett, N. (2016). Morbidity and medication in a large population of individuals with Down syndrome compared to the general population. *Developmental Medicine & Child Neurology*, *58*, 246–254.

Amaddeo, A., Caldarelli, V., Fernandez-Bolanos, M., Moreau, J., Ramirez, A., Khirani, S., & Fauroux, B. (2015). Polygraphic respiratory events during sleep in children treated with home continuous positive airway pressure: Description and clinical consequences. *Sleep Medicine*, *16*, 107–112.

Amaddeo, A., Moreau, J., Frapin, A., Khirani, S., Felix, O., Fernandez-Bolanos, M., . . . Fauroux, B. (2016). Long term continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) in children: Initiation criteria in real life. *Pediatric Pulmonology*, *51*, 968–974.

Amaddeo, A., Frapin, A., & Fauroux, B. (2016). Long-term non-invasive ventilation in children. *The Lancet Respiratory Medicine*, *4*, 999–1008.

Bassell, J. L., Phan, H., Leu, R., Kronk, R., & Visootsak, J. (2015). Sleep profiles in children with Down syndrome. *American Journal of Medical Genetics Part A*, *167A*, 1830–1835.

Berry, R. B., Budhiraja, R., Gottlieb, D. J., Gozal, D., Iber, C., Kapur, V. K., . . . Tangredi, M. M. (2012). Rules for scoring respiratory events in sleep: Update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. *Journal of Clinical Sleep Medicine*, *8*, 597–619.

Breslin, J., Spanò, G., Bootzin, R., Anand, P., Nadel, L., & Edgin, J. (2014). Obstructive sleep apnea syndrome and cognition in Down syndrome. *Developmental Medicine & Child Neurology*, *56*, 657–664.

Brooks, L. J., Olsen, M. N., Bacevice, A. M., Beebe, A., Konstantinopoulou, S., & Taylor, H. G. (2015). Relationship between sleep, sleep apnea, and neuropsychological function in children with Down syndrome. *Sleep and Breathing*, *19*, 197–204.

Caldarelli, V., Borel, J. C., Khirani, S., Ramirez, A., Cutrera, R., Pépin, J. L., & Fauroux, B. (2013). Polygraphic respiratory events during sleep with noninvasive ventilation in children: Description, prevalence, and clinical consequences. *Intensive Care Medicine*, *39*, 739–746.

Churchill, S. S., Kieckhefer, G. M., Bjornson, K. F., & Herting, J. R. (2015). Relationship between sleep disturbance and functional outcomes in daily life habits of children with Down syndrome. *Sleep*, *38*, 61–71.

Edgin, J. O., Tooley, U., Demara, B., Nyhuis, C., Anand, P., & Spanò, G. (2015). Sleep disturbance and expressive language development in preschool-age children with Down syndrome. *Child Development*, *86*, 1984–1998.

Goffinski, A., Stanley, M. A., Shepherd, N., Duvall, N., Jenkinson, S. B., Davis, C., . . . Roper, R. J. (2015). Obstructive sleep apnea in young infants with Down syndrome evaluated in a Down syndrome specialty clinic. *American Journal of Medical Genetics Part A*, *167A*, 324–330.

Kaditis, A. G., Alonso Alvarez, M. L., Boudewyns, A., Alexopoulos, E. I., Ersu, R., Joosten, K., . . . Verhulst, S. (2016). Obstructive sleep disordered breathing in 2- to 18-year-old children: Diagnosis and management. *European Respiratory Journal*, *47*, 69–94.

Kritzinger, F. E., Al-Saleh, S., & Narang, I. (2011). Descriptive analysis of central sleep apnea in childhood at a single center. *Pediatric Pulmonology*, *46*, 1023–1030.

Kushida, C. A., Chediak, A., Berry, R. B., Brown, L. K., Gozal, D., Iber, C., . . . Medicine AAoS. (2008). Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. *Journal of Clinical Sleep Medicine*, *4*, 157–171.

Lal, C., White, D. R., Joseph, J. E., van Bakergem, K., & LaRosa, A. (2015). Sleep-disordered breathing in Down syndrome. *Chest*, *147*, 570–579.

Marcus, C. L., Omlin, K. J., Basinki, D. J., Bailey, S. L., Rachal, A. B., Von Pechmann, W. S., . . . Ward, S. L. (1992). Normal polysomnographic values for children and adolescents. *American Review of Respiratory Disease*, *146*, 1235–1239.

Maris, M., Verhulst, S., Wojciechowski, M., Van de Heyning, P., & Boudewyns, A. (2017). Outcome of adenotonsillectomy in children with Down syndrome and obstructive sleep apnoea. *Archives of Disease in Childhood*, *102*, 331–336.

Montgomery-Downs, H. E., O'Brien, L. M., Gulliver, T. E., & Gozal, D. (2006). Polysomnographic characteristics in normal preschool and early school-aged children. *Pediatrics*, *117*, 741–753.

Parker, S. E., Mai, C. T., Canfield, M. A., Rickard, R., Wang, Y., Meyer, R. E., . . . Network NBDP. (2010). Updated National birth prevalence estimates for selected birth defects in the United States, 2004-2006. *Birth Defects Research Part A, Clinical and Molecular Teratology*, *88*, 1008–1016.

Ramirez, A., Khirani, S., Aloui, S., Delord, V., Borel, J.-C., Pépin, J.-L., & Fauroux, B. (2013). Continuous positive airway pressure and noninvasive ventilation adherence in children. *Sleep Medicine*, *14*, 1290–1294.

Shete, M. M., Stocks, R. M., Sebelik, M. E., & Schoumacher, R. A. (2010). Effects of adeno-tonsillectomy on polysomnography patterns in Down syndrome children with obstructive sleep apnea: A comparative study with children without Down syndrome. *International Journal of Pediatric Otorhinolaryngology*, *74*, 241–244.

Shin, M., Besser, L. M., Kucik, J. E., Lu, C., Siffel, C., & Correa, A. (2009). Prevalence of Down syndrome among children and adolescents in 10 regions of the United States. *Pediatrics*, *124*, 1565–1571.

Sobey, C. G., Judkins, C. P., Sundararajan, V., Phan, T. G., Drummond, G. R., & Srikanth, V. K. (2015). Risk of major cardiovascular events in people with down syndrome. *PLoS ONE*, *10*, e0137093.

Tan, H. L., Gozal, D., Ramirez, H. M., Bandla, H. P., & Kheirandish-Gozal, L. (2014). Overnight polysomnography versus respiratory polygraphy in the diagnosis of pediatric obstructive sleep apnea. *Sleep*, *37*, 255–260.

Uliel, S., Tauman, R., Greenfeld, M., & Sivan, Y. (2004). Normal polysomnographic respiratory values in children and adolescents. *Chest*, *125*, 872–878.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Original article

Sleep in infants with congenital myasthenic syndromes

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ABSTRACT

Background and objectives: Infants with congenital myasthenic syndrome (CMS) are at risk of brief resolved unexplained event (BRUE) and sleep-disordered breathing. The aim of the study was to explore sleep in infants with CMS with a particular focus on heart rate (HR) variability.

Methods: Overnight polygraphy was performed and HR variations associated with respiratory events were analysed. Bradycardia and tachycardia were defined as a variation of HR of ±10 bpm from baseline and analysed as events/hour.

Results: The data of 5 infants with CMS were analysed. Two patients had known mutations (COLQ and RAPSN). One patient had a tracheostomy. The apnoea-hypopnoea index (AHI) was abnormal in all the patients (range 2.8–47.7 events/h), with the highest AHI being observed in the 3 youngest infants. Nocturnal transcutaneous gas exchange was normal in all patients except the tracheostomised patient. Mean HR was 114 ± 23 bpm with a mean HR index of 4.5 ± 4.3 events/h. The amplitudes of HR variations (bradycardia or tachycardia) were around 15–20 bpm, regardless of the type of respiratory event, and comparable between patients. No correlations were found between HR indexes or variations and the type and mean duration of respiratory events. Ventilatory support was initiated in 3

Abbreviations: CMS, congenital myasthenic syndromes; ENMG, electroneuromyography; RNS, repetitive nerve stimulation; Stim-SFEMG, stimulation single fibre electromyography; NIV, non-invasive ventilation; BRUE, brief resolved unexplained event; PSG, polysomnography; SDB, sleep-disordered breathing; HR, heart rate; PG, polygraphy; CSA, central sleep apnoea; OSA, obstructive sleep apnoea; MSA, mixed sleep apnoea; AHI, apnoea-hypopnoea index; $PtcCO_2$, transcutaneous carbon dioxide; DI, desaturation index; ΔDesaturation, maximal variation in SpO_2 desaturation; ΔHR, variations in HR.

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infants immediately after the sleep study because of a high AHI and/or nocturnal hypoventilation.
Conclusions: All 5 infants had an abnormal AHI with younger infants having the highest AHI. Three infants required ventilatory support after the polygraphy, underlining its clinical usefulness. No significant abnormalities of HR were observed during the sleep studies.
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1. Introduction

Congenital myasthenic syndromes (CMS) are a heterogeneous group of disorders caused by an abnormal signal transmission at the motor endplate, a special synaptic contact between the motor axon and the skeletal muscle fibre. The molecular defects involved in CMS may be caused by mutations in different genes encoding presynaptic, synaptic and postsynaptic neuromuscular junction proteins,[1] all leading to muscle weakness. Targeted genetic analysis is done if a phenotypic clue points to one or limited number of genes.[2] However, 40–50% of genes involved in CMS are still not identified.[3] Despite important advances in the understanding of molecular pathogenetic mechanisms involved in CMS, diagnostic challenges remain, particularly in childhood, and diagnosis may be delayed because of symptom overlaps and misdiagnosis.[1,3,4] The diagnosis of CMS is therefore based on the association of clinical signs, electroneuromyography (ENMG) and muscle biopsy.[2] Indeed, fatigable weakness especially of ocular and cranial muscles, a positive family history and ENMG studies, with repetitive nerve stimulation (RNS) and stimulation single fibre electromyography (StimSFEMG),[5] can assist the diagnosis. In case of negative diagnostic tests but suggestive symptoms, a therapeutic trial with short-acting cholinesterase inhibitors is recommended.[6]

Infants with CMS may present with respiratory distress, recurrent episodic apnoeas when awake, bulbar weakness, vocal cord palsy, stridor and laryngospasm requiring non-invasive ventilation (NIV) and/or a tracheostomy.[1,2,7–9] Myasthenic crisis causing respiratory failure has been shown to be associated with about 10% mortality.[10] Moreover, 3 studies reported the presence of severe and recurrent brief resolved unexplained events (BRUE) as first symptoms in infants, which investigations led to the diagnosis of CMS.[6,8,9] Even if the role of polysomnography (PSG) was found to be neither sufficiently distinctive nor predictive of BRUE,[11] recent guidelines recommended a systematic PSG in infants who have experienced a BRUE or when there is clinical evidence of sleep-disordered breathing (SDB).[12] A PSG is thus theoretically recommended in all infants with a suspicion of or confirmed CMS, as these infants are at high risk to develop BRUE and/or SDB due to the combination of hypotonia, apnoea and/or laryngospasms.[13]

Surprisingly, very few studies analysed breathing pattern and heart rate (HR) variations during sleep in infants with CMS.[13] As infants with CMS may present with SDB and as respiratory events are associated with variations in HR, we wanted to see if respiratory events were associated with abnormal HR variations, which could precipitate or explain BRUE in these infants. The aim of our study was therefore to analyse respiratory events and HR variability during sleep in infants with CMS.

2. Patients and methods

2.1. Patients

We conducted a retrospective review of the clinical charts and polygraphies (PG)/PSG of infants with CMS younger than 2 years old, who were referred to the Sleep and Noninvasive ventilation Unit of Necker Hospital in Paris or to the Bronchopneumology Unit of Children Hospital Bambino Gesù in Rome between April 2011 and September 2015. PG/PSG was performed because of the suspicion of a neuromuscular disorder or the confirmation of CMS, SDB and/or the presence of BRUE. Diagnosis of CMS was based on characteristic clinical symptoms, with suggestive ENMG and/or muscular biopsy and/or DNA analysis. Clinical data such as family history, clinical symptoms and their evolution, genetic and metabolic studies, ENMG studies, including RNS and StimSFEMG of orbicularis oculi, muscle biopsy, cardiac monitoring, electroencephalography, upper airway examination, pH monitoring, oesophagus-stomach-duodenum contrast, videofluoroscopy, cerebral magnetic resonance imaging (MRI), chest computed tomography scans, coexisting medical conditions, surgical history such as tracheostomy and gastrostomy, use of NIV and evaluation of symptoms of SDB were gathered. The study was approved by the ethical committee (CPP Ile de France II, n° 2014-03-09 SC) and informed consent was obtained from parents.

2.2. Sleep study

Overnight PG/PSG was performed during spontaneous breathing in room air with the recording of nasal flow, respiratory inductive plethysmography, tracheal sound, body position, HR, and pulse oximetry (SpO_2) (Cidelec polysomnograph, CID102L8D, Angers, France; Alice 6LDX Sleepware by Philips-Respironics, Carquefou, France; Compumedics Sleep Monitoring System C510, Charlotte, NC, USA).[14] The sleep study was recorded on videotape with an infrared video camera. Obstructive sleep apnoea (OSA) was defined as a drop in nasal flow amplitude by 90% of baseline for at least two respiratory cycles, with continued or increased inspiratory effort. Central sleep apnoea (CSA) was

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defined as a drop in nasal flow amplitude by 90% of baseline in absence of inspiratory effort, during at least two breaths associated with an arousal, an awakening, or a 3% SpO_2 desaturation, or of a duration of at least 20 s. In infants under 1 year of age, CSA may be associated with a decrease in HR to less than 50 bpm for at least 5 s or less than 60 bpm for 15 s.[14] A mixed sleep apnoea (MSA) was defined as a drop in nasal flow amplitude by 90% of baseline for at least two respiratory cycles with the absence of inspiratory effort during one portion of the event and the presence of inspiratory effort in another portion, regardless of which portion comes first. Hypopnoea was defined as a drop in nasal air pressure transducer amplitude by 30% of baseline for duration of two missed breaths, associated with an arousal, an awakening, or a 3% SpO_2 desaturation.[14] The duration of each respiratory event was reported.

The apnoea-hypopnoea index (AHI) was calculated as the sum of the apnoea and hypopnoea events per hour of total sleep. Sleep study was considered normal in case of an apnoea index <1 event/h and AHI <1.5 events/h.[15] Mild sleep apnoea syndrome was defined as an AHI between 1.5 and 5 events/h, moderate sleep apnoea syndrome for an AHI between 5 and 10 events/h, and severe sleep apnoea syndrome for an AHI $\geq$10 events/h. Alveolar hypoventilation was defined as a minimal SpO_2 < 90% for 10% of sleep time and/or a transcutaneous carbon dioxide pressure ($PtcCO_2$) >50 mmHg for 10% of sleep time.[16] The 3% desaturation index (DI) was calculated as the number of 3% SpO_2 desaturation per hour of total sleep, and was considered abnormal when >5 events/h. Maximal variation in SpO_2 desaturation (ΔDesaturation) was calculated as SpO_2 drop from baseline to the nadir occurring after each scored respiratory event. Variations in HR (ΔHR) over ±10 bpm, occurring after each scored respiratory event, were reported. A reduction of HR of 10 bpm or more was considered as a bradycardia, while an increase of 10 bpm or more was considered as a tachycardia. The HR, bradycardia and tachycardia indexes were calculated as the number of HR variations, bradycardia or tachycardia per hour of total sleep, respectively.

Transcutaneous carbon dioxide ($PtcCO_2$) was recorded by a SenTec Digital Monitoring System monitor (SenTec AG, Therwil BL Switzerland). The mean and maximum $PtcCO_2$ were calculated.

2.3. *Statistical analysis*

All continuous variables were expressed as mean ± standard deviation, or as median and interquartiles. Correlation between variables was done using the Pearson correlation test in case of normally distributed population or the Spearman correlation test otherwise. A p value < 0.05 was considered as statistically significant.

3. Results

3.1. *Patients*

The data of 5 infants (4 girls) with CMS were analysed (Table 1). Patients #1 and #5 had a positive family history for BRUE. Patients #4 and #5 were preterm infants, born at 35 weeks of gestational age. All the patients but patient #4 had neonatal respiratory distress, requiring intubation with mechanical ventilation at birth in patients #2, #3, and #5. All the patients had hypotonia, swallowing disorders, poor weight gain and/or recurrent episodes of BRUE. Search for metabolic disorders was negative, electroencephalography and brain MRI were normal in all patients, while electrocardiography showed vagal hyperactivity in patient #5. Initial heart ultrasound reported an interventricular communication and a patent foramen ovale in patient #1, an atrial septal defect in patient #3, and an aorta coarctation in patient #5 which was surgically corrected at the age of 12 months. Heart defects resolved in the other patients before the sleep study. Airway endoscopy showed a laryngomalacia in patients #2 and #5. Tracheostomy was performed in patient #3 at the age of 4 months because of severe hypotonia and upper airway obstruction not relieved by NIV. StimSFEMG of orbicularis oculi was performed and abnormal in 4 patients, evidencing abnormal jitter measurement and block conduction.

Genetic exam revealed mutations in *COLQ* and *RAPSN* in patients #1 and #2, respectively, who were consequently treated respectively with salbutamol and ambenomium chloride. No known mutations were found in patient #3 (*SMN1, TRPV4, COLQ, CHRNG, RAPSN*), patient #4 (*COLQ, RAPSN, CHAT, DOK7, DM1, GFPT1, SCN4A*), nor in patient #5 (*CHRNE, RAPSN, DOK7, COLQ, CHAT, CHRNB1, CHRND, SCN4A*). Patients #3 and #4 were treated with pyridostigmine and salbutamol, while patient #5 was treated with ambenomium chloride with improvement of peripheral muscle weakness but not of vocal cord palsy with the persistence of laryngospasms.

3.2. *Sleep study*

The mean age at sleep study was 11.0 ± 9.8 months (range 3–24 months) (Table 2). Mean recording time was 313 ± 107 min (range 146–436 min), and only patient #1 had a nap study. Patient #3 was breathing spontaneously on his tracheostomy. Only patients #1 and #2 were treated at the time of the sleep study.

Mean AHI was 15.4 ± 18.3 events/h (range 2.8–47.7), with the youngest infants having a higher AHI (Fig. 1 and Table 2). The mean hypopnoea index (10.1 ± 15.2 events/h) was higher than the mean total apnoea index (5.1 ± 3.1 events/h). SDB was characterised by predominant hypopnoeas in #1 and #3, OSA in patients #2, MSA in patient #4 and CSA in patient #5 (see Fig. 2).

Sleep SpO_2 and $PtcCO_2$ were normal in all the patients except in patient #3, who had a SpO_2<90% for 7% of night time and a mean $PtcCO_2$ slightly above 50 mmHg (Table 2).

Mean 3% DI was 13.3 ± 14.7 events/h with a wide range (2.8–39.0 events/h). However, the mean ΔDesaturation occurring after the respiratory events was comparable among patients (5.3 ± 1.4%, range 3.7–7.0%) (Table 3).

No BRUE occurred during the sleep studies and no HR values < 60 bpm or >180 bpm were observed. Mean HR was 114 ± 23 bpm, with slightly low values in patients #1, #4 and #5. Mean HR index was 4.5 ± 4.3 events/h, with the tracheotomised patient (patient #3) having no HR variations. Mean bradycardia index was 3.0 ± 2.6 events/h and mean tachycardia index was 1.5 ± 2.0 events/h.

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Table 1 – Patients' characteristics and clinical findings.

Patients	Age at PG/PSG (mo)	Weight (kg)	Height (cm)	Revealing symptoms	Associated symptoms	Diagnosis	Comorbidities	ECG	ENT examination	Indication for PG/PSG
1 (F)	3	4.2	N.A.	Repeated BRUE requiring cardiopulmonary resuscitation, swallowing difficulties	Feeding difficulties, axial hypotonia, poor growth, gastrostomy (at 4 mo), BRUE with severe bradycardia, ophtalmoplegia	Suggestive electroneuromyography and genetic exam (*COLQ* mutation)	Ventricular septal defect, foramen ovale	Normal	No airway abnormalities	BRUE, obstructive apnoeas
2 (F)	3	4.5	N.A.	Hypotonia, weakness and apnoeas requiring intubation, stridor, hypersalivation	Feeding and swallowing difficulties (enteral feeding by NG tube), hypotonia, BRUE	Suggestive electroneuromyography, and genetic exam (*RAPSN* mutation), non specific myopathic changes on muscular biopsy	None	Normal	Posterior laryngomalacia and glossoptosis	Hypotonia, stridor and snoring
3 (F)	6	4.3	58	Hypotonia	Feeding and swallowing difficulties (requiring a NG tube followed by a gastrostomy at 4 mo), stridor, tracheostomy (at 4 mo), GER, bilateral ptosis, walking and speech delay, nocturnal desaturations	Suggestive electroneuromyography, non specific myopathic changes on muscular biopsy	Atrial septal defect	Right ventricular hypertrophy later solved	Suspected laryngomalacia but not found	Neuromuscular disease in patient with tracheostomy
4 (F)	19	N.A.	N.A.	BRUE	Feeding difficulties, walking and speech delay, weakness, downfalls, disorders of equilibrium, hypotonia, ptosis, witnessed nocturnal apnoeas	Non specific myopathic changes on muscular biopsy	Hyporexia	Normal	N.A.	Suspected OSA
5 (M)	24	9.3	84	Feeding difficulties, BRUE with hypotonia, desaturations and bradycardia	Weakness, ptosis, floppy head, swallowing disorders, gastrostomy (at 21 mo), speech delay	Suggestive electroneuromyography	Aorta coarctation (surgery at 12 mo), recurrent respiratory infections, suspected GER	Vagal hyperactivity	Laryngeal hypomobility, vascular tracheal marks	Recurrent desaturations, oxygen dependent

PG: polygraphy; PSG: polysomnography; ECG: electrocardiography; N.A.: not available; BRUE: brief resolved unexplained event; NG: nasogastric; GER: gastro-oesophageal reflux; mo: months; OSA: obstructive sleep apnoea.

Table 2 – Sleep study results.

Patient	Exam condition	Sleep time (min)	AHI (events/h)	OAI (events/h)	CAI (events/h)	MAI (events/h)	HI (events/h)	3% DI (events/h)	Mean HR (bpm)	HR index (events/h)	Bradycardia index (events/h)	Tachycardia index (events/h)	Sleep SpO_2 (%)	Sleep $PtcCO_2$ (mmHg)
1	SB, room air, treated with salbutamol since 1 month before PG	146	47.7	7.4	1.2	0.8	36.6	39.0	98	9.5	4.5	4.9	Mean 97, min 78, time with $SpO_2 < 90\% = 3\%$	Mean 41 max 44
2	SB, room air, treated with ambenomium chloride since 1 month before PG	313	10.7	6.3	0.4	0.0	4.0	8.6	130	8.4	6.3	2.1	Mean 97, min 87, time with $SpO_2 < 90\% = 0\%$	Mean 37 max 40
3	Tracheostomy, room air	303	10.3	0.0	2.0	0.0	8.3	10.3	147	0.0	0.0	0.0	Mean 96, min 69, time with $SpO_2 < 90\% = 7\%$	Mean 53 max 72
4	SB, room air	367	2.8	0.8	0.6	1.3	0.0	2.8	94	1.3	1.0	0.3	Mean 96, min 86, time with $SpO_2 < 90\% = 0.1\%$	Mean 45 max 47
5	SB, room air	436	5.6	0.1	3.9	0.4	1.4	5.6	102	3.2	3.0	0.4	Mean 97, min 79, time with $SpO_2 < 90\% = 1\%$	Mean 43 max 49

AHI: apnoea-hypopnoea index; OAI: obstructive apnoea index; CAI: central apnoea index; MAI: mixed apnoea index; HI: hypopnoea index; DI: desaturation index; HR: heart rate; SpO_2: pulse oximetry; $PtcCO_2$: transcutaneous carbon dioxide; SB: spontaneous breathing; PG: polygraphy.

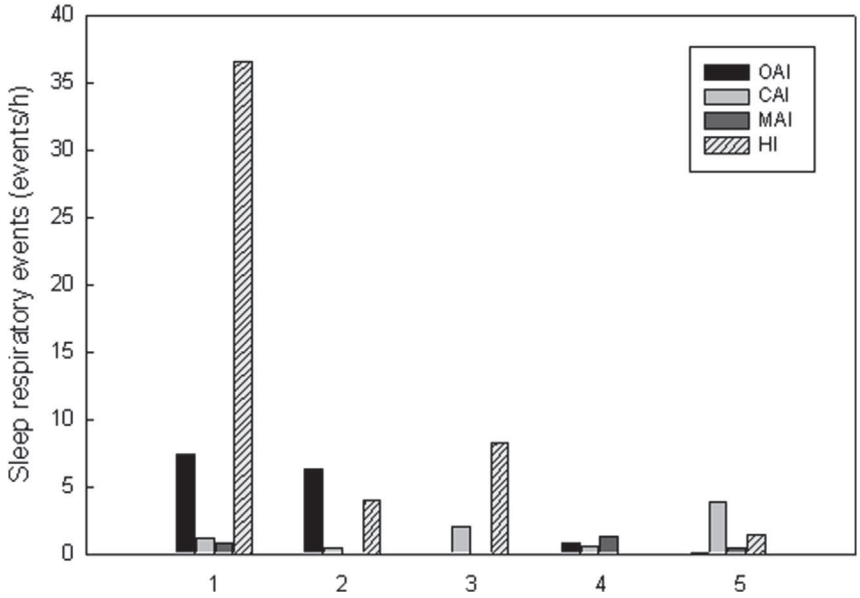

Fig. 1 – Distribution of the respiratory events in the 5 patients. OAI: obstructive apnoea index; CAI: central apnoea index; MAI: mixed apnoea index; HI: hypopnoea index.

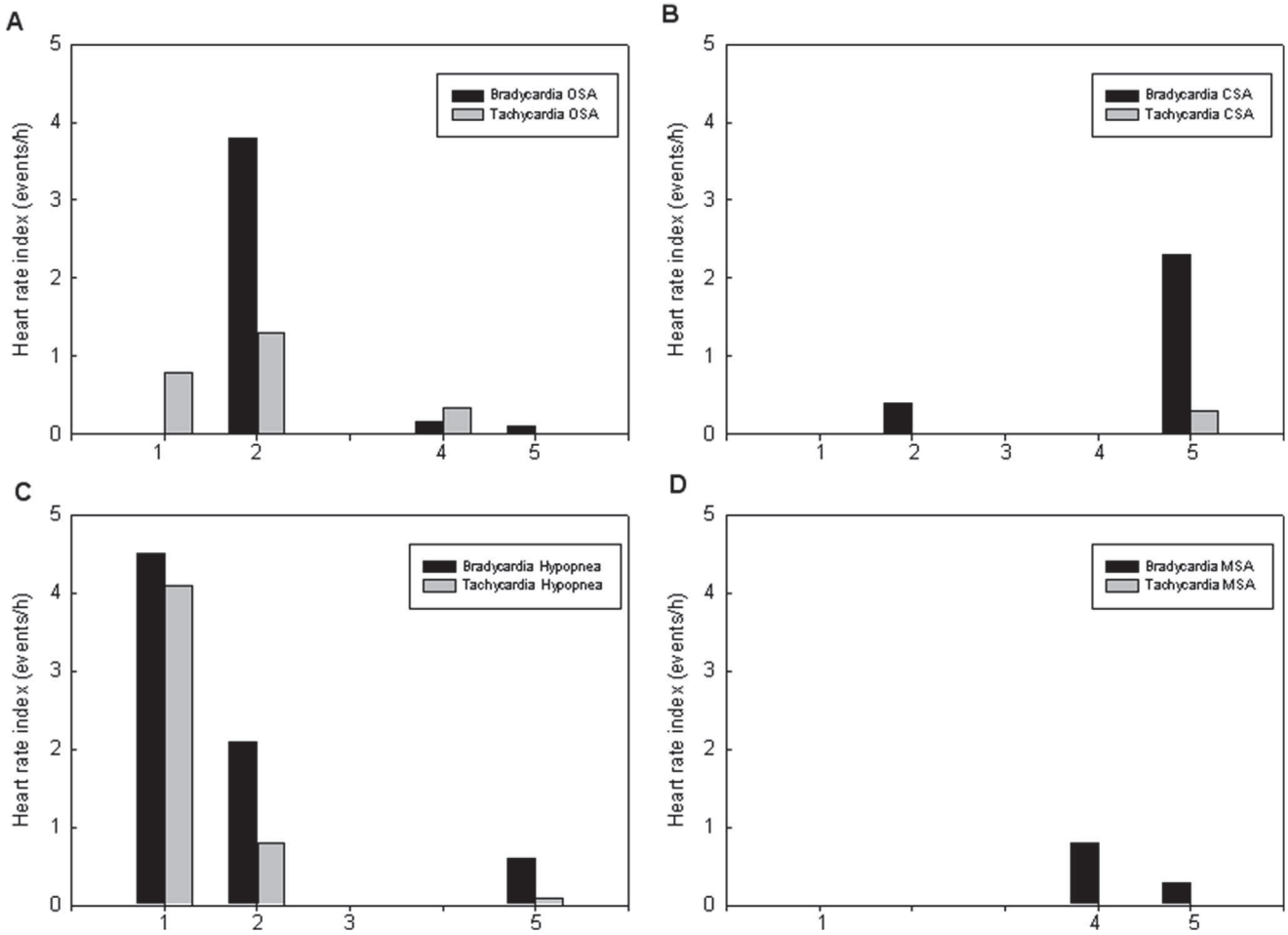

Fig. 2 – Bradycardia and tachycardia indexes according to the patients and the type of respiratory events. A: obstructive sleep apnoeas (OSA): patient #3 had no OSA; B: central sleep apnoeas (CSA); C: hypopnoeas: patient #4 had no hypopnoea; D: mixed sleep apnoeas (MSA): patients #2 and #3 had no MSA.

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Table 3 – Variations in SpO_2 desaturation, heart rate and duration of respiratory events during sleep study.

Patient	ΔDesaturation (%)	ΔHR (bpm)	ΔHR Bradycardia (bpm)	ΔHR Tachycardia (bpm)	Duration PG/PSG events (s)	Duration PG/PSG events when ΔHR (s)	Duration PG/PSG events when bradycardia (s)	Duration PG/PSG events when tachycardia (s)
1	5.2 ± 3.0	0.0 ± 15.2 (−20, +24)	−15.3 ± 2.7	13.9 ± 3.7	10.5 ± 4.9	10.9 ± 4.1	10.0 ± 3.9	11.7 ± 4.2
2	4.4 ± 1.8	−11.8 ± 18.0 (−37, +35)	−21.2 ± 7.3	16.5 ± 6.8	9.1 ± 2.9	9.3 ± 3.1	9.9 ± 3.2	7.5 ± 1.5
3	7.0 ± 3.5	0	0	0	9.0 ± 3.6	2	7.0 ± 3.5	0
4	3.7 ± 0.9	−8.1 ± 15.0 (−20, +20)	−16 ± 3.2	15.5 ± 6.4	9.0 ± 2.6	9.2 ± 2.5	9.3 ± 2.9	9.0 ± 1.4
5	6.4 ± 3.3	−13.3 ± 14.8 (−53, +21)	−17.7 ± 9.6	17.0 ± 4.6	7.5 ± 2.0	7.8 ± 2.3	7.7 ± 2.4	8.5 ± 2.2

Data are presented as mean ± standard deviation (range).
SpO_2: pulse oximetry; ΔDesaturation: variations in SpO_2 desaturation; ΔHR: variations in heart rate; PG: polygraphy; PSG: polysomnography.

Interestingly, the amplitudes of ΔHR during tachycardia or bradycardia were quite similar between patients, around 15–20 bpm, regardless of the type and the duration of respiratory event (Fig. 3 and Table 3). Patient #5 presented a single ΔHR of −53 bpm (bradycardia) associated with a CSA of 11 s of duration. This was the highest ΔHR observed among the patients. The mean duration of respiratory events was similar whether the events were associated either with bradycardia (9.2 ± 1.1 s) or tachycardia (9.2 ± 1.8 s) (Table 3).

When considering the relationship between AHI, 3% DI, and HR indexes, the only significant positive correlations were found between the AHI and the 3% DI and the tachycardia index ($r = 0.934$, $p = .02$ and $r = 0.915$, $p = 0.03$ for the AHI and the 3% DI, respectively) (Fig. 4).

3.3. *Clinical outcomes of the patients*

Three patients (#1, #3, #5) were treated by nocturnal ventilation after the sleep study because of a high AHI and/or nocturnal hypoventilation. Nocturnal NIV was started in patients #1 and #5, while patient #3 was treated by invasive ventilation on her tracheotomy. In patient #4, ventilatory support was started 23 months after our study due to a worsening of nocturnal gas exchange during follow-up. Patient #2 did not require nocturnal ventilation because of normal nocturnal gas exchange at repeated 6-months intervals controls.

4. Discussion

Our study is the first to analyse sleep and HR variations in infants with CMS. Our results show that 1) all the infants had an abnormal AHI with higher values at younger age and 2) no BRUE or significant abnormalities in HR were observed during the sleep studies.

Patients with CMS are at increased risk for SDB due to hypotonia of the upper airway and respiratory muscles which may cause nocturnal hypoventilation, episodic apnoea, laryngospasm, and/or BRUE. None of the patients had a specific respiratory muscle testing,[17,18] but as CMS is characterised by a global muscle weakness, it is highly probable that respiratory muscles are also involved in these patients. This may explain the heterogeneity of the respiratory events scored on the sleep studies. Indeed, hypotonia of the upper airway muscles may cause "real" obstructive events, as observed in the 2 youngest patients (#1 and #2). But these events may also be falsely scored as "obstructive" in case of paradoxical breathing with opposition phase on the thoracic and abdominal belts, due to diaphragmatic dysfunction or weakness of the intercostal muscles.[19,20] Patients with respiratory muscle weakness may also present progressive simultaneous decrease in airflow and thoracic and abdominal movements accompanied or not by a change in gas exchange, suggestive of a global inspiratory muscle weakness or a decrease in central drive.[19–21] These events are scored as a "hypopnea" when followed by a 3% desaturation or an arousal,[14] but are in fact periods of decreased ventilation due to respiratory muscle weakness. Hypoxaemia and hypercapnia occurs only when the level of hypoventilation falls below a certain threshold,

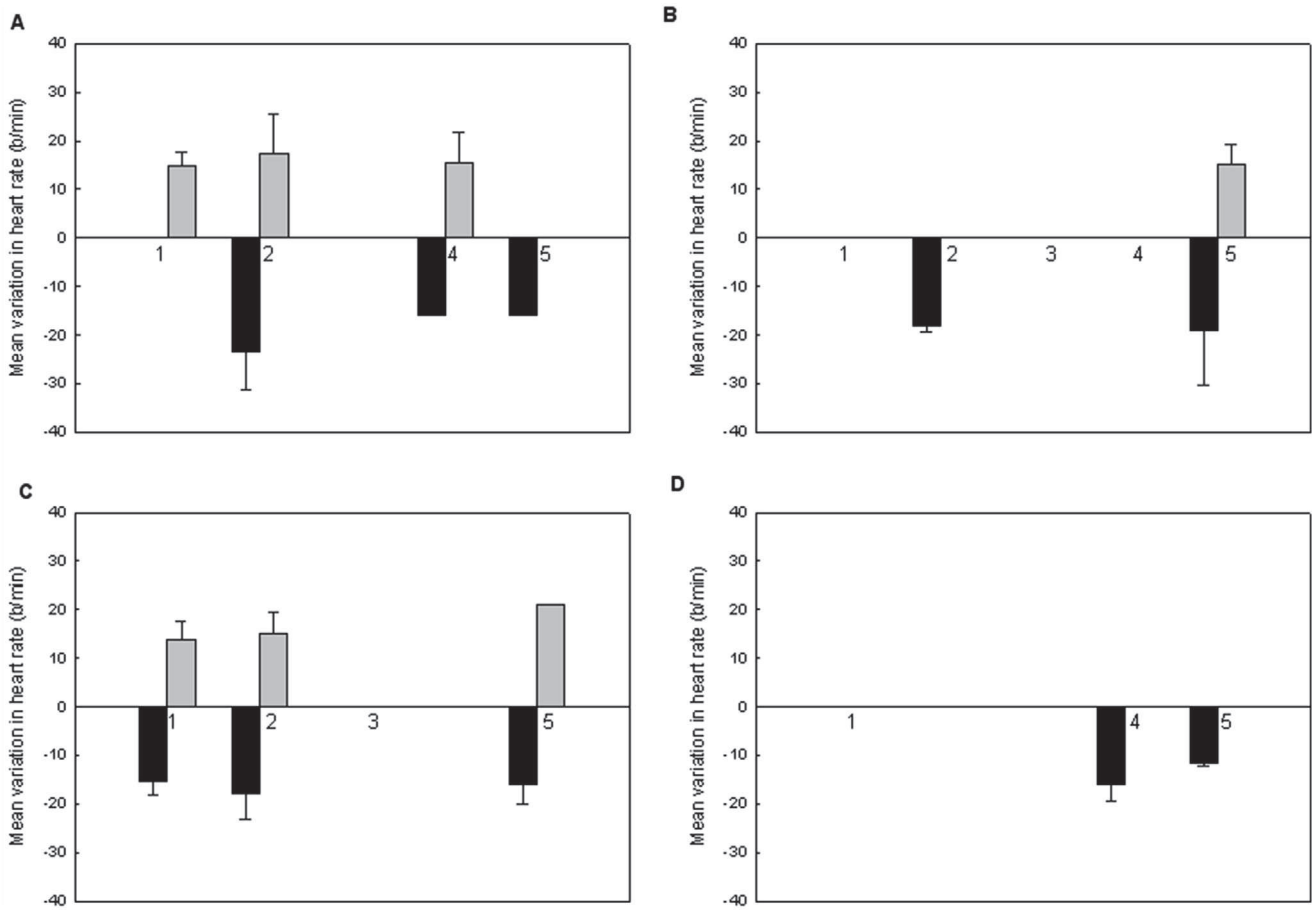

Fig. 3 – Mean variations of heart rate according to the patients and the type of respiratory events. A: obstructive sleep apnoeas (OSA): patient #3 had no OSA; B: central sleep apnoeas (CSA); C: hypopnoeas: patient #4 had no hypopnoea; D: mixed sleep apnoeas (MSA): patients #2 and #3 had no MSA.

which was observed only in the tracheotomised patient. The observation that the 4 other patients had an abnormal AHI despite normal gas exchange underlines the importance of a systematic PSG/PG in infants with CMS.

Of note, a high AHI was observed in the 2 youngest patients, despite treatment with salbutamol and ambenonium. These drugs are effective to treat hypotonia but not to impede sudden vocal cord palsy or laryngospasms, which are thought to be a direct expression of neuromuscular junction dysfunction. The two oldest patients had a lower AHI, suggesting an improvement of SDB with age in CMS patients.

We performed an in depth analysis of HR and HR variations during sleep in the 5 infants in order to test the hypothesis that respiratory events may be associated with abnormal HR variability, which may predispose these infants to BRUE. Indeed, recent guidelines recommend to perform a PSG in infants who have experienced BRUE and/or who present SDB.[11,12] Indeed, the analysis of respiratory events and HR seems interesting as an altered cardiovascular autonomic function and reduced arousability has been reported in infants with BRUE and apnoeas and/or OSA.[22–24] To our knowledge, no such studies have been reported in infants with CMS. Bradycardia is the most common cardiac rhythm abnormality associated with sleep apnoea, with a positive correlation with longer episodes and more severe OSA.[25–27] The role of oxygen desaturation as trigger of severe bradycardia during OSA is controversial, as the prolonged negative intrathoracic pressures during OSA may be more important as a trigger of increased vagal tone than oxygen desaturation.[25,28] Bradycardia occurring during an apnoea represents a vagal response to hypoxaemia aiming at limiting the oxygen consumption of the heart.[29,30] However some studies also reported the occurrence of tachycardia associated with respiratory events during sleep in infants or preschool children with OSA.[31–34] Tachycardia may be due to arousals, as arousals are characterised by an activation of the sympathetic nervous system resulting in brief tachycardia.[32,35] Moreover, cardiovascular alterations may be different according to the sleep stages and vary from infancy to adulthood.[23,29,34] However, as PSG was not available in all our patients, we could not assess HR variations according to sleep stages or arousals. Although we observed significant positive correlations between the AHI and the 3% DI and the tachycardia index, no abnormal HR values or HR variations were observed during the sleep studies in the 5 infants. HR variations associated with respiratory events were observed in all the patients

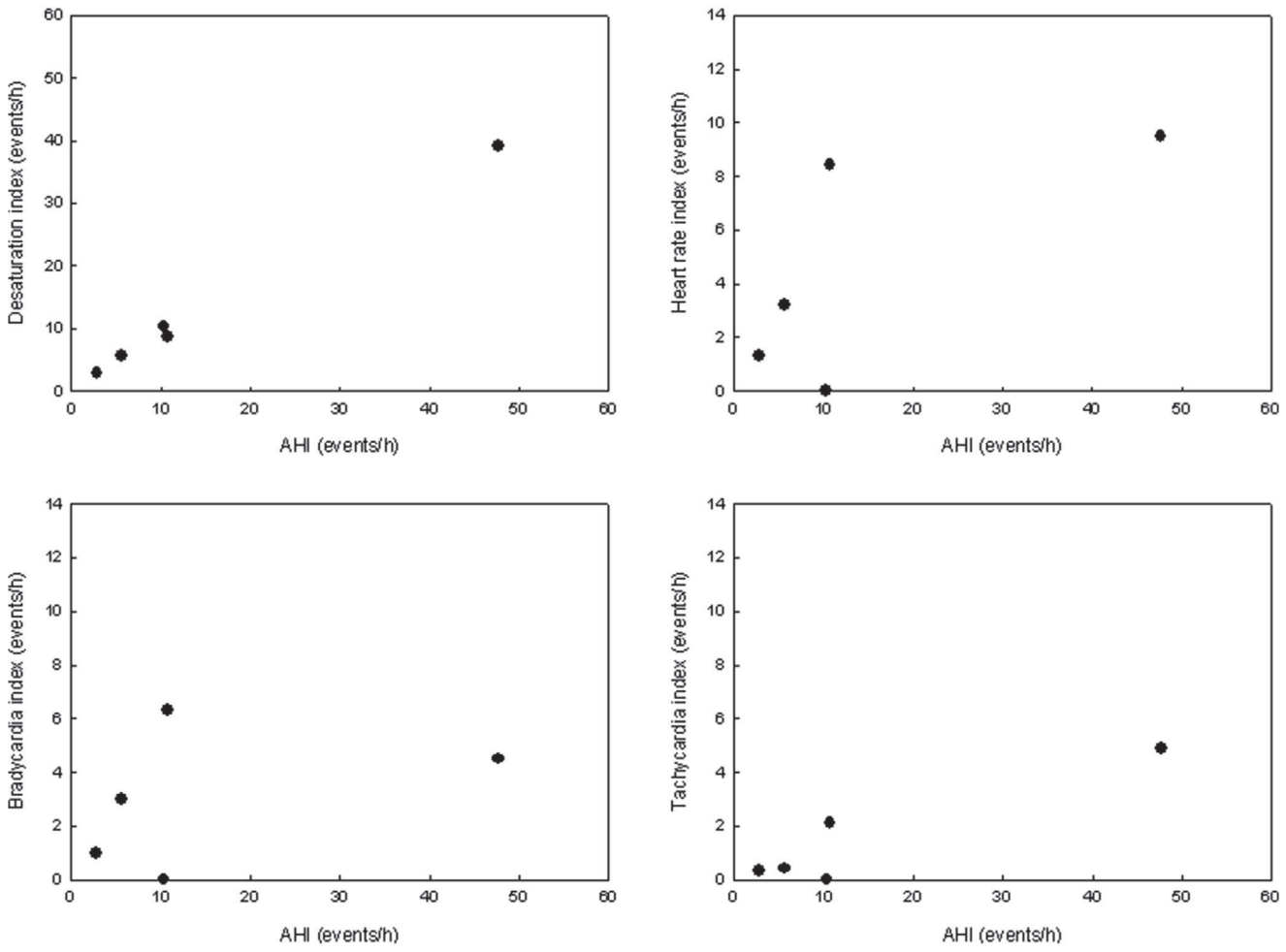

Fig. 4 – Relationship between apnoea-hypopnoea index, 3% desaturation index and heart rate indexes.

except the tracheostomised patient. The absence of HR variations in this patient may be explained by the presence of the tracheostomy, as reported in adult patients.[31,36]

The results of the PG/PSG had a clear direct impact on the patients' management, underlying the interest to prompt a sleep study in patients with suspicion of CMS. Indeed, NIV or invasive mechanical ventilation was required immediately after the sleep study in 3 patients. NIV was started in another patient 23 months later, because of the appearance of nocturnal hypoventilation, emphasizing the importance of long term follow-up sleep studies.

CMS is a rare disease and the small number of patients is a clear limitation of the study. The clinical phenotypes were very different, as usually observed in CMS, with only 2 patients having a known mutation. No generalisation can be made of an increased severity of SDB in younger infants because of the limited number of patients. However, during the study period, no patient with CMS died at our 2 centres, which is not in favour of the hypothesis that older patients survive because they are less affected. PSG was not available in all the patients precluding the analysis of events according to sleep stages. Furthermore, as the fatigability of the respiratory muscles and the clinical symptoms vary typically over time in CMS, a single sleep study may not be representative of the infant's habitual sleep, highlighting the necessity to repeat sleep studies. A follow-up with repeated PSG was not available at the time of the study but is actually ongoing.

5. Conclusion

In conclusion, sleep studies were abnormal in all the 5 infants included in the present study and led to the initiation of nocturnal ventilator support in 3 cases. We did not observe significant HR abnormalities during the sleep studies, despite a history of BRUE in 3 infants. Systematic longitudinal PSG with coupled HR monitoring and autonomic markers should be part of the diagnostic tests and follow-up of infants with CMS, independently of a history of BRUE, to evaluate autonomic control, disease evolution and treatment efficiency.

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REFERENCES

1. Engel AG, Shen XM, Selcen D, Sine SM. Congenital myasthenic syndromes: pathogenesis, diagnosis and treatment. *Lancet Neurol* 2015;**14**:420–34.
2. Beeson D, Hantai D, Lochmuller H, Engel AG. 126th international workshop: congenital myasthenic syndromes, 24–26 September 2004, Narden, The Netherlands. *Neuromusc Disord* 2005;**15**:498–512.
3. Eymard B, Stojkovic T, Sternberg D, et al. Congenital myasthenic syndromes: difficulties in the diagnosis, course and prognosis, and therapy-The French National Congenital Myasthenic Syndrome network experience. *Rev Neurol* 2013;**169**:S45–55.
4. Kinali M, Beeson D, Pitt MC, et al. Congenital myastenic syndromes in childhood: diagnostic and management challenges. *J Neuroimmunol* 2008;**201–202**:6–12.
5. Pitt MC, Jabre JF. Determining jitter values in the very young by use of the e-norms methodology. *Muscle Nerve* 2016. http://dx.doi.org/10.1002/mus.25191.
6. Tresoldi das N, Romaneli M, de S, Castro CCT, de Melo A, Fraga A, et al. Recurrent apparent life-threatening event as the first manifestation of congenital myasthenia. *Rev Paul Pediatr* 2013;**31**:121–3.
7. Mallory LA, Shaw JG, Burgess SL, et al. Congenital myasthenic syndrome with episodic apnea. *Pediatr Neurol* 2009;**41**(1):42–5.
8. Singh RR, Tan SV, Hanna MG, et al. Mutations in SCN4A: a rare but treatable cause of recurrent life threatening laryngospasm. *Pediatrics* 2014;**134**:1447–50.
9. Robb SA, Muntoni F, Simonds AK. Respiratory management of congenital myasthenic syndromes in childhood: workshop 8th December 2009, UCL Institute of Neurology, London, UK. *Neuromusc Disord* 2010;**20**(12):833–8.
10. Argov Z. Management of myasthenic conditions: nonimmune issues. *Curr Opin Neurol* 2009;**22**:493–7.
11. Horne RSC, Nixon GM. The role of physiological studies and apnoea monitoring in infants. *Paediatr Respir Rev* 2014;**15**:312–8.
12. Aurora RN, Zak RS, Karippot A, et al. Practice parameters for the respiratory indications for polysomnography in children. *Sleep* 2011;**34**(3):379–88.
13. Byring RF, Pihko H, Tsujino A, et al. Congenital myasthenic syndrome associated with episodic apnea and sudden infant death. *Neuromusc Disord* 2002;**12**:548–53.
14. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the Sleep apnea definitions task force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2012;**8**(5):597–619.
15. Uliel S, Tauman R, Greenfeld M, Sivan Y. Normal polysomnographic respiratory values in children and adolescents. *Chest* 2004;**125**:872–8.
16. Paiva R, Krivec U, Aubertin G, et al. Carbon dioxide monitoring during long-term noninvasive respiratory support in children. *Intensive Care Med* 2009. http://dx.doi.org/10.1007/s00134-00009-01408-00135.
17. Fauroux B, Quijano-Roy S, Desguerre I, Khirani S. The value of respiratory muscle testing in children with neuromuscular disease. *Chest* 2015;**147**(2):552–9.
18. Quijano-Roy S, Khirani S, Colella M, et al. Diaphragmatic dysfunction in Collagen VI myopathies. *Neuromusc Disord* 2014;**24**(2):125–33.
19. Bourke SC, Gibson GJ. Sleep and breathing in neuromuscular diseases. *Eur Resp J* 2002;**19**:1194–201.
20. Griffon L, Amaddeo A, Mortamet G, et al. Sleep study as a diagnostic tool for unexplained respiratory failure in infants hospitalized in the PICU. *J Crit Care* 2016. http://dx.doi.org/10.1016/j.jcrc.2016.1004.1003.
21. White JE, Drinnan MJ, Smithson AJ, Griffiths CJ, Gibson GJ. Respiratory muscle activity and oxygenation during sleep in patients with muscle weakness. *Eur Respir J* 1995;**8**:807–14.
22. Engelberts AC. The role of obstructive apnea in sudden infant death syndrome and apparent life threatening event. *Intern J Pediatr Otorhinolaryngol* 1995;**32**:S59–62.
23. Harrington C, Kirjavainen T, Teng A, Sullivan C. Altered autonomic function and reduced arousability in apparent life-threatening event infants with obstructive sleep apnea. *Am J Respir Crit Care Med* 2004;**165**:1048–54.
24. Steinschneider A, Richmond C, Ramaswamy V, Curns A. Clinical characteristics of an apparent life-threatening event (ALTE) and the subsequent occurrence of prolonged apnea or prolonged bradycardia. *Clin Pediatr* 1998;**37**:223–30.
25. Henderson-Smart DJ, Butcher-Puech MC, Edwards DA. Incidence and mechanism of bradycardia during apnoea in preterm infants. *Arch Dis Child* 1986;**61**:227–32.
26. Zwillich C, Devlin T, White D, et al. Bradycardia during sleep apnea. *J Clin Investig* 1982;**69**:1286–92.
27. Tilkian AG, Motta J, et al. *Cardiac arrhythmias in sleep apnea syndromes*. In: Guilleminault C, Dement W, editors. New York: Alan R. Liss, Inc. p. 197–210.
28. Huettner M, Koehler U, Nell C, et al. Heart rate response to simulated obstructive apnea while awake predicts bradycardia during spontaneous obstructive sleep apnea. *Int J Cardiol* 2015;**186**:216–8.
29. Koehler U, Becker HF, Grimm W, et al. Relations among hypoxemia, sleep stage, and bradyarrhythmia during obstructive sleep apnea. *Am Heart J* 2000;**139**:142–8.
30. Hanly PJ, George CF, Millar TW, Kryger MH. Hear rate response to breath-hold, Valsalva and Mueller maneuvers in obstructive sleep apnea. *Chest* 1989;**95**:735–9.
31. Tilkian AG, Guilleminault C, Schroeder JS, et al. Sleep-induced apnea Syndrome prevalence of cardiac arrhythmias and their reversal after tracheostomy. *Am J Med* 1977;**63**:348–58.
32. Constantin E, McGregor CD, Cote V, Brouillette RT. Pulse rate and pulse rate variability decrease after adenotonsillectomy for obstructive sleep apnea. *Pediatr Pulmonol* 2008;**43**(5):498–504.
33. Tooley WH. Sudden infant death syndome. *Am Rev Respir Dis* 1975;**112**:157–8.
34. Nisbet LC, Yiallourou SR, Nixon GM, et al. Nocturnal autonomic function in preschool children with sleep-disordered breathing. *Sleep Med* 2013;**14**:1310–6.
35. Olmetti F, La Rovere MT, Robbi E, Taurino AE, Fanfulla F. Nocturnal cardiac arrhythmia in patients with obstructive sleep apnea. *Sleep Med* 2008;**9**:475–80.
36. Coccagna G, Mantovani M, Brignani F, Parchi G, Lugaresi E. Tracheostomy in hypersomnia with periodic breathing. *Bull Physiopathol Respir (Nancy)* 1972;**8**:1217–27.

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Weaning from long term continuous positive airway pressure or noninvasive ventilation in children

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Abstract

Objectives: A significant number of children are able to discontinue long term continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV) but the underlying disorders, weaning criteria, and outcome of these children have not been studied.

Study design: Retrospective cohort follow up.

Subject selection: Consecutive children who were weaned from long term CPAP/NIV between October 2013 and January 2016.

Methodology: Underlying disorders, weaning criteria, and clinical outcome were analyzed.

Results: Fifty eight (27%) of the 213 patients on long term CPAP/NIV could be weaned from CPAP/NIV with 50 patients being weaned from CPAP and 8 from NIV. Most patients were young children with upper airway anomalies, Prader Willi syndrome or bronchopulmonary dysplasia. CPAP/NIV was discontinued following spontaneous improvement of sleep-disordered breathing in 33 (57%) patients, upper airway surgery (n = 14, 24%), maxillofacial surgery (n = 6, 11%), neurosurgery (n = 1, 2%), upper airway and neurosurgery (n = 2, 3%), or switch to oxygen therapy (n = 2, 3%). CPAP/NIV was discontinued due to normal nocturnal gas exchange during spontaneous breathing in all patients, with an obstructive apnea-hypopnea index ≤6 events/h on a combined poly(somno)graphy in 27 patients. A relapse of obstructive sleep apnea was observed after a median delay of 2 years in six patients who resumed CPAP and in one patient who underwent midface distraction.

Conclusions: Weaning from CPAP/NIV is possible in children treated with long term CPAP/NIV but is highly dependent on the underlying disorder. Spontaneous improvement is possible but most children need specific surgery. Long term follow-up is necessary in children with underlying disorders.

KEYWORDS
children, continuous positive airway pressure, nocturnal gas exchange, noninvasive ventilation, polysomnography, sleep apnea

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1 | INTRODUCTION

Long term noninvasive continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) involve the delivery of ventilatory assistance through a noninvasive interface, as opposed to invasive ventilation via a tracheostomy. The number of children treated at home with this type of respiratory support is expanding exponentially.[1–3] The majority of children, and especially those treated with CPAP, have underlying conditions associated with upper airway anomalies that may improve spontaneously with age or after surgical interventions. As such, most children requiring CPAP for Pierre Robin syndrome, achondroplasia, craniofacial stenosis, or laryngo- or tracheomalacia may be weaned from CPAP.[4–9] Infants with bronchopulmonary dysplasia treated with CPAP may also improve with age and may be weaned from CPAP after a variable time delay.[7] On the other hand, weaning from NIV is most often impossible in children with neuromuscular disorders.[10]

Although criteria used to initiate long term CPAP/NIV have been recently analyzed,[11] information on the criteria that are used in clinical practice to discontinue CPAP/NIV is lacking, as well as the clinical outcome of the patients after CPAP/NIV weaning. The aim of the present study was to analyze the clinical characteristics of the children in whom long term CPAP/NIV was discontinued, the criteria that allowed CPAP/NIV weaning, and the clinical outcome of the patients.

2 | MATERIALS AND METHODS

All consecutive children treated with long term CPAP/NIV at the NIV and sleep unit in Necker Children's Hospital, defined as the use of CPAP/NIV for more than 2 months after hospital discharge, and who could be weaned from CPAP/NIV between October 2013 and January 2016 for at least 3 months, were included in the study. Indeed, routine follow-up of children requiring long term CPAP/NIV includes the regular evaluation of CPAP/NIV tolerance and efficacy but also the need to continue CPAP/NIV. In general, the need to continue or not CPAP/NIV is assessed once a year, depending on the patient's underlying disease, his/her age, and the evolution of his/her respiratory status. As such, for each patient, clinical data and overnight gas exchange and/or sleep study data that allowed discontinuation of CPAP/NIV were collected. Long term clinical follow-up was also recorded.

Polysomnography (PSG) or respiratory polygraphy (PG) were performed using CID 102™ (Cidelec, Angers, France) or Alice™ (Respironics, Carquefou, France). The recorded data included airflow, body position, body movements, thoracic, and abdominal movements assessed by inductance belts, and pulse oximetry (SpO_2). Respiratory events were scored according to the American Academy of Sleep Medicine (AASM) manual.[12] The obstructive apnea-hypopnea index (OAHI) was defined as the number of obstructive apneas and hypopneas per hour of time in bed (or total sleep time in case of PSG) with an OAHI <2 events/h being considered as normal.[13–15] Central apnea index (CAI) <5 events/h was considered as normal.[16,17] Oxygen desaturation was defined as a fall in SpO_2 of at least 3% and the oxygen desaturation index (ODI) was defined as the number of oxygen desaturation per hour of time in bed (or total sleep time in case of PSG). Nocturnal hypoxemia was defined as the presence of a SpO_2 ≤90% for at least 2% of night time[18] and the ODI was considered as abnormal when >1.4 events/h.[13]

Overnight transcutaneous carbon dioxide ($PtcCO_2$) recordings were performed with the SenTec Digital Monitor (SenTec Inc., Therwil, Switzerland). Mean, maximal $PtcCO_2$, and the percentage of night time spent with a $PtcCO_2$ greater than 50 mmHg were recorded.[19] Nocturnal hypercapnia was defined by a $PtcCO_2$ ≥50 mmHg for at least 2% of night time.[18]

According to our protocol, discontinuation of NIV or CPAP was authorized when all four major criteria were fulfilled with at least two minor criteria (Table 1). The major criteria were 1) disappearance of nocturnal and daytime symptoms of sleep-disordered breathing after several nights sleeping without CPAP/NIV, such as snoring, sweating, arousals, labored breathing, change in behavior or attention, 2) percentage of recording time spent with a SpO_2 ≤90% <2%, 3) percentage of recording time spent with a $PtcCO_2$ ≥50 mmHg <2%, and 4) OAHI <10 events/h for patients who underwent a PSG/PG. The minor criteria were 1) minimal SpO_2 >90%, 2) maximal $PtcCO_2$ <50 mmHg, and 3) ODI ≤1.4 events/h. All the data are presented as median and range. The protocol was approved by the local ethical committee (CPP Ile de France II, n° 2014-03-09 SC).

3 | RESULTS

A total of 213 patients were treated with long term CPAP/NIV during the 27 months of the study period. Fifty eight (27%) patients could be weaned from CPAP/NIV according to the inclusion criteria. Three patients started on CPAP during the study period were excluded from the study because they never accepted the treatment. All the patients, except two patients with OSA, had an underlying disorder (Table 2).

TABLE 1 Criteria that may allow weaning from continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV)

Major criteria
1) disappearance of nocturnal and daytime symptoms of sleep-disordered breathing after several nights sleeping without CPAP/NIV, such as snoring, sweating, arousals, labored breathing, change in behavior or attention,
2) percentage of recording time spent with a SpO_2 ≤90% <2%,
3) percentage of recording time spent with a $PtcCO_2$ ≥50 mmHg <2%,
4) obstructive apnea-hypopnea index <10 events/h on a poly(somno)graphy
Minor criteria
1) minimal SpO_2 >90%
2) maximal $PtcCO_2$ <50 mmHg
3) oxygen desaturation index ≤1.4 events/h.

SpO_2, pulse oximetry; $PtcCO_2$, transcutaneous carbon dioxide.

TABLE 2 Characteristics and outcome of the weaned patients

Male/Female	38/20	
Age at CPAP/NIV initiation (years), median (range)	1.4 (0.01-16.2)	
Ventilatory mode, *n* (%)		
CPAP	50 (86%)	
NIV	8 (14%)	
Duration of CPAP/NIV (year), median (range)	1.12 (0.16-8.85)	
CPAP	0.98 (0.16-7.49)	
NIV	3.96 (0.27-8.85)	
Primary diagnosis, *n* (%)	Laryngeal obstruction[a]	9 (16%)
	Pierre Robin syndrome	6 (10%)
	Prader Willi syndrome	6 (10%)
	Treacher Collins syndrome	6 (10%)
	Bronchopulmonary dysplasia	4 (7%)
	Achondroplasia	3 (5%)
	Idiopathic OSA	2 (3%)
	Craniofaciostenosis (Crouzon, Apert)	2 (3%)
	Pycnodysostosis	2 (3%)
	Mucopolysaccharidosis	2 (3%)
	Polymalformative syndrome	2 (3%)
	Mandibular hypoplasia	2 (3%)
	Lung sequelae of viral infection/ARDS	2 (3%)
	Other[b]	10 (21%)
Reason of CPAP/NIV weaning, *n* (%)	Spontaneous improvement:	33 (57%)
	Switch to oxygen therapy:	2 (3%)
	After surgery:	
	ENT surgery	14 (24%)
	Maxillofacial surgery	6 (11%)
	Neurosurgery	1 (2%)
	ENT and neurosurgery	2 (3%)

CPAP, continuous positive airway pressure; NIV, noninvasive ventilation; OSA, obstructive sleep apnea; ARDS, acute respiratory distress syndrome; ENT, ear, nose, and throat.
[a]Laryngomalacia (*n* = 5), laryngeal paralysis (*n* = 4).
[b]Down syndrome (*n* = 1), Hanhart syndrome (*n* = 1), Noonan syndrome (*n* = 1), brainstem dysfunction (*n* = 1), thoracic scoliosis (*n* = 1), tracheomalacia (*n* = 1), congenital myasthenia with hypothyroidism (*n* = 1), bifid uvula (*n* = 1), facial macrosomia (*n* = 1), retromicrognathia (*n* = 1).

Median age at CPAP/NIV initiation was 1.4 years (range 0.01-16.2 years) with a median duration of CPAP or NIV of 0.98 (range 0.2-7.5) and 3.96 years (range 0.3-8.9), respectively. Five patients (8%) (laryngeal paralysis (*n* = 2), Crouzon syndrome (*n* = 1), Treacher Collins syndrome (*n* = 1), and Hanhart syndrome (*n* = 1)) had a history of tracheotomy. CPAP allowed weaning from tracheotomy in all these patients. The majority (*n* = 50, 86%) of the weaned patients were treated with CPAP, with only 14% being treated with NIV. The underlying diagnoses of the children treated with NIV were Prader Willi syndrome (*n* = 3), Goldenhar syndrome (*n* = 1), mucopolysaccharidosis type II (*n* = 1), idiopathic OSA (*n* = 1), lung sequelae of a viral infection (*n* = 1) and acute respiratory distress syndrome (*n* = 1).

Thirty three (57%) patients improved spontaneously over time, without need for any specific intervention. The main underlying conditions of these patients were bronchopulmonary dysplasia, Pierre Robin syndrome, laryngomalacia, laryngeal paralysis, and Prader Willi syndrome. Two patients (3%) with polymalformative syndrome were switched from CPAP to oxygen therapy because of the improvement of the airway obstruction but persistence of isolated hypoxemia. The sleep-disordered breathing of the other patients improved after ENT surgery (*n* = 14, 24%, adenotonsillectomy, turbinectomy, and/or resection of the ary-epiglottic folds), maxillofacial surgery (*n* = 6, 11%), neurosurgery (*n* = 1, 2%), or a combination of ENT and neurosurgery (*n* = 2, 3%). No patient included in the study discontinued CPAP or NIV because of intolerance or side effects.

The results of the overnight gas exchange ± PSG/PG during spontaneous breathing that allowed discontinuation of CPAP/NIV are given in Table 3. These sleep studies were performed after a median

TABLE 3 Results of sleep studies that prompted weaning from continuous positive airway pressure or noninvasive ventilation

Duration of spontaneous breathing before the sleep study (months)	1.2 (0.1-7.8)
Nocturnal gas exchange (n = 56)[a]	
Mean SpO_2 (%)	97 (93-100)
Minimal SpO_2 (%)	91 (84-97)
Time spent with SpO_2 <90% (%)	0 (0-1)
Oxygen Desaturation Index (event/h)	2 (0-18)
Mean $PtcCO_2$ (mmHg)	40 (31-47)
Maximal $PtcCO_2$ (mmHg)	44 (38-49)
Time spent with $PtcCO_2$ >50 mmHg (%)	0 (0-0)
Polysomnography/Polygraphy (n = 27)	
Obstructive apnea-hypopnea index (events/h)	1 (0-6)
Obstructive apnea index (events/h)	0 (0-1)

SpO_2, pulse oximetry; $PtcCO_2$, transcutaneous carbon dioxide.
Data are given as median (range).
[a]The nocturnal gas exchange of the two patients who were switched from continuous positive airway pressure to oxygen therapy are not included in the table but detailed in the text.

delay of 1.2 (0.1-7.8) months after discontinuation of CPAP/NIV and showed no significant periods of time with a SpO_2 ≤90% and/or a $PtcCO_2$ ≥50 mmHg. Among the 27 patients who underwent PG/PSG, the maximal OAHI was 6 events/h. The results of the two patients with polymalformative syndrome who were switched from CPAP to oxygen therapy are not included in Table 3. These two patients had normal $PtcCO_2$ values with severe hypoxemia with a mean SpO_2 between 90 and 93%, a minimal SpO_2 between 76 and 85%, an ODI between 15 and 22 events/h, and a time spent with a SpO_2 ≤90 between 4 and 25%.

Figure 1 shows the median age at CPAP/NIV initiation and median duration of treatment for the most common disorders. CPAP was initiated during the first months of life in infants with Pierre Robin syndrome, Treacher Collins syndrome, bronchopulmonary dysplasia, and laryngeal anomalies. Duration of CPAP was short in these infants and did not exceed 1 year. CPAP or NIV was started at an older age in children with achondroplasia or Prader Willi syndrome with the longest duration of CPAP being observed in patients with achondroplasia.

All the patients had a long term clinical follow-up. Thirty-five patients with craniofacial or upper airway malformations had a second sleep study after a median delay of 8 months after the first sleep study. Seven patients had a long term relapse of their OSA with an OAHI ranging between 11 and 53 events/h after a discontinuation of CPAP since 1-3 years (Table 4). OSA was treated with a resumption of CPAP in six patients and a neurosurgical intervention (Lefort III midface distraction) in the patient with pycnodysostosis. In two out of the six patients, CPAP was started prior to maxillofacial surgery. Finally, no patient died or required a tracheotomy.

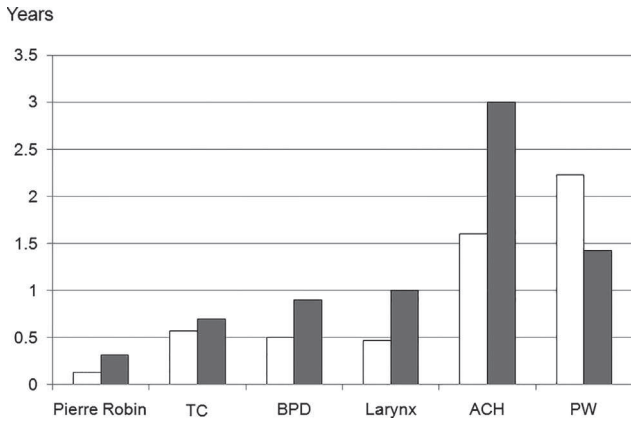

FIGURE 1 Median age at continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV) initiation (white bars) and median duration (gray bars) of CPAP or NIV for the most common disorders (in years). Pierre Robin, Pierre Robin syndrome; TC, Treacher Collins syndrome; BPD, bronchopulmonary dysplasia; larynx, laryngeal obstruction, that is, laryngomalacia or laryngeal paralysis; ACH, achondroplasia; PW, Prader Willi syndrome

4 | DISCUSSION

This study is one of the first to analyze the characteristics of consecutive children who were weaned from CPAP or NIV over a period of 27 months in a large NIV center at a pediatric university hospital. Approximately one quarter of the patients could be weaned from CPAP or NIV, with 57% of the patients improving spontaneously with age, whereas the others improved after specific surgery. Nearly all the patients had an underlying disorder, with the majority having malformations of the upper airways. Although the results of the sleep studies that allowed the discontinuation of CPAP or NIV were within the normal limits, long term follow-up is mandatory as a relapse of OSA was observed in seven patients.

Discontinuation of CPAP or NIV is common in the pediatric population. Indeed, as many as 21% of a cohort of 144 children followed at a single center in Vancouver could be weaned from CPAP or NIV after 5 years, and 42% after 10 years.[2] But this percentage is highly dependent on the underlying disorders. Indeed, the children who could be weaned from CPAP/NIV presented mainly neuromuscular disorders, spinal injury, abnormal ventilator control, craniofacial abnormalities, and airway malacia. In another center in the Netherlands, where the majority of children had neuromuscular disorders, only 7 of the 197 children followed over a period of nearly 30 years could discontinue CPAP or NIV.[1] The number of children who can be weaned from CPAP or NIV is particularly high in disorders or conditions which improve spontaneously with age such as bronchopulmonary dysplasia, Pierre Robin syndrome and airway malacia. In our experience, infants with bronchopulmonary dysplasia or laryngeal obstruction requiring CPAP could all be weaned from their ventilator support after a period of 6 months to 3 years.[7] Some infants with Down syndrome or Prader Willi syndrome may also improve spontaneously over time but relapses of OSA are common at an older age mainly because of overweight and obesity.[20]

TABLE 4 Characteristics of the patients with a relapse of obstructive sleep apnea after a first successful weaning of continuous positive airway pressure

Patient gender	Diagnosis	Age at CPAP weaning (years)	Reason of CPAP weaning	Time delay between CPAP weaning and follow-up polygraphy (years)	Obstructive apnea-hypopnea index (events/h)	Intervention
1 male	Polymalformative syndrome with thoracic scoliosis	2	Spontaneous improvement	1	18	Resumption of CPAP
2 female	Down syndrome	3	Spontaneous improvement	3	18	Resumption of CPAP
3 male	Treacher Collins syndrome	8	Spontaneous improvement	2	11	Resumption of CPAP
4 male	Achondroplasia	8	Adenotonsillectomy	1	11	Resumption of CPAP
5 male	Pycnodysostosis	8	Spontaneous improvement	1	20	Lefort III midface distraction
6 male	Treacher Collins syndrome	13	Mandibular distraction	2	24	Resumption of CPAP followed by a second mandibular distraction
7 male	Mandibular hypoplasia due to juvenile idiopathic arthritis	14	Mandibular distraction	3	53	Resumption of CPAP followed by a second mandibular distraction

CPAP, continuous positive airway pressure.

Almost half of the patients improved after specific interventions. This is explained by the fact that patients had some type of upper airway obstruction that could be relieved by surgical interventions aiming at enlarging or stabilizing the upper airway such as adenotonsillectomy, turbinectomy, resection of the ary-epiglottic folds, mandibular distraction osteogenesis or midface distraction. As these interventions are not possible at any age, CPAP may be necessary as a "bridge" to wait for the optimal timing of surgical intervention. This is particularly true for children with craniofaciostenosis in whom corrective craniofacial surgery is not possible at a too young age.[21] We have also observed recently that tonsillectomy is a very effective treatment of OSA in young children with achondroplasia, but this intervention is neither possible at a too young age.[9] Mandibular distraction osteogenesis should also be timed optimally. The two adolescents, one with Treacher Collins syndrome and one with mandibular hypoplasia due to juvenile idiopathic arthritis, had a mandibular distraction osteogenesis at a pre-pubertal age, 13 and 12 years old respectively, with complete resolution of their OSA. After the completion of pubertal growth, they developed severe symptomatic OSA requiring resumption of CPAP (Table 3). They could be definitely weaned from CPAP only after a second mandibular distraction osteogenesis once the pubertal growth spurt was completed. This underlines the necessity of a regular long term follow-up of these children by pediatric ENT and maxillofacial specialists having an expertise in genetic disorders. Indeed, OSA relapsed in these patients without any additional risk factor such as weight gain or hypertrophy of the lingual tonsils.

There are no recommendations or guidelines for weaning children from ventilator support.[10] In our clinical practice, weaning is considered in the following situations. In patients with OSA, a sleep study during spontaneous breathing is normally performed once a year. Due to the long lasting effects of CPAP and NIV, a delay of at least 2 weeks is recommended for a sleep study during spontaneous breathing. Indeed, several mechanisms such as a reduction in mucosal edema,[22] a beneficial effect on sleep fragmentation which is known to enhance airway collapsibility,[23] an improvement of the central ventilator response to hypercapnia,[24] and an increase in upper airway muscle tone,[25] may account for this prolonged benefit. In patients having abnormalities of the upper airway, corrective surgery may cure their OSA. A minimal delay corresponding to the timing associated with the maximal benefit is recommended to perform a sleep study during spontaneous breathing. This delay may last from approximately 2-6 months, according to the type of surgery. Finally, a progressive reduction of CPAP or NIV tolerance or compliance, in the absence of technical problems such as masks intolerance, may be due to a spontaneous improvement of sleep disordered breathing. For weaning patients from CPAP/NIV, we took arbitrarily the inverse criteria we use for the initiation for CPAP/NIV, that is, no symptoms of sleep-disordered breathing, normal nocturnal gas exchange and an OAHI <10 events/h.[11] In clinical practice, however, the situation is not always so clear cut and individual specificities such as the age of the patient and the underlying diagnosis, the tolerance and the subjective benefit of CPAP/NIV, potential side effects of treatment such as skin injury or facial deformity, are important to be taken in account.

We acknowledge that our study has several limitations. Our data reflect clinical practice at a single specialized center in pediatric NIV and may not be applicable to other centers. Moreover, our recruitment may also differ from other centers with a majority of patients having complex genetic disorders. However, the pathologies presented by our

patients are comparable to that of other pediatric centers in Europe.[3,6] Secondly, we defined weaning from long-term CPAP/NIV as the use of CPAP/NIV for more than 2 months after hospital discharge with a successful weaning for at least 3 months. This excluded thus all the patients who failed to tolerate CPAP/NIV for more than 2 months or who could not discontinue their treatment for at least 3 months. The time elapsed between the discontinuation of CPAP or NIV and the sleep study was variable with a median delay of 1.2 months and a range of 0.1-7.8 months. Finally, we arbitrarily selected a core of weaning criteria for CPAP/NIV. These criteria have not been validated or compared to criteria used in other centers. Also, a PSG/PG was not performed in all the patients. Future multicenter studies would be helpful at validating the most pertinent clinical and sleep criteria to allow weaning from CPAP/NIV.

In conclusion, weaning from CPAP/NIV is possible in children treated with long term CPAP/NIV but is highly dependent on the underlying disorder. Spontaneous improvement is possible but most children need specific surgery. Long term follow-up is necessary in children with associated disorders.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

REFERENCES

1. Paulides FM, Plötz FB, Verweij-van den Oudenrijn LP, van Gestel JP, Kampelmacher MJ. Thirty years of home mechanical ventilation in children: escalating need for pediatric intensive care beds. *Intensive Care Med*. 2012;38:847–852.
2. McDougall CM, Adderley RJ, Wensley DF, Seear MD. Long-term ventilation in children: longitudinal trends and outcomes. *Arch Dis Child*. 2013;98:660–665.
3. Pavone M, Verrillo E, Caldarelli V, Ullmann N, Cutrera R. Non-invasive positive pressure ventilation in children. *Early Hum Dev*. 2013;89:S25–S31.
4. Leboulanger N, Picard A, Soupre V, et al. Physiologic and clinical benefits of noninvasive ventilation in infants with Pierre Robin sequence. *Pediatrics*. 2010;126:e1056–e1063.
5. Julliand S, Boulé M, Baujat G, et al. Lung function, diagnosis, and treatment of sleep-disordered breathing in children with achondroplasia. *Am J Med Genet A*. 2012;158A:1987–1993.
6. Girbal IC, Gonçalves C, Nunes T, et al. Non-invasive ventilation in complex obstructive sleep apnea: a 15 year experience of a pediatric tertiary center. *Rev Port Pneumol*. 2014;20:146–151.
7. Khirani S, Ramirez A, Aloui S, Leboulanger N, Picard A, Fauroux B. Continuous positive airway pressure titration in infants with severe upper airway obstruction or bronchopulmonary dysplasia. *Crit Care*. 2013;17:R167.
8. Amaddeo A, Abadie V, Chalouhi C, et al. Continuous positive airway pressure for upper airway obstruction in infants with Pierre Robin Sequence. *Plast Reconstr Surg*. 2016;137:609–612.
9. Tenconi R, Khirani S, Amaddeo A, et al. Sleep-disordered breathing and its management in children with achondroplasia. *Am J Med Genet A*. 2017;173:868–878.
10. Amaddeo A, Frapin A, Fauroux B. Long-term non-invasive ventilation in children. *Lancet Respir Med*. 2016;4:999–1008.
11. Amaddeo A, Moreau J, Frapin A, et al. Long term continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) in children: initiation criteria in real life. *Pediatr Pulmonol*. 2016;51:968–974.
12. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2012;8:597–619.
13. Marcus CL, Omlin KJ, Basinki DJ, et al. Normal polysomnographic values for children and adolescents. *Am Rev Respir Dis*. 1992;146: 1235–1239.
14. Uliel S, Tauman R, Greenfeld M, Sivan Y. Normal polysomnographic respiratory values in children and adolescents. *Chest*. 2004;125: 872–878.
15. Montgomery-Downs HE, O'Brien LM, Gulliver TE, Gozal D. Polysomnographic characteristics in normal preschool and early school-aged children. *Pediatrics*. 2006;117:741–753.
16. Kritzinger FE, Al-Saleh S, Narang I. Descriptive analysis of central sleep apnea in childhood at a single center. *Pediatr Pulmonol*. 2011;46: 1023–1030.
17. Felix O, Amaddeo A, Olmo Arroyo J, et al. Central sleep apnea in children: experience at a single center. *Sleep Med*. 2016;25:24–28.
18. Hukins CA, Hillman DR. Daytime predictors of sleep hypoventilation in Duchenne muscular dystrophy. *Am J Respir Crit Care Med*. 2000;161: 166–170.
19. Paiva R, Krivec U, Aubertin G, Cohen E, Clément A, Fauroux B. Carbon dioxide monitoring during long-term noninvasive respiratory support in children. *Intensive Care Med*. 2009;35:1068–1074.
20. Pavone M, Caldarelli V, Khirani S, et al. Sleep disordered breathing in patients with Prader-Willi syndrome: a multicenter study. *Pediatr Pulmonol*. 2015;50:1354–1359.
21. Arnaud E, Paternoster G, James S, et al. Craniofacial strategy for syndromic craniosynostosis. *Ann Chir Plast Esthet*. 2016;61:408–419.
22. Ryan CF, Lowe AA, Li D, Fleetham JA. Magnetic resonance imaging of the upper airway in obstructive sleep apnea before and after chronic nasal continuous positive airway pressure therapy. *Am Rev Respir Dis*. 1991;144:939–944.
23. Sériès F, Roy N, Marc I. Effects of sleep deprivation and sleep fragmentation on upper airway collapsibility in normal subjects. *Am J Respir Crit Care Med*. 1994;150:481–485.
24. Berthon-Jones M, Sullivan CE. Time course of change in ventilatory response to CO2 with long-term CPAP therapy for obstructive sleep apnea. *Am Rev Resp Dis*. 1987;135:144–147.
25. Rapoport DM, Garay SM, Goldring RM. Nasal CPAP in obstructive sleep apnea: mechanisms of action. *Bull Eur Physiopathol Respir*. 1983;19:616–620.

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Sleep study as a diagnostic tool for unexplained respiratory failure in infants hospitalized in the PICU

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Sleep study as a diagnostic tool for unexplained respiratory failure in infants hospitalized in the PICU

Running title: Sleep study in the PICU

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Summary

Purpose

The aim of the study was to analyze the diagnostic and therapeutic value of a polygraphy (PG) in infants hospitalized for unexplained respiratory failure or life-threatening events in the PICU.

Material and Methods

The PG of 13 infants (4 girls), mean age 6.8 ± 7.7 months, were analyzed.

Results

Eight infants were admitted for unexplained respiratory failure and 5 for life-threatening events. PG showed features suggestive of respiratory muscle weakness in 5 infants whose final diagnoses were nemaline rod myopathy (n=2), congenital myasthenia (n=2), and diaphragmatic dysfunction (n=1). Four of these patients were successfully treated with noninvasive ventilation (NIV). PG was suggestive of brainstem dysfunction in 4 infants; 2 were treated successfully with NIV and another with caffeine. PG showed obstructive sleep apnea in 3 infants; 2 were treated successfully with NIV and one patient was lost during follow up. A typical pattern of congenital central hypoventilation syndrome was observed in the last patient who was treated successfully with invasive ventilation. One patient with diaphragmatic dysfunction and one with brain stem dysfunction died.

Conclusions

PG may assist the diagnosis and guide the management of unexplained respiratory failure or life-threatening events in infants hospitalized in the PICU.

Keywords: polygraphy, respiratory failure, pediatric intensive care unit, infant, neuromuscular disorder, brainstem dysfunction.

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Introduction

Respiratory failure is the most common reason of admission to the pediatric intensive care unit (PICU). Indeed, in a recent prospective multicentre survey including more than 10,000 children, the respiratory system was the most common primary system of dysfunction representing 33.5% of admissions [1]. In the majority of patients, the cause of the respiratory failure is obvious such as acute asthma, bronchiolitis or another type of respiratory infection in a previously healthy or an immunocompromised child. More rarely, the respiratory failure is due to the exacerbation of an underlying disease such as a neuromuscular or lung disease. Acute "unexplained" respiratory failure occurring without a precipitating factor or any clinical context (such as fever) that may orientate a diagnosis, in an infant without a known or defined underlying condition, is rare and requires a prompt diagnosis in order to institute the most appropriate treatment.

Respiratory polygraphy (PG) analyzes the breathing pattern and gas exchange during sleep, enabling the diagnosis of central and/or obstructive apneas or hypopneas [2]. But, by recording simultaneously airflow and thoracic and abdominal movements, it may also show tracings evocative of a respiratory muscle dysfunction or a hypoventilation, characterized by a decrease in the amplitude of breathing, which may not fulfil the strict criteria of apnea or hypopnea [3, [4]. PG has the advantage that it is totally noninvasive and may be performed at the bedside, inside the PICU. PG, by giving information on the breathing pattern and consequent abnormal gas exchange, may also guide treatment, and in particular noninvasive ventilation (NIV) in case of alveolar hypoventilation and noninvasive continuous positive airway pressure (CPAP) in case of obstructive events [5].

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The aim of the study was to describe the PG findings and the therapeutic implications of this investigation in infants admitted to the PICU with unexplained respiratory failure or life threatening events.

Material and methods

Patients

The PG of all consecutive infants admitted to the medical PICU between September 2013 and September 2015 were analyzed. The PICU comprises 13 beds and admits a mean of 500 children between the age of one month and 18 years for acute medical conditions per year.

The medical records of the patients were systematically reviewed and medical history and demographics data were collected for each patient. Interventions after the PG and the patient's outcome were analyzed. The study was conducted in agreement with the French regulations and received appropriate legal and ethical approval from the Ethical Committee of Necker university hospital (CPP Ile de France II).

Polygraphy

PG with the recording of nasal pressure by means of a nasal canula, thoraco-abdominal movements by means of inductive plethysmography, respiratory sound, body position, pulse oximetry (SpO_2), and heart rate was performed during spontaneous breathing in room air (Cidelec, Saint Gemme sur Loire, France or Alice 6, Respironics, Carquefou, France). All events were scored according to the American Academy of Sleep Medicine (AASM) manual and following update [2, [6]. Obstructive apnea was defined as the absence of nasal airflow, with continued chest wall and abdominal movements for at least two breaths. Central apnea was

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defined as the absence of airflow with the cessation of respiratory effort, lasting more than 20 seconds or of shorter duration and associated with a bradycardia in infants less than one year of age and/or a3% desaturation; central apnea occurring after gross body movements or after sighs was not considered as a pathological finding. Mixed apnea was defined as an apnea that usually began as central and ended as obstructive according to changes in the chest, abdominal, and flow traces. Hypopnea was defined as a decrease in nasal airflow of at least 30% with a corresponding decrease in $SpO_2$of at least 3% and/or an arousal. The apnea-hypopnea index (AHI) was calculated as the sum of apnea and hypopnea events per hour of total sleep time [2].

Besides these apneic and hypopneic events, other events were looked for:

- progressive simultaneous decrease in airflow and thoracic and abdominal movements accompanied or not by a change in gas exchange, suggestive of a decrease in central drive or global inspiratory muscle weakness [3, [4]
- paradoxical breathing with opposition phase on the thoracic and abdominal belts, suggestive of diaphragmatic dysfunction or weakness of the intercostal muscles [4].

Mean, minimal pulse oximetry (SpO_2) values and the percentage of total sleep time spent with SpO_2 < 90% were calculated. The oxygen desaturation index (ODI) was defined as the number of SpO_2 drops of at least 3% per hour of total sleep time. Transcutaneous carbon dioxide pressure ($PtcCO_2$) was recorded using the SenTec Digital Monitor (software version SMB SW-V06.10; MPB SW-V04.03). Mean and maximal values of $PtcCO_2$ were calculated. All the SpO_2/$PtcCO_2$ data that were not interpretable (probe detachment, outlier data, artifacts) were discarded from the analysis.

Statistical analysis

Data are expressed as mean ± standard deviation or median [25%-75% interquartiles].

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Results

During the 2 year period, 19 PGs were performed in children hospitalized in the PICU. Six PG were performed in children with a known underlying disease (bronchopulmonary dysplasia (n=2), Pierre Robin syndrome (n=1), Rubinstein-Taybi syndrome (n=1), tongue hemangioma (n=1), and brainstem dysfunction (n=1). Thirteen PG were performed in infants (4 girls), median age 7 months (range 1 to 24 months) without a known underlying condition. The reason for PICU admission was acute respiratory failure in 8 infants and life-threatening events requiring resuscitation maneuvers with hypoxemia ± hypercapnia, and bradycardia in the 5 other patients (Table 1). None of the patients had fever and no precipitating factor was identified for all patients. Chest X-rays, electrocardiography, echocardiography were normal in all patients. All the infants presented a least one for the following clinical features: peripheral or axial muscle weakness (n=8, patients #1 to #9 with the exception of patient #5), swallowing difficulties with false passages (n=4, patients #6 to #9), episodes of bradycardia (n=5, patients #6 to #9 and patient #12), and/or acute obstructive events (n=3, patients #10 to #12). Patient #5 presented features of generalized scleroderma and patient #13 was tracheotomised in his country because of recurrent severe episodes of respiratory failure and referred to our center with the suspicion of metabolic disease.

The results of the PG are presented in Table 2. A daytime nap PG was performed in the 10 infants aged less than 6 months whereas an overnight PG was performed in the 3 older patients (Table 2). All the studies were performed in room air with a medianananalysable time of 146 min (range 64 to 510 min).

Patients #1 and #2 had a high AHI, composed mainly of hypopneas, with severe hypoxemia and hypercapnia. The PG tracings showed tachypnea with repeated episodes associating a simultaneous decrease in airflow and thoracic and abdominal movements followed

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by a desaturation and an arousal, suggestive of global inspiratory muscle weakness (Figures 1a and 1b). Nemaline rod myopathy was confirmed in the 2 patients. Respiratory status improved spontaneously in patient #1 who did not require ventilator support. NIV during night and nap sleep corrected the alveolar ventilation in patient #2. Patient #3 had few respiratory events but repeated episodes of a simultaneous decrease in airflow and opposition phase on the thoracic and abdominal belts followed by a desaturation, occurring at the end of the night, suggestive of a decrease of diaphragmatic endurance (Figure 2a). Patient #4 had an AHI of 52/h and an ODI of 34/h. The PG tracing showed recurrent episodes of a simultaneous decrease in airflow and thoraco-abdominal belts (Figure 2b). The PG recordings were suggestive of a respiratory muscle weakness or dysfunction. Further investigations showed that these 2 patients had congenital myasthenia. Both were successfully treated with NIV. Patient #5 had a tracing evocative of diaphragmatic dysfunction. Indeed, when she was awake, airflow was present, with an opposition phase on the thoraco-abdominal belts, which was explained by the fact that she breathed exclusively with her accessory inspiratory muscles. When she felt asleep, because of the reduction of the activity of the inspiratory intercostal muscles during rapid eye movement (REM) sleep, airflow decreased to almost zero, with a simultaneous disappearance of the opposition phase. This lead to a profound desaturation and an arousal, and the cycle restarted again (Figure 3).

Patients #6, #8, and #9 had extremely high AHI (between 63 and 104 events/h), with mainly obstructive events for patient #6 and central events for patients #8 and #9 (Figure 4). They spent between 6 and 12% of the recording time with a SpO_2< 90%, without overt hypercapnia. In these 3 patients, as well in patient #7, breathing pattern was very irregular. The PG findings, in association with swallowing dysfunction, bradycardia, axial hypotonia, and a normal cerebral magnetic resonance imaging led to the diagnosis of brainstem dysfunction in these 4 infants. Patients #6 and #9 were treated with NIV but patient #6 died when NIV was

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withdrawn during a travelling abroad. Evolution was spontaneously favourable in patient #7 and patient #8 improved with caffeine.

PG showed severe obstructive respiratory events in patients #10 to #12 (Figure 1 online). Patients #10 and #11 were found to have severe laryngomalacia on an endoscopic evaluation and were treated successfully with noninvasive CPAP. The endoscopic evaluation showed severe pharyngeal hypotonia in patient #12 who returned to his country without treatment and was lost during follow up.

Patient #13 was an otherwise healthy infant who had undergone a tracheotomy in Ukraine because of recurrent episodes of severe respiratory failure. His PG showed a severe simultaneous decrease in airflow and thoraco-abdominal movements as soon as he felt asleep, with profound hypoxemia and hypercapnia, without causing an arousal reflex (Figure 2 online). This tracing was suggestive of central congenital hypoventilation syndrome which was confirmed by a genetic analysis revealing a de novo heterozygous mutation in the PHOX2B gene responsible for a 5 alanine expansion within the 20 alanines on the C-terminal of the PHOX2B protein. This patient is doing well with invasive ventilation on his tracheotomy during sleep.

Discussion

To our knowledge, this is the first study showing the diagnostic value of a PG in the PICU in infants admitted for unexplained respiratory failure or life-threatening events. Indeed, sleep studies are generally used to diagnose OSA and prescribed and interpreted within that context. But the analysis of the airflow and thoraco-abdominal breathing pattern can show more very useful information, outside the context of OSA, and in particular in case of respiratory muscle weakness and/or dysfunction, or abnormalities of the respiratory drive. In the present study, the PG tracings showed features suggestive of respiratory muscle dysfunction, abnormal central

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drive or obstructive respiratory events, guiding appropriate diagnostic investigations and an effective treatment.

Studies on polysomnography (PSG) or PG in the PICU are scarce [7]. None of these studies dealt with the diagnostic value of PG. Indeed, the aim of these studies was to analyze sleep quality in children hospitalized for burns or to evaluate the effects of neuromuscular blockade on sleep quality [7].

PG is rarely used as a diagnostic tool in neuromuscular diseases. However, it may be informative by showing features evocative of respiratory muscle weakness [8]. Global inspiratory muscle weakness is characterized by a decrease in tidal volume, with a simultaneous decrease in airflow and thoraco-abdominal expansion in the PG tracing. These events may be misinterpreted as “central apneas” when the clinical context is not taken into account as neuromuscular patients are unable to generate large inspiratory pressures [3]. On the other hand, other events, such as severe diaphragmatic weakness as observed in patient #5, may be misinterpreted as “obstructive” when the diaphragmatic weakness causes paradoxical movement of the chest and the abdomen even without narrowing of the upper airway [4]. Finally, the high desaturation index in these patients may be explained by the reduction in lung volume and thus the “oxygen reserve” [3]. In order to maintain minute ventilation, breathing rate increases with the appearance of a rapid shallow breathing. This index has been shown to be significantly increased in children with neuromuscular disease requiring NIV [9]. Respiratory muscle fatigue may be evoked when these above mentioned features appear after a certain delay, as in patient #3 in whom features of alveolar hypoventilation appeared at the end of the night and who was shown to have congenital myasthenia. The PG tracing was particularly helpful in patient #5. The disappearance of opposition phase on the thoraco-abdominal belts every time she felt asleep, was explained by the physiological decrease of the activity of the accessory inspiratory muscles during REM sleep [3, [4]. Indeed, during this phase, breathing efficiency relies solely on the diaphragm. As she had severe diaphragmatic dysfunction, sleep

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resulted in a profound decrease in tidal volume and pulse oximetry, which ended with an arousal.

Brainstem dysfunction in the newborn is an association of symptoms rather than an established disease, originally described in the Pierre Robin sequence [10, [11]. Patients present with neonatal suck and swallowing difficulties, pharyngo-oesophageal uncoordination, upper airway obstruction due to upper airway hypotonia, vagal overreactivity, and a normal cerebral magnetic resonance imaging. Abnormalities in central drive are common but have been rarely documented on a sleep study. In these patients, PG showed an irregular breathing pattern, which may concern breathing frequency and/or breathing amplitude with a variable association of central and obstructive events. An extremely high central apnea index was observed in patients #8 and #9 (Figure 4) whereas the respiratory were obstructive in patient #6, which may be explained by hypotonia of the upper respiratory airway.

Most infants with obstruction of the upper airways have suggestive clinical symptoms such as stridor, inspiratory retractions, hyperextension of the neck, which predominate during sleep and agitation. However, in the 3 patients in our study, the clinical symptoms were permanent, causing respiratory failure or severe life-threatening events with bradycardia. The observation of severe typical obstructive respiratory events on the PG was in agreement with the endoscopy of the upper airways which showed severe laryngomalacia in 2 patients.

Congenital central hypoventilation syndrome is a rare neurocristopathy with disordered central drive [12]. The clinical presentation is typically during the newborn period with alveolar hypoventilation during sleep, or in more severely affected patients, during sleep and wakefulness. The severity of the clinical presentation is correlated to the number of alanine repeats on the PHOX2B gene. PG tracing, showing an immediate profound decrease in flow and thoraco-abdominal belts as soon as he felt asleep, causing severe hypoxia and hypercapnia without any arousal reflex, was highly suggestive of the diagnosis of congenital central hypoventilation syndrome which was confirmed by the genetic analysis.

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Our study has several limitations. Most of the patients had a daytime nap PG and not an overnight recording. It has been showed that nap sleep study parameters are not very sensitive in predicting abnormal overnight sleep findings, but when nap study parameters are abnormal, the chance of an abnormal overnight sleep study is very high [13, [14]. As we did not perform a PSG, we were not able to check sleep architecture and quality. Another limitation of PG as compared to PSG is the underestimation of hypopneas due to the impossibility to detect autonomic arousals. However, we do not think that a PSG would have changed the results of our study since the majority of the patients had an extremely abnormal AHI with profound desaturations during respiratory events. Paradoxical breathing is not always an expression of respiratory muscle weakness. Indeed, this breathing pattern is physiological in newborns and infants and decreases with age to disappear around the age of 3 years [15, [16]. PG can detect reductions of airflow and thoracic-abdominal respiratory movements during sleep, these findings are graphically displayed and detectable but they are not quantitatively measurable. Finally, the number of patients is small but sufficiently informative to underline the usefulness of PG in infants with unexplained respiratory failure or life-threatening events.

In conclusion, this study shows for the first time the diagnostic usefulness of a PG in infants hospitalized in the PICU for unexplained respiratory failure or life-threatening events. The PG tracings, when interpreted taking in account some pivotal clinical features, can orientate the diagnosis and guide the therapeutic management of these infants. This noninvasive investigation should be integrated in the diagnostic arsenal of these patients.

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References

[1] Pollack MM, Holubkov R, Funai T, Berger JT, Clark AE, Meert K, Berg RA, Carcillo J, Wessel DL, Moler F, Dalton H, Newth CJ, Shanley T, Harrison RE, Doctor A, Jenkins TL, Tamburro R, Dean JM, Network. EKSNIoCHaHDCPCCR. Simultaneous Prediction of New Morbidity, Mortality, and Survival Without New Morbidity From Pediatric Intensive Care: A New Paradigm for Outcomes Assessment. Crit Care Med 2015;43:1699-709.

[2] Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF, Redline S, Strohl KP, Davidson Ward SL, Tangredi MM. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 2012;8:597-619.

[3] White JE, Drinnan MJ, Smithson AJ, Griffiths CJ, Gibson GJ. Respiratory muscle activity and oxygenation during sleep in patients with muscle weakness. Eur Respir J 1995;8:807-14.

[4] Bourke SC, Gibson GJ. Sleep and breathing in neuromuscular diseases. Eur Resp J 2002;19:1194-201.

[5] Leboulanger N, Picard A, Soupre V, Aubertin G, Denoyelle F, Galliani E, Roger G, Garabedian E-N, Fauroux B. Physiologic and clinical benefits of noninvasive ventilation in infants with Pierre Robin sequence. Pediatrics 2010;126:e1056-63.

[6] Iber C, Ancoli-Israel S, Chesson AL, Quan SF, Medicine ftAAoS. The AASM manual for the scoring of sleep and associated events. . Westchester, IL: American Academy of Sleep Medicine 2007;

[7] Kudchadkar SR, Aljohani OA, Punjabi NM. Sleep of critically ill children in the pediatric intensive care unit: a systematic review. Sleep Med Rev 2014;18:103-10.

[8] Fauroux B, Quijano-Roy S, Desguerre I, Khirani S. The value of respiratory muscle testing in children with neuromuscular disease. Chest 2015;147:552-9.

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[9] Fauroux B, Aubertin G, Clément A, Lofaso F, Bonora M. Which tests may predict the need for noninvasive ventilation in children with neuromuscular disease? Respir Med 2009;103:574-81.

[10] Abadie V, Chéron G, Lyonnet S, Hubert P, Morisseau-Durand MP, Jan D, Manac'h Y, Couly G. Isolated neonatal dysfunction of brainstem. Arch Pediatr 1996;3:130-6.

[11] Abadie V, Morisseau-Durand MP, Beyler C, Manach Y, Couly G. Brainstem dysfunction: a possible neuroembryological pathogenesis of isolated Pierre Robin sequence. Eur J Pediatr 2002;161:275-80.

[12] Gozal D. Congenital central hypoventilation syndrome: an update. Pediatr Pulmonol 1998;26:273-82.

[13] Marcus CL, Keens TG, Ward SL. Comparison of nap and overnight polysomnography in children. Pediatr Pulmonol 1992;13:16-21.

[14] Saeed MM, Keens TG, Stabile MW, Bolokowicz J, Davidson Ward SL. Should children with suspected obstructive sleep apnea syndrome and normal nap sleep studies have overnight sleep studies? Chest 2000;118:360-5.

[15] Gaultier C, Praud JP, Canet E, Delaperche MF, D'Allest AM. Paradoxical inward rib cage motion during rapid eye movement sleep in infants and young children. J Dev Physiol 1987;9:391-7.

[16] Kohyama J, Sakuma H, Shiiki T, Shimohira M, Hasegawa T. Quantitative analysis of paradoxical inward rib cage movement during sleep in children. Psychiatry Clin Neurosci 2000;54:328-9.

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Legends of the figures

Legend of figure 1

a) Polygraphy tracing of patient #1 showing an irregular breathing rate of 29/minute with tachycardia (heart rate around 155 beats/minute) and repeated episodes associating a simultaneous decrease in airflow and thoracic and abdominal expansion without opposition phase followed by a desaturation suggestive of global inspiratory muscle weakness.
b) Polygraphy tracing of patient #2 showing and irregular breathing pattern with a progressive decrease in airflow and thoracic and abdominal expansion without opposition phase, accompanied by a profound desaturation and an arousal with a repeat of the previous breathing pattern, suggestive of global inspiratory muscle weakness.

Legend of figure 2

a) Polygraphy tracing of patient #3 showing repeated episodes of a simultaneous decrease in airflow and opposition phase on the thoracic and abdominal belts followed by a desaturation, occurring at the end of the night, suggestive of a decrease of diaphragmatic endurance
b) Polygraphy tracing of patient #4 showing a very irregular breathing pattern with recurrent episodes of a simultaneous decrease in airflow and thoraco-abdominal belts with profound desaturations

Legend of figure 3

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Polygraphy tracing of patient #5 showing that after an arousal when she is is not still asleep, airflow is present, with an opposition phase on the thoraco-abdominal belts, which is explained by the fact that the patient breathes exclusively with her accessory inspiratory muscles. When the patient falls asleep, because of the reduction of the activity of the inspiratory intercostal muscles during rapid eye movement sleep, airflow decreased to almost zero, with a simultaneous disappearance of the opposition phase. This leads to a profound desaturation and an arousal, and the cycle restarts again.

Legend of figure 4

Polygraphytracing of patient #9 showing repeated central apneas causing severe desaturations.

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Figure 1

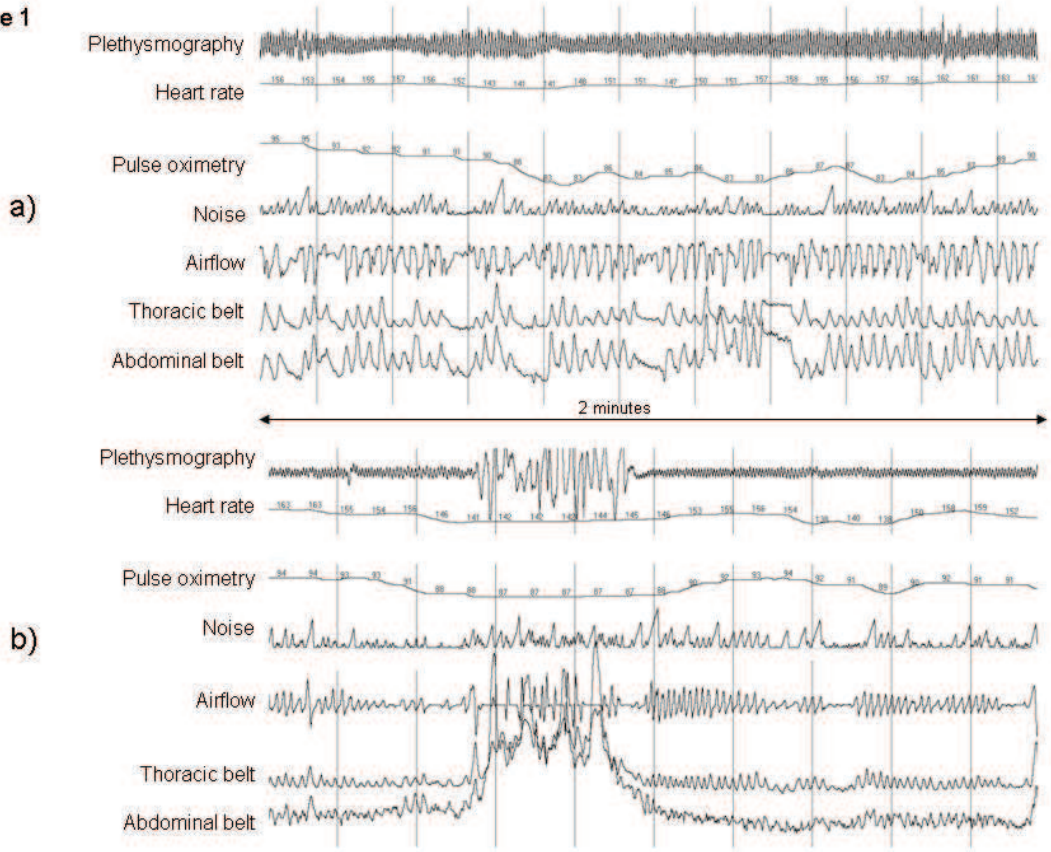

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Figure 2

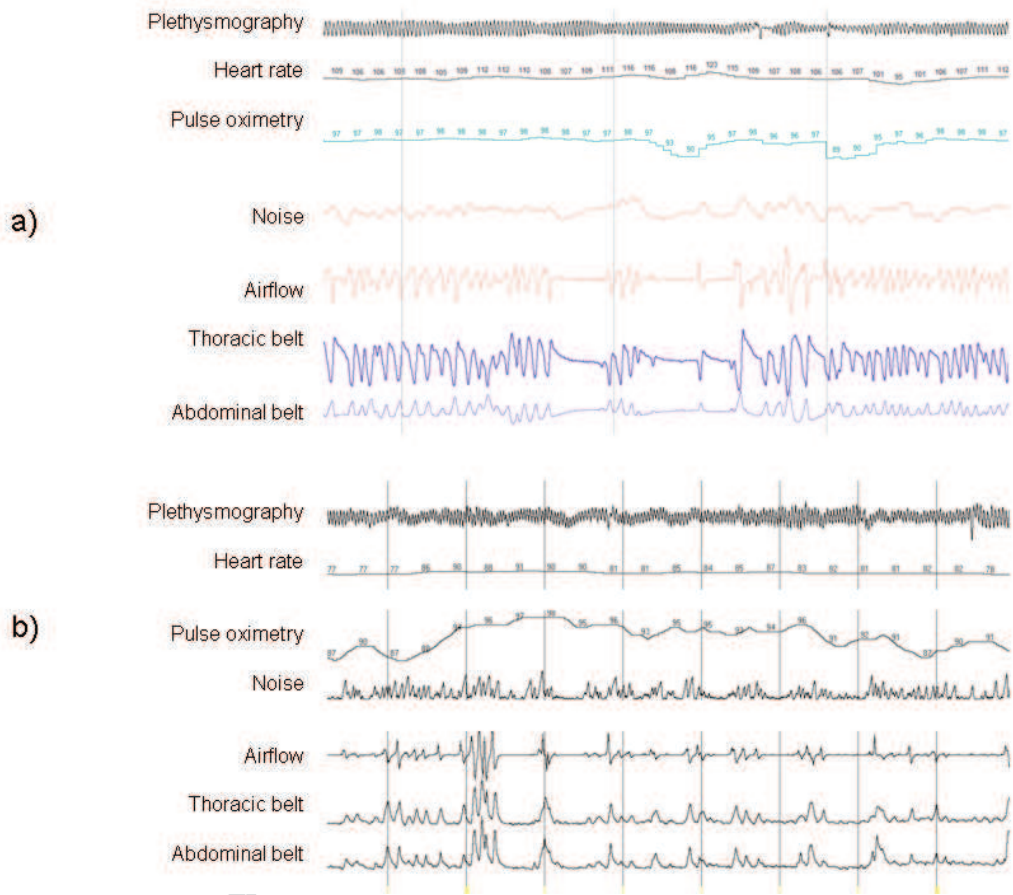

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Figure 3

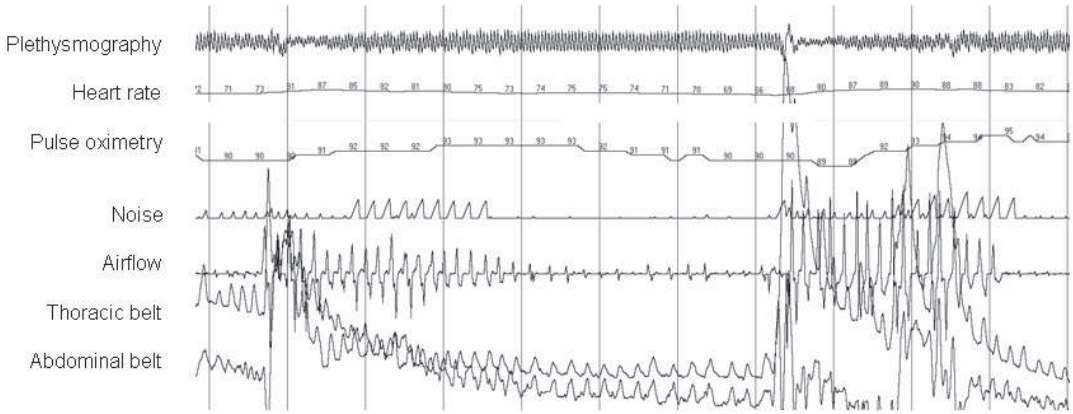

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Figure 4

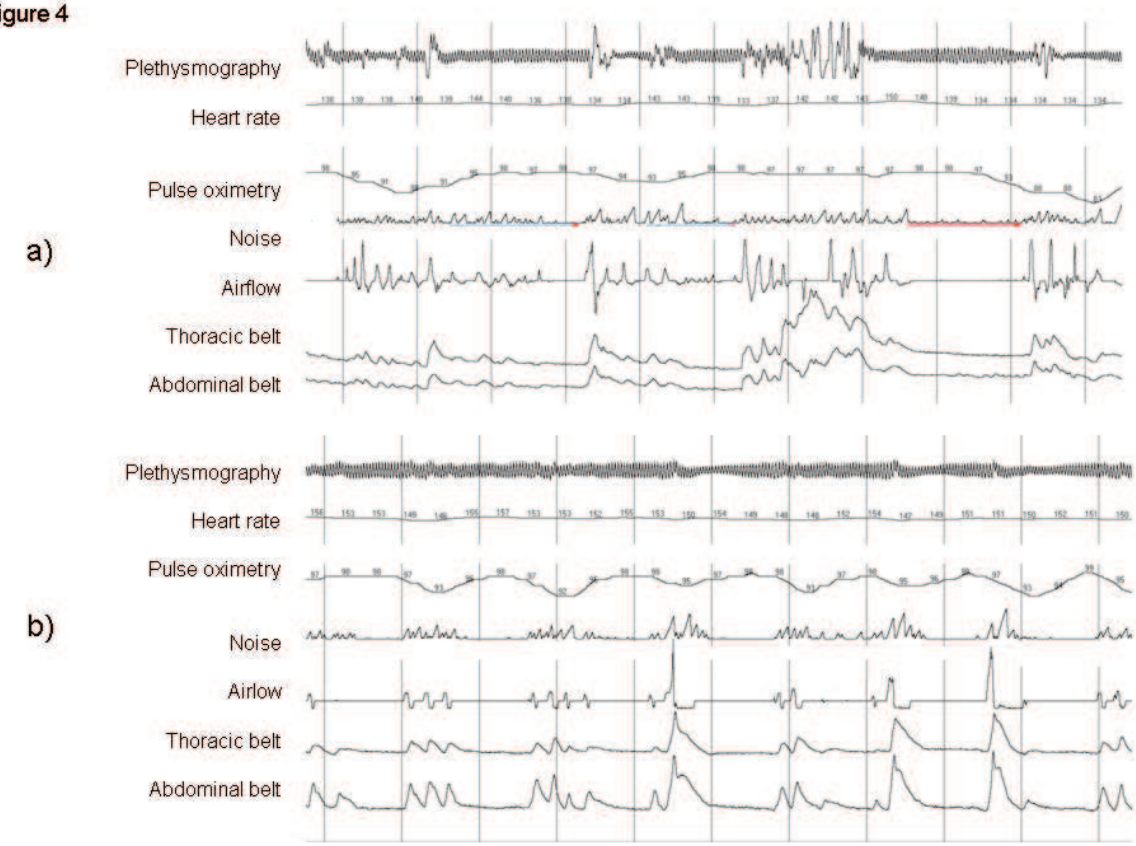

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Table 1: Anthropometrics, clinical presentation, final diagnosis and outcome of the patients

Patient gender	Age (months)	Weight (kg)	Height (cm)	PICU admission	Associated clinicalfeatures	Final diagnosis	Outcome	Duration of follow up (months)
1 male	3	5	56	Respiratory distress	Peripheral muscle weakness, swallowing dysfunction	Nemaline rod myopathy	Therapeutic abstention	4 - alive
2 female	4	5	40	Respiratory distress	Peripheral muscle weakness	Nemaline rod myopathy	NIV	12 -alive
3 male	24	19	84	Life threatening events	Generalized muscle weakness and fatigability, swallowing dysfunction	Congenital myasthenia	NIV	11 - alive
4 female	3	6	62	Respiratory distress	Axial hypotonia, swallowing dysfunction	Congenital myastenia	NIV	31 - alive
5 female	14	8	75	Respiratory distress	Generalized inflammatory disorder	Diaphragmatic dysfunction	NIV	15 -death
6 female	2	4	60	Life threatening events	Swallowing dysfunction, bradycardia, axial hypotonia, acute obstructive events	Brainstem dysfunction	NIV	2 - death
7 male	4	6	55	Life threatening events	Swallowing dysfunction, bradycardia, axialhypotonia	Brainstem dysfunction	Therapeutic abstention	2 - alive
8 male	1	3	50	Life threatening events	Swallowing dysfunction, bradycardia, axial hypotonia	Brainstem dysfunction	cafeine	5 - alive
9 male	2	5	57	Respiratory distress	Swallowing dysfunction, bradycardia, axial hypotonia	Brainstem dysfunction	NIV	4 - alive
10 male	6	5	60	Respiratory distress	Acute obstructive events	SCID T-B-NK+ and laryngomalacia	CPAP	8 - alive
11 male	3	4	45	Respiratory distress	Acute obstructive events	Laryngomalacia	CPAP	52 -alive
12 male	2	6	59	Life threatening events	Acute obstructive events with bradycardia	Pharyngomalacia	Lost for follow up	Lost for follow up
13 male	21	15	80	Respiratory distress	Recurrent episodes of respiratory failure	CCHS	Invasive ventilation on tracheotomy	14 - alive

Abbreviations: PICU: pediatric intensive care, SCID: severe combined immune deficiency, OSA: obstructive sleep apnea, CCHS: congenital central hypoventilation syndrome, CPAP: continuous positive airway pressure, NIV: noninvasive ventilation.

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Table 2: Polygraphic results

	Recording time (minutes)	Respiratory events			Gas exchange							Main polygraphic findings
		CAI (events/h	OAI (events/h)	AHI (events)	Mean SpO_2 (%)	Minimal SpO2 (%)	ODI (events/h)	% time with SpO_2<90%	Mean $PtcCO_2$ (mmHg)	Maximal $PtcCO_2$ (mmHg)	% time with $PtcCO_2$> 50mmHg	
1 male	149	5	0	11	93	75	28	21	51	56	100	Homogeneous decrease in ventilation
2 female	117	0	6	50	91	79	56	27	46	53	1	Homogeneous decrease in ventilation
3 male	420	4	0	7	97	76	21	1	na	na	na	Homogeneous decrease in ventilation at the end of the night with phase opposition on thoracic and abdominal belts
4 female	146	3	5	52	97	78	34	3	41	45	0	Homogeneous decrease in ventilation
5 female	510	0	0	0	95	85	85	2	67	83	100	Tracing evocative of diaphragmatic weakness
6 female	159	8	36	63	94	76	62	6	40	42	0	Obstructive events with decrease in respiratory drive
7 male	85	0	0	6	97	90	13	0	39	43	0	Irregular breathing
8 male	188	34	7	64	95	65	67	10	42	46	0	Central events
9 male	224	71	17	104	94	73	117	12	48	55	33	Central events
10 male	64	0	8	22	96	89	14	0	49	64	39	Obstructive events with hypoventilation
11 male	84	0	31	95	89	51	95	31	54	64	100	Obstructive events with hypoventilation
12 male	113	5	12	20	98	94	3	0	39	41	0	Obstructive events with bradycardia
13 male	120	0	0	0	92	82	30	40	68	70	100	Decrease in central drive during sleep, normalization during awakening

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Abbreviations: CAI: central apnea index, OAI: obstructive apnea index, AHI: apnea-hypopnea index, SpO_2: pulse oximetry, $PtcCO_2$: transcutaneous carbon dioxide, na: not available.

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Long-term non-invasive ventilation in children

Alessandro Amaddeo, Annick Frapin, Brigitte Fauroux

Use of long-term non-invasive ventilation is increasing exponentially worldwide in children of all ages. The treatment entails delivery of ventilatory assistance through a non-invasive interface. Indications for use of non-invasive ventilation include conditions that affect normal respiratory balance (eg, those associated with dysfunction of the central drive or respiratory muscles) and disorders characterised by an increase in respiratory load (eg, obstructive airway or lung diseases). The type of non-invasive ventilation used depends on the pathophysiological features of the respiratory failure. For example, non-invasive ventilation will need to either replace central drive if the disorder is characterised by an abnormal central drive or substitute for the respiratory muscles if the condition is associated with respiratory muscle weakness. Non-invasive ventilation might also need to unload the respiratory muscles in case of an increase in respiratory load, as seen in upper airway obstruction and some lung diseases. Technical aspects are also important when choosing non-invasive ventilation—eg, appropriate interface and device. The great heterogeneity of disorders, age ranges of affected children, prognoses, and outcomes of patients needing long-term non-invasive ventilation underline the need for management by skilled multidisciplinary centres with technical competence in paediatric non-invasive ventilation and expertise in sleep studies and therapeutic education.

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Introduction

Long-term non-invasive ventilation entails delivery of ventilatory assistance through a non-invasive interface, as opposed to invasive ventilation via tracheostomy. The number of children treated at home with this type of respiratory support is increasing exponentially around the world.[1–3] Some evidence suggests mortality is decreased with non-invasive ventilation, but the main benefit of the treatment is indisputably better family experience and health-related quality of life.[2,4–7] However, the increase in use of non-invasive ventilation contrasts with the shortage of validated criteria for initiation and the scant proven physiological benefits.[8]

There are two main types of non-invasive ventilation. First, continuous positive airway pressure (CPAP) delivers a constant positive pressure to the airways and aims to maintain airway patency throughout the entire breathing cycle. Second, biphasic positive airway pressure (BiPAP) aims to assist the breathing of the patient by delivering a supplemental higher positive pressure during every inspiration.

In this Review, we summarise paediatric disorders that might benefit from long-term non-invasive ventilation and discuss indications and expected and proven benefits. Further, we describe available equipment and detail the follow-up and monitoring of patients. Finally, we conclude with questions about ethics of non-invasive ventilation and areas for future research.

Paediatric disorders that might benefit from non-invasive ventilator support

Non-invasive ventilation is indicated for disorders that cause disequilibrium in the respiratory balance. Components of respiratory balance are the load imposed on the respiratory system, the capacity of the respiratory muscles, and the central drive (figure). In healthy people, the respiratory load—ie, the effort the individual has to exert to generate a breath—is low, the capacity of the respiratory muscles is normal, and the central drive appropriately commands the respiratory muscles (figure A). In disorders characterised by an increase in respiratory load, or by a weakness of the respiratory muscles, the central drive increases its demands on the respiratory muscles (figure C). When this imbalance exceeds a certain threshold, hypoventilation (defined by hypercapnia and hypoxaemia) occurs. Severe upper airway obstruction, airway malacia, and advanced lung diseases (eg, cystic fibrosis, bronchopulmonary dysplasia, or bronchiolitis obliterans) might account for an excessive respiratory load (panel 1).[9–15] Neuromuscular diseases that involve the motor neuron, the peripheral nerve, the neuromuscular junction, or the respiratory muscles can cause respiratory muscle weakness. Chest wall disorders (eg, kyphoscoliosis) could be associated with an increase in respiratory load and dysfunction of the respiratory

Key messages

- Use of non-invasive ventilation is increasing exponentially worldwide in children of all ages
- Increased use of non-invasive ventilation contrasts with scant validated criteria for initiation of the treatment and few proven benefits
- Continuous positive airway pressure (CPAP) is not appropriate for treatment of sleep-disordered breathing in children with neuromuscular disease, and biphasic support (BiPAP) should be used when non-invasive ventilation is implemented in these patients
- Technical aspects of non-invasive ventilation—eg, interface and device—are crucial when choosing non-invasive ventilation
- Training of caregivers and patients and organisation of adapted home care are essential
- Heterogeneity of disorders, ages of affected children, prognosis, and outcomes of patients all underline the need for management by skilled paediatric multidisciplinary centres

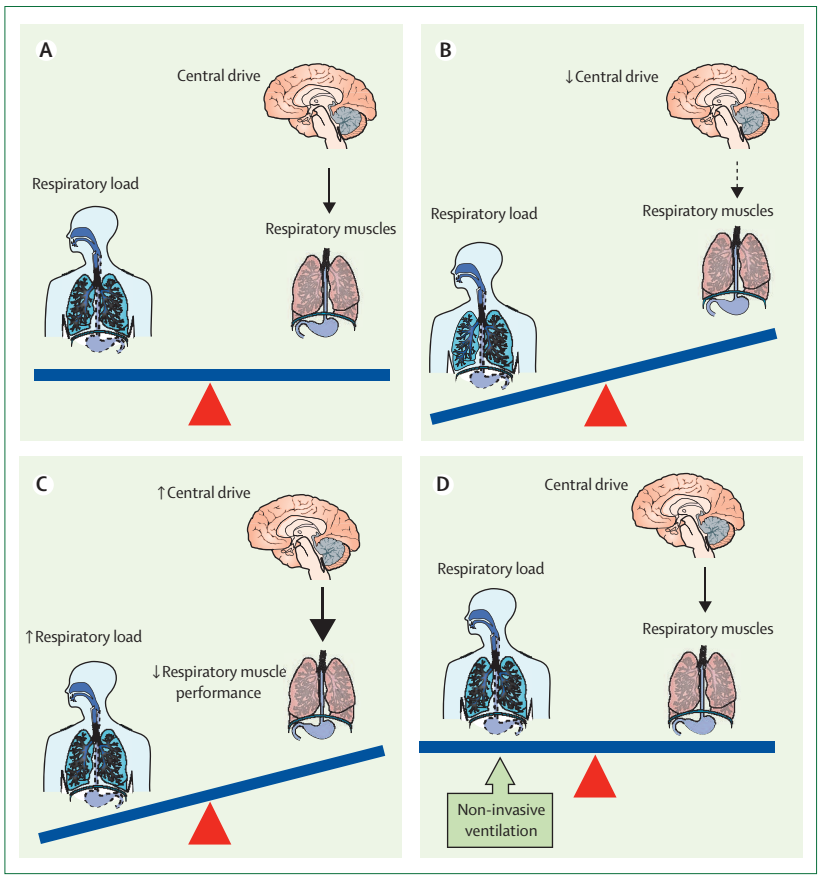

Figure: **Respiratory balance**
(A) Normal respiratory balance is when the load imposed on the respiratory system, the capacity of the respiratory muscles, and the central drive are in equilibrium. (B) A decrease in central drive (dotted line) causes a decrease in the activity of the respiratory muscles and, subsequently, a reduction in alveolar ventilation. (C) A weakness of the respiratory muscles or an increase in respiratory load causes an increase in central drive (bold arrow). Alveolar ventilation occurs when the imbalance exceeds a specific threshold. (D) Non-invasive ventilation can correct disequilibrium in the respiratory balance by replacing central drive, unloading (in case of an increase in respiratory load, as shown), or assisting the respiratory muscles (in case of respiratory muscle weakness).

Panel 1: **Examples of disorders that can cause disequilibrium in the respiratory balance**

Increase in respiratory load

Anatomical abnormalities of the upper airway
- Treacher Collins syndrome
- Craniofaciostenosis
- Pierre Robin syndrome
- Pycnodysostosis
- Achondroplasia
- Tracheomalacia or laryngomalacia
- Congenital or acquired laryngotracheal stenosis
- Vocal cord paralysis
- Other upper airway malformation
- Storage diseases
- Neck masses or tumours
- Down's syndrome
- Beckwith-Wiedemann syndrome

Lower airway obstruction
- Cystic fibrosis
- Bronchopulmonary dysplasia
- Bronchiolitis obliterans

Decrease in performance of respiratory muscles
- Spinal muscular atrophy
- Spinal cord injury
- Phrenic nerve injury
- Myasthenia
- Myopathies and dystrophies

Dysfunction of central drive
- Congenital central hypoventilation syndrome
- Brain injury by tumours or infection (encephalitis)
- Brainstem dysfunction (eg, Chiari malformation)

muscles, with the respiratory muscles having a mechanical disadvantage because of distorsion of the chest wall. Disorders of the central drive are rare and could be congenital (eg, congenital central hypoventilation syndrome [Ondine's curse]) or acquired due to compression of or injury to the brainstem. Other disorders involving an impairment of two or more components of respiratory balance (eg, achondroplasia and mucopolysaccharidoses) can cause upper airway obstruction and brainstem compression.

The type of non-invasive ventilation needed by patients depends on the pathophysiological features of their respiratory failure. CPAP is the simplest type of non-invasive respiratory support and is indicated in cases of isolated obstruction of the upper or lower airways. Indeed, in the case of airway obstruction causing an increase in respiratory load, the two other components of respiratory balance (ie, the respiratory muscles and central drive) are unaffected, and restoration of sufficient airway patency throughout the entire breathing cycle normalises breathing (figure D).[9,12] BiPAP is indicated when these two other components of respiratory balance are also impaired.

In lung diseases associated with an increase in respiratory load, the aim of non-invasive ventilation is to unload the respiratory muscles.[10,11,14,16] Since affected individuals have a normal central drive and preserved respiratory muscle capacity, ventilatory assistance that maintains the patient's own breathing pattern by allowing them to trigger assisted breaths will be the most appropriate and comfortable.[10,11] Conversely, in individuals with weak respiratory muscles, the role of BiPAP will be to assist or replace, according to the severity of the weakness, the respiratory muscles by delivering positive pressure during inspiration. For these patients, triggering of the ventilator might be difficult or impossible. A controlled mode with a back-up rate (ie, a minimum number of breaths delivered per min by the ventilator) close to the normal respiratory rate during sleep for age is recommended. Thus, CPAP is clearly not the treatment for sleep-disordered breathing in patients with neuromuscular disease. Finally, in individuals with an

abnormal central drive, the BiPAP ventilator should be able to take over command of the respiratory muscles by means of a controlled mode.

Equipment and settings for non-invasive ventilation

Equipment for non-invasive ventilation comprises the interface, the circuit, and the device. Important improvements have been made in interfaces available for children (table). Interfaces can cover the nose (nasal mask), the nose and the mouth (nasobuccal mask), the face (total face mask), and, exceptionally, the mouth only (mouthpiece).[17,18] Nasal pillows (or prongs or cannulas) are minimum contact interfaces that are available for children aged 5–7 years or older and are very well tolerated.[17]

Interfaces can be either vented or non-vented. Vented interfaces incorporate intentional leaks and are to be used with a single circuit (ie, with only an inspiratory line, the expiration occurring through the intentional leak on the interface) and a minimum positive expiratory pressure. Non-vented masks can be used with a double circuit (ie, with a separate inspiratory and expiratory line) or a circuit with an expiratory valve (ie, with only an inspiratory line, the expiration occurring through a valve that opens exclusively during expiration), with or without positive expiratory pressure. A minimum level of expiratory pressure is mandatory for vented masks, to allow the clearing of carbon dioxide during expiration.[19,20]

The choice of interface is decided by the patient's age, weight, facial and skull anatomy for the fitting of the headgear, nasal permeability and the eventual presence of mouth breathing, ventilatory mode (requiring a vented or non-vented interface), comfort and tolerance with the interface, and the patient's ability and need to remove the interface unaided. Nasal masks and full face masks are also available for neonates and infants, which have contributed to the rapid expansion in use of non-invasive ventilation in young children.[21] Children with maxillofacial deformities—eg, those with Treacher Collins syndrome—will generally need a nasobuccal mask.[22]

Different modes of non-invasive ventilation are available. Constant CPAP is the simplest mode and has proven efficacy in children with severe upper airway obstruction.[9,12,15,23–25] Autotitrated CPAP is a mode during which positive airway pressure is adjusted automatically between a minimum and maximum airway pressure set by the prescriber, according to analysis of the flow curve and airway resistance by device software. More advanced modes—associated with a moderate decrease in airway pressure at the onset of expiration, or a variable increase in airway pressure during inspiration—are also available.[26] Since all CPAP devices have been designed for adult patients, manufacturers recommend a minimum weight, usually between 10 kg and 30 kg, for use of the autotitrated and advanced CPAP modes. A few studies have compared constant CPAP with autotitrated and advanced CPAP modes, but superiority of these more complex modes has not been shown with respect to comfort or efficacy, compared with constant CPAP.[27,28]

The aim of CPAP titration is to suppress any residual respiratory event and is usually done during polysomnography.[29] Titration might also be done by means of recording oesogastric pressures, which reflect the inspiratory and expiratory work of breathing. In infants with severe upper airway obstruction, setting the CPAP pressure to the highest tolerated pressure is recommended, because a setting based on non-invasive clinical variables (eg, improvement in oxygenation and CO_2 levels, reduction in respiratory rate and heart rate, and increase in tidal volume) has been shown to underestimate the optimum CPAP pressure by a mean of 2 cm H_2O in these patients.[15]

During BiPAP, a higher level of positive pressure is delivered during inspiration by means of a volume-targeted or pressure-targeted mode. With volume-targeted ventilation, the ventilator delivers a fixed volume throughout a given time span. The advantage of this mode is strict delivery of a preset volume; the main disadvantage is that this mode is not able to adjust to the variable requirements of the patient during sleep—eg, physiological changes in central drive, lung compliance, and airway resistance. Moreover, compensation for unintentional air leaks is not possible, which puts the patient at risk of receiving an insufficient effective inspired volume.[30] With pressure-targeted ventilation, the airflow is adjusted to generate a constant positive pressure during a given time span. The

	Advantages	Disadvantages	Side-effects
Nasal mask	Small internal volume; large choice of different industrial models	Not usable in case of mouth leaks	Pressure sores, eye irritation if leaks, facial deformity
Nasobuccal mask	Prevents mouth leaks	Large volume; risk of inhalation of gastric content in case of gastro-oesophageal reflux; impairs communication and vocalisation; increased aerophagia	Pressure sores, eye irritation if leaks, facial deformity
Total face mask	Prevents mouth leaks	Larger volume than nasobuccal mask; risk of inhalation of gastric content in case of gastro-oesophageal reflux; impairs communication and vocalisation; increased aerophagia	Pressure sores, facial deformity
Nasal pillows	Small and light; no pressure sores	Not usable in case of mouth leaks	Nasal irritation
Mouthpiece	Small and light; no pressure sores; can be used intermittantly	Not useable during sleep	None

Table: **Advantages, disadvantages, and side-effects of interfaces for children**

delivered volume depends on the interaction between the preset pressure, the patient's inspiratory effort, and the respiratory mechanics.[31] The main advantage of pressure-targeted ventilation compared with volume-targeted ventilation is its ability to compensate for unintentional leaks. Patient–ventilator synchronisation is improved because flow can vary on a breath-to-breath basis. However, this mode requires that the device is able to detect the onset and end of inspiration of the patient, which can be difficult in young children because of small airflows and volumes.[12] Innovative modes, also called hybrid modes, use intelligent algorithms to adjust one or more settings automatically to achieve predefined targets.[32] These hybrid modes, known as volume-targeting pressure ventilation (VTPV) or average volume-assured pressure support (AVAPS), combine the characteristics of both volume-targeted and pressure-targeted ventilation to overcome previous limitations. These modes provide a predetermined target volume while maintaining the physiological benefits of the pressure-targeted mode. The ventilator measures or estimates the volume of each expired breath and adjusts inspiratory pressure automatically within a predetermined range to ensure a stable target volume. Hybrid modes are used increasingly in paediatric patients despite scarcity of validated studies in children.[33]

BiPAP settings should be adjusted to the patient's underlying disorder. In children with neuromuscular disease, the aim is to deliver a physiological tidal volume. This goal can be achieved with low inspiratory pressures in young infants with compliant lungs and chest wall, but higher inspiratory pressures will be necessary in older children, those with scoliosis, or patients who are obese. Expiratory pressures should be set at the lowest values, because patients with neuromuscular disease usually have no airway obstruction. A back-up rate close to the physiological breathing rate during sleep is recommended; inspiratory triggering of the ventilator can be difficult for a child with weakened respiratory muscles and, therefore, a back-up rate is needed to avoid apnoea. In children with cystic fibrosis, the optimum settings for non-invasive ventilation have been assessed in physiological studies measuring the work of breathing.[10,11,16] In these patients, the optimum mean inspiratory pressure was 16 cm H_2O with no expiratory pressure, the inspiratory trigger should be sensitive, and a back-up rate is recommended to avoid apnoea.[11,16] In other lung diseases (eg, bronchiolitis obliterans), a high level of expiratory pressure might be necessary to counterbalance the intrinsic positive end-expiratory pressure.[14] In any case, settings for CPAP or BiPAP should be set and adapted individually.

Negative pressure ventilation comprises the application of negative pressure around the chest during inspiration, to expand the thorax and generate a tidal volume. This method has been used for several decades, mainly in adult patients with neuromuscular disease, and its use in children is limited.[5] However, use of negative pressure ventilation has expanded during the past few years because devices have improved greatly in performance and have become smaller. This type of ventilation could be worthwhile at night or for patients who cannot tolerate a non-invasive interface. However, the biggest problem with use of negative pressure ventilation is that of obstructive sleep-disordered breathing due to suppression of the normal preinspiratory activation of upper airway muscles. The effectiveness of this approach should, therefore, be checked carefully because of the risk of persistent respiratory events and desaturations.[34]

Indications for and benefits of non-invasive ventilation

No criteria have been validated for when to start long-term non-invasive ventilation in children. In clinical practice, non-invasive ventilation can be initiated in several situations: in an acute setting; after failure to wean a patient off non-invasive ventilation in the paediatric intensive care unit; in cases of abnormal nocturnal gas exchange alone; or in patients with a high apnoea-hypopnoea index on polysomnography.[8] The main challenges or difficulties for initiation of non-invasive ventilation in children are: deciding on the timing and type of investigation that should be done (eg, polysomnography, polygraphy, or an overnight gas exchange recording); and defining the values or thresholds of variables that are retained (eg, the oxygen or CO_2 level, or the apnoea-hypopnoea index) with the assumption that their correction will be associated with a benefit of non-invasive ventilation.[8] These difficulties are attributable to the paucity of markers for end-organ morbidity associated with sleep-disordered breathing and chronic respiratory failure in children. Neurocognitive dysfunction and behavioural disturbances are the most common and severe outcomes of obstructive sleep apnoea in children, but these deleterious effects are highly variable from one child to another.[35] Of note, morbidity associated with sleep-disordered breathing has been studied little in children needing non-invasive ventilation for disorders other than obstructive sleep apnoea.

A sleep study forms part of the routine assessment for a child with obstructive sleep apnoea. Polysomnography represents the gold standard, but polygraphy or continuous monitoring of nocturnal gas exchange by measurement of pulse oximetry (SpO_2) and transcutaneous partial pressure of CO_2 ($PtcCO_2$) can be used as an alternative procedure if full polysomnography is not available.[36] Usual indications for CPAP are residual obstructive sleep apnoea after adenotonsillectomy (defined as an apnoea-hypopnoea index greater than five events per h) and obstructive sleep apnoea related to obesity or craniofacial abnormalities.[36] Every therapeutic intervention in a child with obstructive sleep apnoea should be evaluated after 6 weeks to 12 months. In practice, CPAP is prescribed in children with complex

obstructive sleep apnoea due to anatomical or structural abnormalities of the upper airways—eg, craniofacial malformations, Down's syndrome, Prader-Willi syndrome, or morbid obesity.[6,37,38] BiPAP is indicated if nocturnal hypoventilation persists despite optimum CPAP.[36] CPAP is associated with an improvement in sleep variables—eg, the apnoea-hypopnoea index, gas exchange, attention deficits, behaviour, sleepiness, and quality of life.[6]

Less consensus exists about the type of investigation and criteria for initiation of BiPAP in children with neuromuscular diseases. First, BiPAP might be justified without a sleep study when the child presents with episodes of acute respiratory failure triggered by a respiratory infection or an anaesthetic procedure, since these events are markers of insufficient respiratory reserve.[39] Concerning the timing of a sleep study, validated recommendations are sparse, possibly because of the heterogeneity of neuromuscular disorders in children and the variability of respiratory involvement within a specific disease—eg, spinal muscular atrophy or collagen 6 (COL6) myopathies.[40,41] Symptoms suggestive of sleep-disordered breathing did not differ in children with a neuromuscular disorder with or without overt nocturnal hypoventilation.[42] These symptoms, therefore, cannot be used as predictors or markers of nocturnal hypoventilation; moreover, they can be difficult to assess in young children and typically arise too late in the course of the disease to be of diagnostic value. With respect to the predictive value of lung function and other respiratory variables, researchers on a large prospective study of children with neuromuscular disorders did not identify a sensitive and specific daytime lung function or respiratory muscle test that was associated with or predictive of nocturnal hypoxaemia or hypercapnia.[43] The type of neuromuscular disorder should be taken into account, because nocturnal hypoventilation occurs more often in disorders characterised by prominent diaphragmatic weakness. Children with a COL6 myopathy should be screened systematically for sleep-disordered breathing.[44] Prioritised screening is also recommended for infants or young children with congenital myopathies or rapidly progressive neuromuscular diseases.[45] In children with neuromuscular disease, documentation of nocturnal hypoventilation by means of polysomnography is recommended but not essential before starting BiPAP, because isolated abnormal nocturnal gas exchange can be sufficient to show hypoventilation and justify BiPAP initiation.[46] Indeed, nine of ten patients with neuromuscular disease or thoracic deformity and isolated nocturnal hypercapnia without daytime hypercapnia progressed to overt daytime respiratory failure within a period of 2 years.[46] Moreover, in the presence of an abnormal overnight gas exchange recording or full polysomnography, criteria that are used to define nocturnal hypoventilation are highly variable, which has practical outcomes because an indication for long-term non-invasive ventilation relies on detection of hypoventilation.[47] The scoring of polysomnography in patients with neuromuscular disease needs specific expertise. Indeed, instead of apnoeic and hypopnoeic events, patients can present with a progressive simultaneous decrease in airflow and thoracic and abdominal movements accompanied or not by a change in gas exchange, suggestive of global inspiratory muscle weakness.[48] Paradoxical breathing with opposition phase on the thoracic and abdominal belts can be a result of diaphragmatic dysfunction or weakness of the intercostal muscles and should not be interpreted falsely as obstructive events.[48–50]

Periods of reduced ventilation or paradoxical breathing (more so than obstructive or central apnoea-hypopnoea, particularly during rapid-eye movement sleep), which are associated with SpO_2 less than 90% or $PtcCO_2$ greater than 50 mm Hg, are indicative of insufficient respiratory muscle performance and justify long-term BiPAP in children with neuromuscular disease. In clinical practice, however, many children with a progressive neuromuscular disease (eg, spinal muscular atrophy or Duchenne muscular dystrophy) are started on non-invasive ventilation empirically. Indeed, limited access to sleep studies should not delay these patients accessing an effective treatment, the most important requisite being that children should be followed up by a paediatric team with expertise in non-invasive ventilation.

Widespread use of BiPAP in children with neuromuscular disease contrasts with the few studies in which the benefits of BiPAP have been assessed in children. Findings of studies in small numbers of patients show that BiPAP is associated with normalisation of nocturnal and daytime gas exchange, an improvement in sleep quality, and a reduction in symptoms associated with sleep-disordered breathing.[51–53] Non-invasive ventilation associated with mechanical insufflation-exsufflation, prevents thoracic deformities and consequent thoracic and lung hypoplasia in young children with neuromuscular disease.[54] Intermittent positive-pressure breathing, which entails delivery of high inspiratory pressures generally on a daily basis during daytime, can increase ventilation in patients with neuromuscular disease.[55] Both non-invasive ventilation and intermittent positive-pressure breathing are also effective at prevention of atelectasis and the risk of pneumonia in children with neuromuscular disease.[56]

Children with cystic fibrosis do not have a validated indication for a sleep study or BiPAP. In a prospective multicentre study of 80 paediatric and adult patients with stable cystic fibrosis, who had a forced expiratory volume in 1 s (FEV_1) less than 60% predicted, 13 (18%) patients spent more than 10% of night-time with SpO_2 less than 90% and 33 (47%) had $PtcCO_2$ greater than 45 mm Hg.[57] Nocturnal gas exchange correlated with daytime arterial blood gases, and nocturnal SpO_2 correlated with FEV_1. However, no correlation was recorded between the

subjective assessment of sleep quality (by means of questionnaires) and the objective evaluation of nocturnal gas exchange. No consensus exists about clinical situations or criteria that justify initiation of BiPAP in children with cystic fibrosis. Similar to adult patients with chronic obstructive pulmonary disease, BiPAP is recommended as a first-line treatment for an acute hypercapnic respiratory exacerbation, without any evidence from prospective randomised studies.[58–60] BiPAP is also prescribed largely for patients on lung transplant lists and those with insufficient improvement after oxygen therapy.[61] This usage contrasts with the conclusion of a Cochrane review, in which improvement of nocturnal gas exchange and diminished oxygen desaturation and respiratory muscle fatigue during chest physiotherapy were the only proven benefits of BiPAP in cystic fibrosis.[62] An unresolved question is the use of non-invasive ventilation for CO_2 clearance in children with pulmonary hypertension due to primary lung or complex congenital heart disease; children with congenital heart disease are a burgeoning population with high-risk home needs.

In clinical practice, non-invasive ventilation is associated with improved feeding, weight gain, and growth, which supports findings of physiological studies showing that non-invasive ventilation decreases the work of breathing and resultant caloric burn.[9,63] In some studies, non-invasive ventilation was also associated with improved sleep quantity and quality, which has a positive effect on neurocognitive and behavioural outcomes.[6,64]

Screening with at least an overnight gas exchange recording to detect nocturnal hypoxaemia or hypercapnia, and if possible with a complete sleep study, should be a priority in all children with upper airway obstruction and any type of neuromuscular or lung disease that might be associated with nocturnal hypoventilation. Symptoms of sleep-disordered breathing are insufficiently sensitive and specific and tend to arise late in the course of the different diseases. Since poor sleep quality is associated with neurocognitive dysfunction, abnormal behaviour, and decreased quality of life, a trial of 1–3 months of non-invasive ventilation with a thorough assessment before and after the period of non-invasive ventilation, seems a reasonable option.

Practical follow-up of children

Non-invasive ventilation is a technically challenging treatment, but the ultimate aim is to perform it at home. It is usually initiated in hospital during a short admission, to acclimatise the patient to their treatment. Because non-invasive ventilation will be administered during sleep, overnight monitoring of sleep with the optimum settings—at least with an assessment of overnight gas exchange and ideally with polygraphy or polysomnography—is recommended before discharge. However, non-invasive ventilation might also be implemented in the home care setting, according to local resources, family capacity, patient's stability, and other socioeconomic factors. Because of a shortage of hospital beds at our institution (Hôpital Necker Enfants-Malades, Paris, France), we have started outpatient initiation of non-invasive ventilation for selected patients, with efficacy and compliance comparable with in-hospital initiation (unpublished data). A sleep study with non-invasive ventilation is recommended but can be postponed until the patient is well adapted to their treatment and is able to sleep at least 6 h with the device. Training of caregivers and the patient is essential. Caregivers must not only be familiar with putting on and taking off the interface and device but also must have training for the different problems that might arise at home.[65] Careful checking of the caregiver's competence is mandatory. Availability of a trained home care provider, who is able to visit the patient at home on a regular as-needed basis, is an important requisite of success for outpatient initiation. However, the large variability in availability and quality of home care nursing to buttress parental care remains a limitation of home non-invasive ventilation in children.

Compliance with non-invasive ventilation is a major issue, because treatment efficiency is related to length of nocturnal use.[6] In most studies, fairly low compliance has been reported, with mean night-time use between 3 h and 5 h.[6,27,28] However, objective compliance close to the recommended sleep duration in children can be achieved by expert centres having a specific non-invasive ventilation therapeutic education programme.[66] Close collaboration is necessary between the hospital team and the home care provider. Home care provider systems vary from one country to another, but the team visiting the patient at home must have expertise in paediatric non-invasive ventilation. Caregivers should be able to contact the home care provider for any technical assistance and the hospital team for any medical issue at any time.[65]

No validated guidelines are available for monitoring or long-term follow-up of children undergoing non-invasive ventilation. Timing of follow-up visits depends on the age and medical condition of the child. At our institution, we undertake a sleep study in hospital 1 month after initiation of non-invasive ventilation, then have at least one outpatient follow-up visit and one in-hospital full sleep study with non-invasive ventilation every 2–6 months. However, practice at other institutions and in other countries varies, with no evidence for superiority of one approach over another. However, overnight measurement of SpO_2 with $PtcCO_2$ recording during non-invasive ventilation usually takes place at every follow-up visit because many asymptomatic patients remain hypercapnic during sleep with non-invasive ventilation, despite a normal overnight SpO_2 and normal daytime blood gases.[67] This residual nocturnal hypercapnia can be corrected easily by simple measures—eg, changing the interface or the ventilator settings.[67] Check-ups can also be done at home with adequate training of staff.[68] Simultaneous

analysis of the in-built software of the ventilator and the overnight gas exchange gives useful information on important issues such as objective compliance, unintentional leaks, respiratory rate, airway pressure, and respiratory events. However, because most devices are designed for adults, this information is not always reliable for children.[69] Systematic polygraphic studies are recommended during non-invasive ventilation because residual respiratory events—eg, patient–ventilator asynchronies, unintentional leaks, persistent obstructive events with or without reduction in central drive, and persistent central or mixed events—are common in asymptomatic children with stable disease and might be accompanied by desaturations or arousals.[70,71] Residual respiratory events are less common in asymptomatic children with stable disease after treatment with CPAP.[38]

Compared with most adult patients, a substantial number of children could be weaned off their ventilator support over time.[2] Indeed, some conditions (eg, Pierre Robin syndrome or bronchopulmonary dysplasia) improve spontaneously with increasing age.[21,63] Other disorders, such as tracheal or laryngeal stenosis, Treacher Collins syndrome, or craniofaciostenosis, might improve after upper airway surgery, maxillofacial surgery, or neurosurgery. No recommendations or guidelines are available for weaning children off ventilator support. Depending on the type of corrective surgery, a minimum delay of about 2–6 months is typical for weaning off non-invasive ventilation, corresponding to the timing associated with the maximum benefit of the surgical intervention. In the case of spontaneous improvement, a sleep study without CPAP or non-invasive ventilation is indicated at least 2–4 weeks after weaning off ventilator support because of the long-lasting effects of CPAP and non-invasive ventilation. In any case, long-term follow-up is recommended because of the possibility of recurrence of sleep-disordered breathing.[72]

Side-effects, limitations, and ethical aspects

Non-invasive ventilation can be associated with side-effects (table). The most common are those caused by the interface and include skin injury from pressure sores, eye irritation because of unintentional air leaks, and facial deformity in young patients.[73] Skin injury is less common than several years ago because of improvements in interfaces for children and the use of minimum contact interfaces such as nasal pillows. Mouth leaks can be minimised by use of a chin strap or a pacifier in infants, or a change to a nasobuccal mask. Facial flattening and maxillary retrusion can be prevented by use of nasal pillows or by alternating different interfaces—eg, a nasal mask and a nasobuccal mask. Other side-effects might be attributable to the positive pressure. Aerophagia or gastric distension, and increased gastro-oesophageal reflux, can be seen with high CPAP pressures or, in case of patient–ventilator asynchrony, with BiPAP. These abdominal side-effects can be managed by decreasing the airway pressures or correcting patient–ventilator asynchrony. Autonomic arousals might be seen during persistent obstructive events with CPAP and during unintentional leaks with BiPAP.[8,71]

Non-invasive ventilation still has some limitations in the youngest children. A minimum weight of 5 kg is generally recommended as a cutoff for this treatment in the community. However, recommendations vary by country and, most importantly, these cutoffs have not been validated clinically.

Sleep affects the three components of the respiratory balance: respiratory load, the respiratory muscles, and central drive (figure). Physiological changes in respiratory and upper airway function, respiratory muscle power, and ventilatory response lead to reduced ventilation during sleep. Most patients need non-invasive ventilation only during sleep,[1,2] but some patients will also need this treatment during the daytime, particularly individuals with advanced neuromuscular disease.[74,75] In children with neuromuscular disease, mouthpiece ventilation during the daytime can prolong the duration of non-invasive ventilation and delay the timing of a tracheostomy.[74–76] In a study of 30 adult patients with neuromuscular disease, patient-reported benefits of mouthpiece ventilation included a reduction in dyspnoea and fatigue and an improvement in speech and eating.[75] However, mouthpiece ventilation can be impossible or difficult in very young children. Even if non-invasive ventilation is very effective, it can be difficult to apply around the clock on a long-term basis. Some expert teams have had successful experiences with non-invasive ventilation in children with neuromuscular disease who are totally dependent on a ventilator.[77] Other clinicians consider that the child should be able to breathe spontaneously without non-invasive ventilation for a minimum time per day so they can be discharged home safely. However, this practice is also dependent on local experience and patient's preference. A tracheostomy represents a possible option for children with a progressive neuromuscular disease, which has to be prepared and discussed thoroughly with the child and their parents. However, this invasive procedure is not always associated with a decrease in quality of life.[78]

The decision to transition to tracheostomy is complex for children with severe underlying disease with a fatal outcome and rapid decline, developmental delay, or severe physical or cognitive disabilities. Determining the best interests of the child is important, and the Royal College of Paediatrics and Child Health states that the decision must balance the "benefits and burdens of treatment and outcomes, whilst considering ascertainable wishes, beliefs and values and preferences of the child and their family, the cultural and religious views of the matter, the views of those providing care for the child and what choice is less restrictive for future options".[79] The transition from non-invasive ventilation

Panel 2: Goals for future studies of long-term non-invasive ventilation in children

- Investigation of the correlation between clinical scenarios, symptoms, and physiological respiratory variables used for initiation of long-term non-invasive ventilation and outcomes
- Validation of criteria for weaning off long-term non-invasive ventilation
- Better understanding of neurocognitive and behavioural benefits of non-invasive ventilation in children with disorders other than obstructive sleep apnoea
- Validation of the optimum follow-up for children treated with long-term non-invasive ventilation

Search strategy and selection criteria

We searched the Cochrane Library, MEDLINE, and relevant specialty journals for articles published between Jan 1, 1980, to Jan 1, 2016, with the terms: ("noninvasive ventilation", "noninvasive ventilatory support", "noninvasive mechanical ventilation", "positive pressure ventilation", "continuous positive airway pressure", "bilevel ventilation", "BiPAP", OR "negative pressure ventilation") AND ("pediatric", "children", OR "infants"). We selected publications from 2004 to 2016, with an emphasis on those published after 2011, but we did not exclude commonly referenced and highly regarded older publications. We searched only for articles published in English, or those translated into English. We also searched reference lists of articles identified by this strategy and selected those we judged relevant. We included randomised controlled trials, observational studies, retrospective studies, meta-analyses, review articles, editorials, and case reports.

to tracheostomy can be associated with a great burden with respect to the improvement in quality of life of the child and their family.[80] Non-invasive ventilation might then be used as part of a palliative care approach, without prolonging excessively a poor or unbearable quality of life. The confidence, transparency, and quality of the relationship of the family with the health-care team are of crucial importance and determine the individual nature of these decisions. However, this area of health-related quality of life remains complex and is evolving.[81–84]

Concluding remarks

Long-term non-invasive ventilation is a very effective type of respiratory support that has transformed the scope of chronic respiratory failure and severe sleep-disordered breathing in children by avoiding tracheostomies and allowing patients to live at home with a good quality of life for themselves and their families. The great heterogeneity of disorders, patients' ages, prognosis, and outcomes underline the need for management by skilled multidisciplinary centres having technical competence in paediatric non-invasive ventilation and expertise in sleep studies and therapeutic education. The increased use of non-invasive ventilation contrasts with the scant proven benefits. Future studies should aim to define disease and age-appropriate initiation and weaning criteria, and objective physiological and quality of life benefits (panel 2).

Contributors

BF wrote the Review, with contributions from AA and AF. All authors approved the final version.

Declaration of interests

We declare no competing interests.

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References

1 Paulides FM, Plötz FB, Verweij-van den Oudenrijn LP, van Gestel JP, Kampelmacher MJ. Thirty years of home mechanical ventilation in children: escalating need for pediatric intensive care beds. *Intensive Care Med* 2012; **38:** 847–52.
2 McDougall CM, Adderley RJ, Wensley DF, Seear MD. Long-term ventilation in children: longitudinal trends and outcomes. *Arch Dis Child* 2013; **98:** 660–65.
3 Pavone M, Verrillo E, Caldarelli V, Ullmann N, Cutrera R. Non-invasive positive pressure ventilation in children. *Early Hum Dev* 2013; **89** (suppl 3)**:** S25–31.
4 Simonds A, Muntoni F, Heather S, Fielding S. Impact of nasal ventilation on survival in hypercapnic Duchenne muscular dystrophy. *Thorax* 1998; **53:** 949–52.
5 Graham RJ, Fleegler EW, Robinson WM. Chronic ventilator need in the community: a 2005 pediatric census of Massachusetts. *Pediatrics* 2007; **119:** e1280–87.
6 Marcus CL, Radcliffe J, Konstantinopoulou S, et al. Effects of positive airway pressure therapy on neurobehavioral outcomes in children with obstructive sleep apnea. *Am J Respir Crit Care Med* 2012; **185:** 998–1003.
7 Nozoe KT, Polesel DN, Moreira GA, et al. Sleep quality of mother-caregivers of Duchenne muscular dystrophy patients. *Sleep Breath* 2016; **20:** 129–34.
8 Amaddeo A, Moreau J, Frapin A, et al. Long term continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) in children: initiation criteria in real life. *Pediatr Pulmonol* 2016; published online April 25. DOI:10.1002/ppul.23416.
9 Fauroux B, Pigeot J, Polkey MI, et al. Chronic stridor caused by laryngomalacia in children: work of breathing and effects of noninvasive ventilatory assistance. *Am J Respir Crit Care Med* 2001; **164:** 1874–78.
10 Fauroux B, Pigeot J, Isabey D, Harf A, Clément A, Lofaso F. In vivo physiological comparison of two ventilators used for domiciliary ventilation in children with cystic fibrosis. *Crit Care Med* 2001; **29:** 2097–105.
11 Fauroux B, Nicot F, Essouri S, et al. Setting of pressure support in young patients with cystic fibrosis. *Eur Respir J* 2004; **24:** 624–30.
12 Essouri S, Nicot F, Clément A, et al. Noninvasive positive pressure ventilation in infants with upper airway obstruction: comparison of continuous and bilevel positive pressure. *Intensive Care Med* 2005; **31:** 574–80.
13 Hart N, Polkey MI, Clément A, et al. Changes in pulmonary mechanics with increasing disease severity in children and young adults with cystic fibrosis. *Am J Respir Crit Care Med* 2002; **166:** 61–66.
14 Giovannini-Chami L, Khirani S, Thouvenin G, Ramirez A, Fauroux B. Work of breathing to optimize noninvasive ventilation in bronchiolitis obliterans. *Intensive Care Med* 2012; **38:** 722–24.
15 Khirani S, Ramirez A, Aloui S, Leboulanger N, Picard A, Fauroux B. CPAP titration in infants with severe airway obstruction. *Crit Care* 2013; **17:** R167.

16 Fauroux B, Louis B, Hart N, et al. The effect of back-up rate during non-invasive ventilation in young patients with cystic fibrosis. *Intensive Care Med* 2004; **30:** 673–81.

17 Ramirez A, Delord V, Khirani S, et al. Interfaces for long-term noninvasive positive pressure ventilation in children. *Intensive Care Med* 2012; **38:** 655–62.

18 Khirani S, Kadlub N, Delord V, Picard A, Fauroux B. Nocturnal mouthpiece ventilation and medical hypnosis to treat severe obstructive sleep apnea in a child with cherubism. *Pediatr Pulmonol* 2013; **48:** 927–29.

19 Lofaso F, Brochard L, Touchard D, Hang T, Harf A, Isabey D. Evaluation of carbon dioxide rebreathing during pressure support ventilation with airway management system (BiPAP) devices. *Chest* 1995; **108:** 772–78.

20 Gregoretti C, Navalesi P, Ghannadian S, Carlucci A, Pelosi P. Choosing a ventilator for home mechanical ventilation. *Breathe* 2013; **9:** 394–409.

21 Amaddeo A, Abadie V, Chalouhi C, et al. Continuous positive airway pressure for upper airway obstruction in infants with Pierre Robin Sequence. *Plast Reconstr Surg* 2016; **137:** 609–12.

22 Ramirez A, Delord V, Khirani S, et al. Interfaces for long term noninvasive positive pressure ventilation in children. *Intensive Care Med* 2012; **38:** 655–62.

23 Guilleminault C, Nino-Murcia G, Heldt G, Baldwin R, Hutchinson D. Alternative treatment to tracheostomy in obstructive sleep apnea syndrome: nasal continuous positive airway pressure in young children. *Pediatrics* 1986; **78:** 797–802.

24 Guilleminault C, Pelayo R, Clerk A, Leger D, Bocian RC. Home nasal continuous positive airway pressure in infants with sleep-disordered breathing. *J Pediatr* 1995; **127:** 905–12.

25 Waters WA, Everett FM, Bruderer JW, Sullivan CE. Obstructive sleep apnea: the use of nasal CPAP in 80 children. *Am J Respir Crit Care Med* 1995; **152:** 780–85.

26 Chihara Y, Tsuboi T, Hitomi T, et al. Flexible positive airway pressure improves treatment adherence compared with auto-adjusting PAP. *Sleep* 2013; **36:** 229–36.

27 Marcus CL, Rosen G, Ward SL, et al. Adherence to and effectiveness of positive airway pressure therapy in children with obstructive sleep apnea. *Pediatrics* 2006; **117:** e442–51.

28 Marcus CL, Beck SE, Traylor J, et al. Randomized, double-blind clinical trial of two different modes of positive airway pressure therapy on adherence and efficacy in children. *J Clin Sleep Med* 2012; **8:** 37–42.

29 Kushida CA, Chediak A, Berry RB, et al. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. *J Clin Sleep Med* 2008; **4:** 157–71.

30 Fauroux B, Leroux K, Desmarais G, et al. Performance of ventilators for noninvasive positive-pressure ventilation in children. *Eur Respir J* 2008; **31:** 1300–07.

31 Brochard L, Pluskwa F, Lemaire F. Improved efficacy of spontaneous breathing with inspiratory pressure support. *Am Rev Respir Dis* 1987; **136:** 411–15.

32 Rabec C, Emeriaud G, Amaddeo A, Fauroux B, Georges M. New modes in non-invasive ventilation. *Paediatr Respir Rev* 2016; **18:** 73–84.

33 Lofaso F, Prigent H, Tiffreau V, et al. Long-term mechanical ventilation equipment for neuromuscular patients: meeting the expectations of patients and prescribers. *Respir Care* 2014; **59:** 97–106.

34 Hill NS, Redline S, Carskadon MA, Curran FJ, Millman RP. Sleep-disordered breathing in patients with Duchenne muscular dystrophy using negative pressure ventilators. *Chest* 1992; **102:** 1656–62.

35 Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 2012; **130:** e714–55.

36 Kaditis AG, Alonso Alvarez ML, Boudewyns A, et al. Obstructive sleep disordered breathing in 2- to 18-year-old children: diagnosis and management. *Eur Respir J* 2016; **47:** 69–94.

37 Girbal IC, Gonçalves C, Nunes T, et al. Non-invasive ventilation in complex obstructive sleep apnea: a 15 year experience of a pediatric tertiary center. *Rev Port Pneumol* 2014; **20:** 146–51.

38 Amaddeo A, Caldarelli V, Fernandez-Bolanos M, et al. Polygraphic respiratory events during sleep in children treated with home continuous positive airway pressure: description and clinical consequences. *Sleep Med* 2015; **16:** 107–12.

39 Hull J, Aniapravan R, Chan E, et al. Respiratory management of children with neuromuscular weakness guideline group on behalf of the British Thoracic Society Standards of care committee. *Thorax* 2012; **67:** i1–40.

40 Khirani S, Colella M, Caldarelli V, et al. Longitudinal course of lung function and respiratory muscle strength in spinal muscular atrophy type 2 and 3. *Eur J Paediatr Neurol* 2013; **17:** 552–60.

41 Foley AR, Quijano-Roy S, Collins J, et al. Natural history of pulmonary function in collagen VI-related myopathies. *Brain* 2013; **136:** 3625–33.

42 Katz SL, Gaboury I, Keilty K, et al. Nocturnal hypoventilation: predictors and outcomes in childhood progressive neuromuscular disease. *Arch Dis Child* 2010; **95:** 998–1003.

43 Bersanini C, Khirani S, Ramirez A, et al. Nocturnal hypoxemia and hypercapnia in children with neuromuscular disorders. *Eur Respir J* 2012; **39:** 1206–12.

44 Quijano-Roy S, Khirani S, Colella M, et al. Diaphragmatic dysfunction in collagen VI myopathies. *Neuromuscul Disord* 2014; **24:** 125–33.

45 Rutkowski A, Chatwin M, Koumbourlis A, Fauroux B, Simonds A, on behalf of the CMD Respiratory Physiology Consortium. 203rd ENMC international workshop: respiratory pathophysiology in congenital muscle disorders—implications for pro-active care and clinical research 13–15 December, 2013, Naarden, The Netherlands. *Neuromuscul Disord* 2015; **25:** 353–58.

46 Ward S, Chatwin M, Heather S, Simonds AK. Randomised controlled trial of non-invasive ventilation (NIV) for nocturnal hypoventilation in neuromuscular and chest wall disease patients with daytime normocapnia. *Thorax* 2005; **60:** 1019–24.

47 Ogna A, Quera Salva MA, Prigent H, et al. Nocturnal hypoventilation in neuromuscular disease: prevalence according to different definitions issued from the literature. *Sleep Breath* 2016; **20:** 575–81.

48 Griffon L, Amaddeo A, Mortamet G, et al. Sleep study as a diagnostic tool for unexplained respiratory failure in infants hospitalized in the PICU. *J Crit Care* 2016; published online April 14. DOI:10.1016/j.jcrc.2016.04.003.

49 White JE, Drinnan MJ, Smithson AJ, Griffiths CJ, Gibson GJ. Respiratory muscle activity and oxygenation during sleep in patients with muscle weakness. *Eur Respir J* 1995; **8:** 807–14.

50 Steier J, Jolley CJ, Seymour J, et al. Sleep-disordered breathing in unilateral diaphragm paralysis or severe weakness. *Eur Respir J* 2008; **32:** 1479–87.

51 Simonds AK, Ward S, Heather S, Bush A, Muntoni F. Outcome of paediatric domiciliary mask ventilation in neuromuscular and skeletal disease. *Eur Respir J* 2000; **16:** 476–81.

52 Mellies U, Ragette R, Dohna Schwake C, Boehm H, Voit T, Teschler H. Long-term noninvasive ventilation in children and adolescents with neuromuscular disorders. *Eur Respir J* 2003; **22:** 631–36.

53 Young HK, Lowe A, Fitzgerald DA, et al. Outcome of noninvasive ventilation in children with neuromuscular disease. *Neurology* 2007; **68:** 198–201.

54 Chatwin M, Bush A, Simonds AK. Outcome of goal-directed non-invasive ventilation and mechanical insufflation/exsufflation in spinal muscular atrophy type I. *Arch Dis Child* 2011; **96:** 426–32.

55 Guérin C, Vincent B, Petitjean T, et al. The short-term effects of intermittent positive pressure breathing treatments on ventilation in patients with neuromuscular disease. *Respir Care* 2010; **55:** 866–72.

56 Dohna-Schwake C, Podlewski P, Voit T, Mellies U. Non-invasive ventilation reduces respiratory tract infections in children with neuromuscular disorders. *Pediatr Pulmonol* 2008; **43:** 67–71.

57 Fauroux B, Pepin JL, Boelle PY, et al. Sleep quality and nocturnal hypoxaemia and hypercapnia in children and young adults with cystic fibrosis. *Arch Dis Child* 2012; **97:** 960–66.

58 Sood N, Paradowski LJ, Yankaskas JR. Outcomes of intensive care unit care in adults with cystic fibrosis. *Am J Respir Crit Care Med* 2001; **163:** 335–38.

59 Ellaffi M, Vinsonneau C, Coste J, et al. One-year outcome after severe pulmonary exacerbation in adults with cystic fibrosis. *Am J Respir Crit Care Med* 2005; **171:** 158–64.

60 Texereau J, Jamal D, Choukroun G, et al. Determinants of mortality for adults with cystic fibrosis admitted in intensive care unit: a multicenter study. *Respir Res* 2006; **7:** 14–24.

61 Fauroux B, Burgel PR, Boelle PY, et al. Practice of noninvasive ventilation for cystic fibrosis: a nationwide survey in France. *Respir Care* 2008; **53:** 1482–89.

62 Moran F, Bradley JM, Piper AJ. Non-invasive ventilation for cystic fibrosis. *Cochrane Database Syst Rev* 2013; **4:** CD002769.

63 Leboulanger N, Picard A, Soupre V, et al. Physiologic and clinical benefits of noninvasive ventilation in infants with Pierre Robin sequence. *Pediatrics* 2010; **126:** e1056–63.

64 Mellies U, Dohna-Schwake C, Stehling F, Voit T. Sleep disordered breathing in spinal muscular atrophy. *Neuromuscul Disord* 2004; **14:** 797–803.

65 Chatwin M, Heather S, Hanak A, Polkey MI, Simonds AK. Analysis of home support and ventilator malfunction in 1,211 ventilator-dependent patients. *Eur Respir J* 2010; **35:** 310–16.

66 Ramirez A, Khirani S, Aloui S, et al. Continuous positive airway pressure and noninvasive ventilation adherence in children. *Sleep Med* 2013; **14:** 1290–94.

67 Paiva R, Krivec U, Aubertin G, Cohen E, Clément A, Fauroux B. Carbon dioxide monitoring during long-term noninvasive respiratory support in children. *Intensive Care Med* 2009; **35:** 1068–74.

68 Felemban O, Leroux K, Aubertin G, et al. Value of gas exchange recording at home in children receiving non-invasive ventilation. *Pediatr Pulmonol* 2011; **46:** 802–08.

69 Contal O, Vignaux L, Combescure C, Pepin JL, Jolliet P, Janssens JP. Monitoring of noninvasive ventilation by built-in software of home bilevel ventilators: a bench study. *Chest* 2012; **141:** 469–76.

70 Gonzalez-Bermejo J, Perrin C, Janssens JP, et al. Proposal for a systematic analysis of polygraphy or polysomnography for identifying and scoring abnormal events occurring during non-invasive ventilation. *Thorax* 2012; **67:** 546–52.

71 Caldarelli V, Borel JC, Khirani S, et al. Polygraphic respiratory events during sleep with noninvasive ventilation in children: description, prevalence, and clinical consequences. *Intensive Care Med* 2013; **39:** 739–46.

72 Fauroux B, Leboulanger N, Roger G, et al. Noninvasive positive-pressure ventilation avoids recannulation and facilitates early weaning from tracheotomy in children. *Pediatr Crit Care Med* 2010; **11:** 31–37.

73 Fauroux B, Lavis JF, Nicot F, et al. Facial side effects during noninvasive positive pressure ventilation in children. *Intensive Care Med* 2005; **31:** 965–69.

74 Toussaint M, Steens M, Wasteels G, Soudon P. Diurnal ventilation via mouthpiece: survival in end-stage Duchenne patients. *Eur Respir J* 2006; **28:** 549–55.

75 Khirani S, Ramirez A, Delord V, et al. Evaluation of ventilators for mouthpiece ventilation in neuromuscular disease. *Respir Care* 2014; **59:** 1329–37.

76 Bach JR, Alba AS, Saporito LR. Intermittent positive pressure ventilation via the mouth as an alternative to tracheostomy for 257 ventilator users. *Chest* 1993; **103:** 174–82.

77 Bach JR, Niranjan V. Spinal muscular atrophy type I: a noninvasive respiratory management approach. *Chest* 2000; **117:** 1100–05.

78 Raphael JC, Dazord A, Jaillard P, et al. Indices de satisfaction des patients atteints d'une dystrophie musculaire de Duchenne de Boulogne et ventilés à domicile. *Rev Neurol* 2002; **158:** 453–60.

79 Larcher V, Craig F, Bhogal K, Wilkinson D, Brierley J, on behalf of the Royal College of Paediatrics and Child Health. Making decisions to limit treatment in life-limiting and life-threatening conditions in children: a framework for practice. *Arch Dis Child* 2015; **100** (suppl 2): s3–23.

80 Fine-Goulden MR, Ray S, Brierley J. Decision making in long-term ventilation for children. *Lancet Respir Med* 2015; **3:** 745–46.

81 Graham RJ, Robinson WM. Integrating palliative care into chronic care for children with severe neurodevelopmental disabilities. *J Dev Behav Pediatr* 2005; **26:** 361–65.

82 Ramelli GP, Hammer J. Swiss physicians' practices of long-term mechanical ventilatory support of patients with Duchenne muscular dystrophy. *Swiss Med Wkly* 2005; **135:** 599–604.

83 Kinali M, Manzur AY, Mercuri E, et al. UK physicians' attitudes and practices in long-term non-invasive ventilation of Duchenne muscular dystrophy. *Pediatr Rehabil* 2006; **9:** 351–64.

84 Graham RJ, Rodday AM, Parsons SK. Family centered assessment and function for children with chronic mechanical respiratory support. *J Pediatr Health Care* 2014; **28:** 295–304.

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Original Article

Can the analysis of built-in software of CPAP devices replace polygraphy in children?

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ABSTRACT

Objectives: Polysomnography (PSG) is the gold standard for the scoring of residual respiratory events during continuous positive airway pressure (CPAP). Studies comparing PSG scoring with automatic scoring by the built-in software of CPAP devices have reported acceptable agreements except for the hypopnea index (HI) in adult patients, but no study has yet been conducted in children. The aim of the present study was to compare the automatic scoring by CPAP device and manual scoring using the software tracings of the CPAP device integrating pulse oximetry (SpO_2) with in-lab polygraphy (PG).
Methods: Consecutive clinically stable children treated with constant CPAP (ResMed) for at least one month and scheduled for a nocturnal PG were recruited. A pulse oximeter was connected to the CPAP device. The PG apnea-hypopnea index (AHI_{PG}), scored according to modified AASM guidelines, was compared with the automatic AHI reported by the CPAP device ($AHI_{A\ CPAP}$) and the manual scoring of the AHI on the CPAP software ($AHI_{M\ CPAP}$).
Results: Fifteen children (1.5–18.6 years) were included. Mean residual AHI_{PG} was 0.9 ± 1.2/hour (0.0–4.6/hour) vs. $AHI_{A\ CPAP}$ of 3.6 ± 3.6/hour (0.5–14.7/hour) ($p < 0.001$), and $AHI_{M\ CPAP}$ of 1.2 ± 1.6/hour (0.0–5.1/hour) ($p = 0.01$). Correlation between AHI_{PG} and $AHI_{A\ CPAP}$ was good ($r = 0.667$; $p = 0.007$), and improved when considering $AHI_{M\ CPAP}$ ($r = 0.933$; $p < 0.001$). Strong correlations were also observed between the PG apnea index (AI) and HI, and the manually scored AI and HI on CPAP, respectively.
Conclusions: Manual scoring of respiratory events on the built-in software tracings of CPAP devices integrating SpO_2 signal may be helpful. These results have to be confirmed in patients with higher AHI.
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1. Introduction

In-lab overnight polysomnography (PSG) is considered the gold standard for continuous positive airway pressure (CPAP) titration and follow-up, both in children and adults [1,2]. However, there is considerable interest in validating alternative strategies to reduce the need for in-lab follow-up sleep studies, which are of limited access, costly and labor intensive [3].

Several studies have assessed the ability of different CPAP devices to identify residual respiratory events in adult patients with obstructive sleep apnea, and compared the data of the built-in software of CPAP devices with respiratory events simultaneously determined by in-lab PSG [4–14] or home type III polygraphy (PG) [15]. Despite the good correlation between the automatic apnea-hypopnea index (AHI) given by the built-in software of the CPAP device and the AHI scored by PSG/PG, the correlation was weaker for the hypopnea index (HI) alone. However, variable ranges of limits of agreement have been observed between the AHI scored by different CPAP devices and PSG/PG, which may lead to a misdiagnosis of residual respiratory events and, thus, inappropriate management. One explanation for the discrepancy between the AHI scoring by the CPAP device and that performed by PSG/PG is that the AHI automatically scored by the CPAP device depends entirely on the CPAP airflow signal, whereas the PSG/PG scoring takes in account the airflow signal and changes in arterial oxygen saturation

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(SpO_2) [9,15]. No study has yet assessed the residual respiratory events in pediatric patients by the different CPAP devices.

As one of the limitations of the CPAP built-in software is the scoring of hypopneas, the present study investigated the value of the adjunct of a SpO_2 oximeter to the CPAP devices to improve hypopnea scoring in children. Therefore, the AHI scored automatically by the built-in software of the CPAP device ($AHI_{A\ CPAP}$) was compared with the manual analysis of the CPAP built-in software tracings with the SpO_2 signal ($AHI_{M\ CPAP}$) and the AHI scored on an in-lab PG (AHI_{PG}).

2. Materials and methods

2.1. Patients

All consecutive stable patients treated with noninvasive constant CPAP for at least one month at home and with scheduled overnight PG between October 2015 and June 2016 were included. A dedicated noninvasive ventilation and sleep unit in a tertiary pediatric university hospital performed all sleeps studies. The study was conducted in agreement with the French regulations and received appropriate legal and ethical approval from the Ethical Committee CPP Ile de France II, n° 2015-11-3.

2.2. In-lab polygraphy

In-lab overnight PG (Cidelec, Saint Gemme sur Loire, France or Alice 6, Respironics, Carquefou, France) was performed with CPAP. Respiratory movements were recorded by respiratory inductance plethysmography, tracheal sound, body position, movements by actigraphy, heart rate, and SpO_2 (Nonin Medical Inc., USA) [16]. The SpO_2 signal was averaged on a four pulse-window and displayed with a sampling frequency of 1 Hz. Airflow was recorded using a pneumotachograph (pediatric/adult flow sensor, Hamilton Medical AG, Switzerland) placed on the single limb circuit next to the nasal/facial mask of the patient or a tubular flow sensor (Cidelec or Alice 6). The tubular flow sensor consisted of two connectors that were placed on the single limb circuit, one at the CPAP device exit and one next to the nasal/facial mask, which estimated airflow as the pressure difference between the two connectors [2]. The sleep study was recorded on videotape with an infrared video camera.

Respiratory events were scored according to 'modified' AASM guidelines, as electroencephalographic (EEG) arousals could not be scored on PG [16]. Obstructive apnea was defined as a drop in airflow amplitude by 90% of baseline for at least two respiratory cycles, with continued or increased inspiratory efforts. Central apnea was defined as a drop in airflow amplitude by 90% of baseline without inspiratory effort, duration of at least two breaths, and associated with an awakening, and/or a 3% oxygen desaturation (OD), or of a duration of at least 20 s. Mixed apnea was defined as a drop in airflow amplitude by 90% of baseline for at least two respiratory cycles with the absence of inspiratory effort during one portion of the event and the presence of inspiratory effort during another portion, regardless of which portion came first. Hypopnea was defined as a drop in airflow amplitude by 30% of baseline of a duration of at least two breaths, associated with an awakening, and/or an OD [16]. Recording time (Trec) was defined as the time between the reported sleep time and wakefulness. Total sleep time (TST) was defined as the Trec minus the wake periods recorded by actigraphy.

AHI_{PG} was calculated as the sum of the apnea and hypopnea events per hour of TST. The apnea index (AI_{PG}) and HI_{PG} were calculated as the number of apneas and hypopneas per hour of TST, respectively. Sleep study was considered normal in case of an AI_{PG} <1 event/hour and an AHI_{PG} <1.5 events/hour [17]. Mild sleep apnea was defined as an AHI_{PG} between 1.5 and 5 events/hour, moderate sleep apnea as an AHI_{PG} between 5 and 10 events/hour, and severe sleep apnea as an $AHI_{PG} \geq 10$ events/hour.

2.3. CPAP device

Only devices with a fixed CPAP mode from the ResMed brand (S9 series, Airsense 10, Stellar) were used because of the necessity to have a cycle-by-cycle airflow display together with SpO_2 signal on the software (ResScan 5.6, ResMed Limited, Australia). A SpO_2 sensor (Nonin Xpod, Nonin Medical Inc., USA) was connected directly to the external port of the CPAP device. The SpO_2 signal was displayed on ResScan software with a sampling frequency of 1 Hz. In patients treated with another CPAP device, a ResMed device with the same CPAP pressure was used for the night.

According to information provided by the manufacturer, obstructive apnea was defined as a 75% reduction of baseline airflow, for at least 10 s, with upper airway closure. Central apnea was defined as a 75% reduction of baseline airflow, for at least 10 s, without upper airway closure. The distinction between obstructive and central apneas was performed by means of the forced oscillation technique that enabled detection of upper airway closure/opening. Unknown apnea was defined as apneas that could not be characterized precisely because of total air leak over 30 L/minute. Hypopnea was defined as a partial upper airway closure (ie, a 50% reduction of baseline airflow associated with inspiratory airflow limitation) for at least 10 s. This scoring did not integrate the changes in SpO_2.

2.4. Procedure

Expert staff manually scored PG, and the residual AHI_{PG}, AI_{PG} and HI_{PG} were reported. Two readers, who were blinded from the PG results, scored the respiratory events using the built-in CPAP software. Automatic AHI ($AHI_{A\ CPAP}$), AI ($AI_{A\ CPAP}$) and HI ($HI_{A\ CPAP}$) assessed by the built-in CPAP software were reported. Automatic AHI, AI and HI were also calculated as indexes per hour of polygraphic Trec ($AHI_{A\ CPAP}$ Trec, $AI_{A\ CPAP}$ Trec, $HI_{A\ CPAP}$ Trec) and per hour of polygraphic TST ($AHI_{A\ CPAP}$ TST, $AI_{A\ CPAP}$ TST, $HI_{A\ CPAP}$ TST).

All the respiratory events were then manually scored using the CPAP software as follows: (i) all the respiratory events following the AASM guidelines [16] were validated, (ii) all the events preceded by a sigh [18] or a movement (unstable airflow tracing), or central apnea lasting <20 s and hypopnea not associated with an OD, were removed, (iii) all the respiratory events scored according to the AASM guidelines but not scored by the CPAP software were added, (iv) all the respiratory events falsely scored by CPAP were modified. The AHI, AI and HI were calculated as the number of events scored using the CPAP software per hour of polygraphic Trec ($AHI_{M\ CPAP}$ Trec, $AI_{M\ CPAP}$ Trec, $HI_{M\ CPAP}$ Trec) and as the number of events per hour of polygraphic TST ($AHI_{M\ CPAP}$ TST, $AI_{M\ CPAP}$ TST, $HI_{M\ CPAP}$ TST). Periods with air leaks >24 L/min were discarded. Fig. 1 describes the different time periods to which the indexes of respiratory events refer.

2.5. Statistical analysis

The data were presented as mean and standard deviation (SD), or median and range. Comparisons between AHI_{PG}, AI_{PG} and HI_{PG} and automatic and manually scored events per hour of Trec and per hour of TST were performed using the Student *t*-test (parametric test) or the Mann–Whitney Rank Sum Test (nonparametric test). Pearson product moment correlation (parametric test) or Spearman rank order correlation (nonparametric test) coefficient (r) was calculated to assess the correlation between the respiratory events scored by PG, and CPAP software. Furthermore, agreement

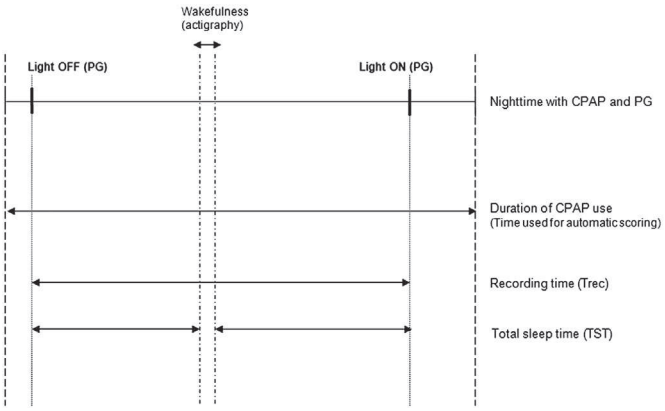

Fig. 1. Explanation of the different time periods used to calculate the indexes of the respiratory events.

between the respiratory events scored by PG and by CPAP software was assessed by the method of differences against the means [19]. The limits of agreement (95% CI) were calculated. A *p*-value <0.05 was considered for significance.

3. Results

Nineteen patients were included in the study. Four patients had no exploitable data, due to the intermittent airflow recorded on the CPAP software because of a low weight in two patients and a technical problem in two patients; therefore, the data of 15 patients were retained for subsequent analysis. Table 1 summarizes the anthropometric data of the patients. Mean age was 11.4 ± 5.1 years (range 1.5–18.6). Mean CPAP level was 9 ± 1 cmH_2O (range 6–12). Five patients were overweight and one patient was obese.

Mean residual AHI_{PG} was 0.9 ± 1.2 events/hour (range 0.0–4.6) with a mean residual AI_{PG} of 0.7 ± 0.9 events/hour and a mean HI_{PG} of 0.2 ± 0.4 events/hour. Table 2 shows the PG findings.

Table 1
Anthropometric data of the patients.

Patient	Gender	Age (years)	Height (cm)	Weight (kg)	BMI *z*-score	Underlying diagnosis (previous surgery)	CPAP device	CPAP level (cmH_2O)
1	F	13.9	153	43	−0.3	Crouzon syndrome	S9 Autoset EPR	8
2	M	8.9	139	74	2.8	Obesity (adenotonsillectomy)	S9 Elite	10
3	M	7.8	125	21	−2.0	Di Georges syndrome (22q11) (velopharyngoplasty)	AirSense 10	10
4	M	17.5	184	58	−2.2	Treacher-Collins syndrome	S9 Autoset EPR	10
5	M	14.9	139	38	0.1	Charge syndrome Tracheomalacia Glossoptosis	S9 Autoset EPR	9
6	F	10.4	138	36	0.7	Di Georges syndrome (22q11) Pharyngolaryngeal hypotonia	S9 VPAP ST	8
7	F	16.7	142	59	1.6	Mucopolysaccharidosis type I	AirSense 10	12
8	F	8.6	136	27	−0.9	Laryngeal paralysis History of tracheostomy	ICON (Fisher & Paykel) changed for S9 VPAP ST	8
9	F	14.7	152	56	1.1	Crouzon syndrome History of tracheostomy	S9 Autoset EPR	9
10	M	18.6	166	64	0.3	Crouzon syndrome	AirSense 10	11
11	M	16.4	167	75	1.5	Obesity with psychomotor delay	S9 Autoset EPR	10
12	M	5.1	103	17	0.5	Cardiomyopathy	AirSense 10	10
13	M	8.6	136	35	1.2	Crouzon syndrome History of tracheostomy (Adenotonsillectomy)	S9 VPAP ST	8
14	M	1.5	78	10	–	Chiari type 2 Myelomeningocele, hydrocephaly	Stellar 150	6
15	M	6.9	110	22	1.5	Pycnodysostosis	AirSense 10	8

BMI: body mass index; CPAP: continuous positive airway pressure.

Table 2
In-lab polygraphic findings during CPAP.

Patient	Trec (min)	TST (min)	AHI_{PG} (events/hour)	Total AI_{PG} (events/hour)	OAI_{PG} (events/hour)	CAI_{PG} (events/hour)	HI_{PG} (events/hour)
1	402	402	1.3	0.6	0.6	0.0	0.9
2	391	362	0.3	0.3	0.0	0.3	0.0
3	416	390	3.7	0.6	0.3	0.3	3.1
4	408	408	0.0	0.0	0.0	0.0	0.0
5	394	394	0.9	0.8	0.5	0.3	0.2
6	439	420	0.0	0.0	0.0	0.0	0.0
7	490	490	0.5	0.5	0.5	0.0	0.0
8	410	409	0.4	0.3	0.1	0.1	0.1
9	400	400	0.5	0.5	0.3	0.2	0.0
10	526	526	0.5	0.5	0.5	0.0	0.0
11	210	199	0.3	0.3	0.3	0.0	0.0
12	419	413	0.4	0.4	0.1	0.3	0.0
13	512	509	0.2	0.0	0.0	0.0	0.2
14	389	374	2.1	2.1	0.2	1.9	0.0
15	403	446	0.7	0.6	0.6	0.0	0.1

CPAP: continuous positive airway pressure; Trec: recording time; TST: total sleep time; AHI_{PG}: apnea-hypopnea index; AI_{PG}: apnea index; OAI_{PG}: obstructive apnea index; CAI_{PG}: central apnea index; HI_{PG}: hypopnea index.

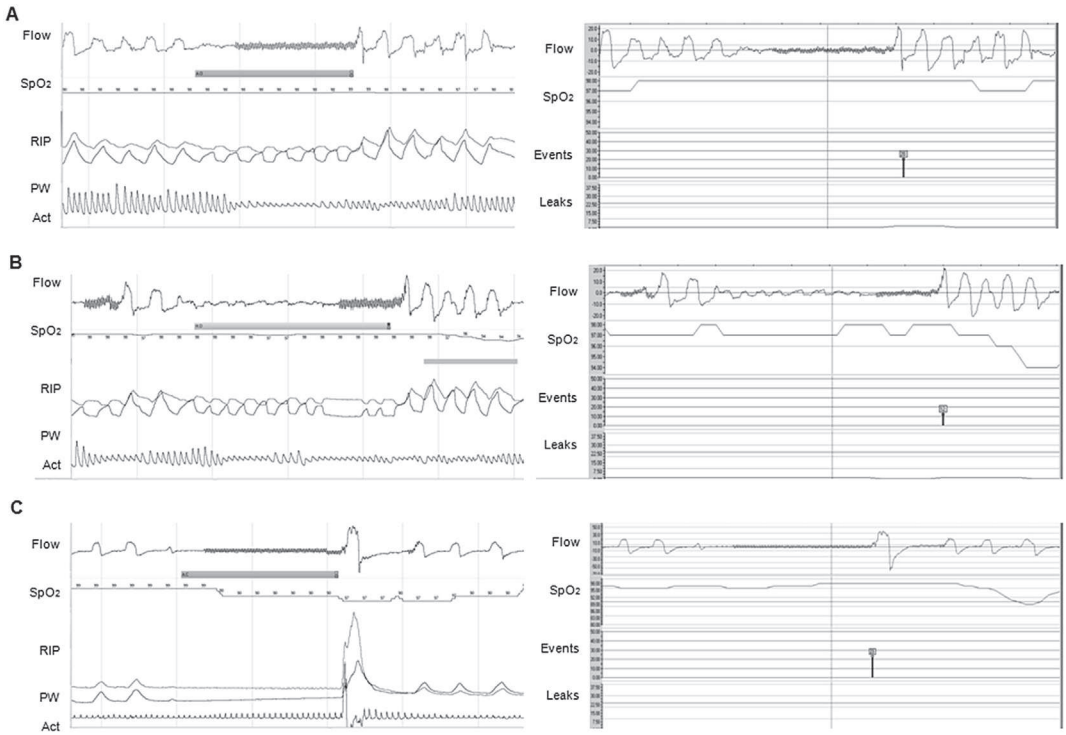

Fig. 2. Agreements between PG and CPAP software for events detection. A: Obstructive apnea without 3% OD. B: Hypopnea with 3% OD. The event was scored as obstructive apnea on the CPAP because of the end of the event. C: Central apnea of >20 s but no 3% OD, possibly due to an artifact on SpO_2 (note the artifacted pulse wave plethysmography), on PG compared with a central apnea of >20 s with 3% OD on CPAP. On PG: Flow is expressed in L/min; SpO_2 in %. On CPAP software: Flow is expressed in L/min; SpO_2 in %; events represent the type of automatic scored event; leaks is expressed in L/min. The continuous line represents the threshold of excessive leaks (24 L/min). (1 min period-window) Act, actimetry; CPAP, continuous positive airway pressure; OD, oxygen desaturation; PG, polygraphy; PW, pulse wave plethysmography; SpO_2, arterial oxygen saturation; RIP, respiratory inductance plethysmography.

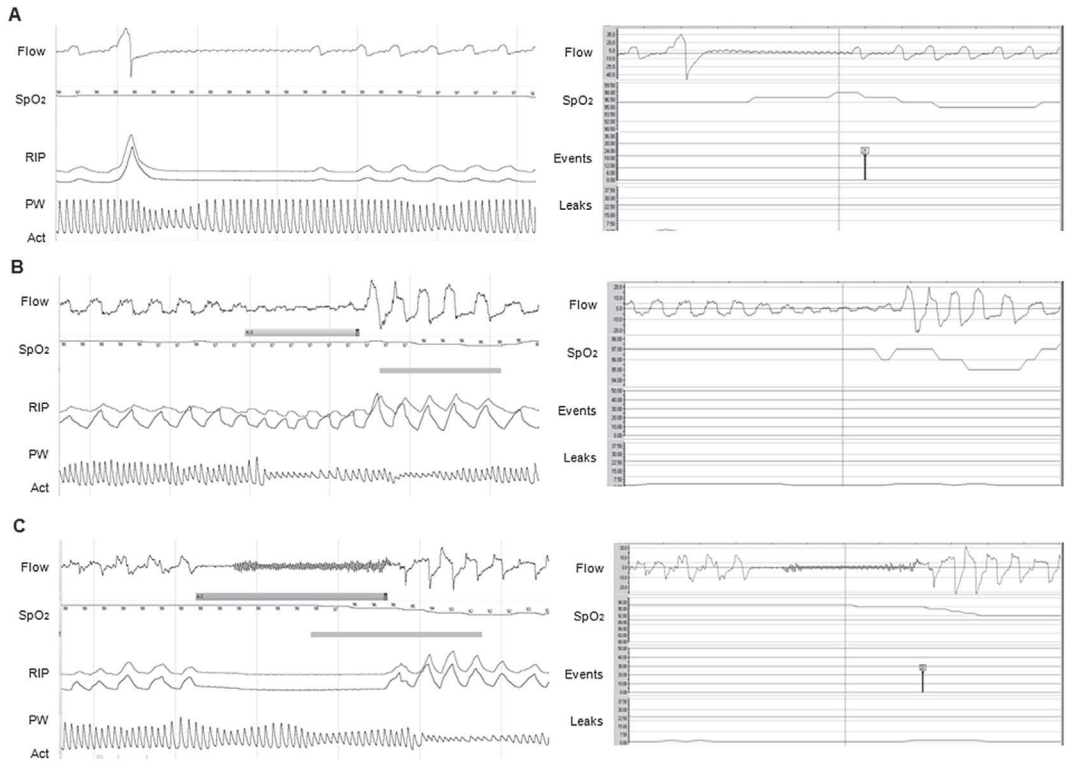

Fig. 3. Discrepancies between PG and CPAP for events detection. A: Central apnea preceded by a sigh, not scored on PG but automatically scored as "Apnea" on CPAP (S9 VPAP ST). Note the presence of a 3% OD on CPAP but not present on PG. B: Obstructive hypopnea with consecutive 3% OD scored on PG but not scored automatically on CPAP, neither manually because of the absence of 3% OD. C: Apnea with 3% OD scored as central on PG because of the absence of inspiratory effort, but falsely characterized as obstructive on CPAP (3% OD also present on CPAP). On PG: Flow is expressed in L/min; SpO_2 in %. On CPAP software: Flow is expressed in L/min; SpO_2 in %; events represent the type of automatic scored event; leaks is expressed in L/min. The continuous line represents the threshold of excessive leaks (24 L/min). (1 min period-window) Act, actimetry; CPAP, continuous positive airway pressure; OD, oxygen desaturation; PG, polygraphy; PW, pulse wave plethysmography; SpO_2, arterial oxygen saturation; RIP, respiratory inductance plethysmography.

Mean $AHI_{A\ CPAP}$ was 3.6 ± 3.6 events/hour (range 0.5–14.7) and was significantly higher than AHI_{PG} ($p < 0.001$). Mean $AHI_{A\ CPAP}$ Trec and $AHI_{A\ CPAP}$ TST were 2.9 ± 3.5 events/hour (range 0.1–14.3) and 2.8 ± 3.6 events/hour (range 0.1–14.6), respectively, and were significantly higher than AHI_{PG} ($p < 0.01$). Mean $AHI_{M\ CPAP}$ Trec and $AHI_{M\ CPAP}$ TST were 1.2 ± 1.7 events/hour (range 0.0–5.4) and 1.2 ± 1.6 events/hour (range 0.0–5.1), respectively. Mean $AHI_{M\ CPAP}$ values were lower than $AHI_{A\ CPAP}$, but still significantly higher than AHI_{PG} ($p < 0.05$).

Fig. 2 and Fig. 3 show some examples of agreements and discrepancies between the scoring of the respiratory events by PG and CPAP software, for patients #2, #3 and #6. Discrepancies were mainly due to the inappropriate scoring of a sigh or a movement by the CPAP software, the absence of concomitant OD on the PG and

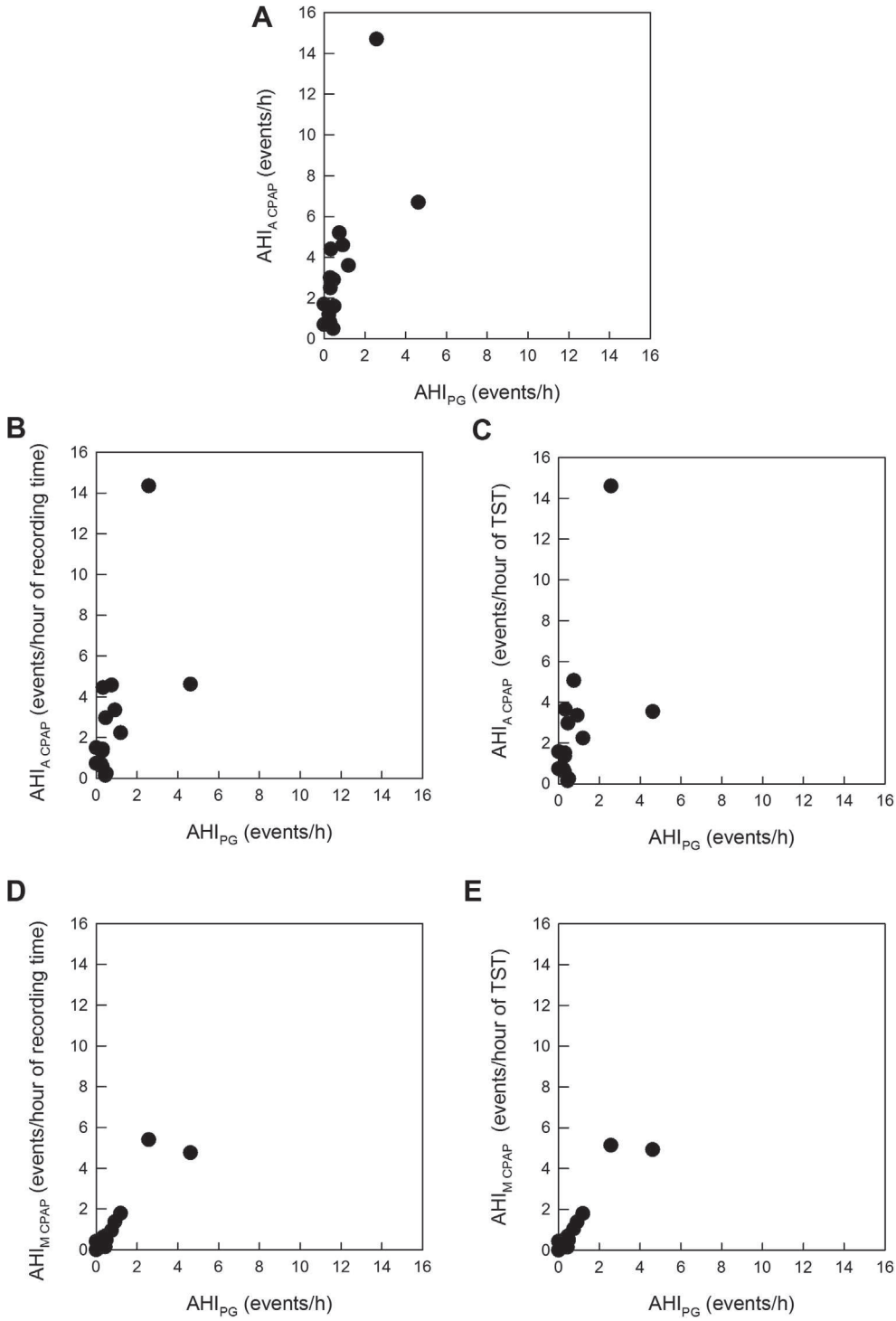

Fig. 4. Correlations between apnea-hypopnea indexes obtained by polygraphic scoring and automatic CPAP scoring (A), automatic CPAP scoring for the recording time (B), automatic CPAP scoring for TST (C), manual CPAP scoring for the recording time (D), and manual CPAP scoring for the TST (E). AHI_{PG}, polygraphic apnea-hypopnea index; $AHI_{A\ CPAP}$, automatic apnea-hypopnea index assessed by CPAP software; $AHI_{M\ CPAP}$, manual apnea-hypopnea index calculated using CPAP software; TST, total sleep time.

CPAP software, or to the inability or failure to distinguish an obstructive from a central apnea on the CPAP software.

Fig. 4 shows the correlations between the AHI scored by PG and CPAP and Table 3 presents the correlations between the indexes obtained with PG and CPAP software. AHI scored by the CPAP software tended to overestimate the AHI_{PG}. However, strong correlations were observed between AHI_{PG}, AI_{PG} and HI_{PG} and the indexes obtained by the manual scoring on the CPAP software ($p < 0.001$). The greatest differences were observed for the correlations between HI_{PG} and $HI_{A\ CPAP}$ versus HI_{PG} and $HI_{M\ CPAP}$. Fig. 5 displays the Bland–Altman plots of AHI_{PG} versus $AHI_{A\ CPAP}$ and $AHI_{M\ CPAP}$. The bias between AHI_{PG} and $AHI_{A\ CPAP}$ was −2.7 events/hour with wide limits of agreement (−8.6 to 3.1 events/hour). This bias reduced slightly when analyzing the agreement between AHI_{PG} and $AHI_{A\ CPAP}$ Trec (−2.0 events/hour; limits of agreement, −8.1 to 4.0 events/hour) and $AHI_{A\ CPAP}$ TST (−2.0 events/hour; limits of agreement, −8.2 to 4.3 events/hour). The bias and limits of agreement greatly decreased when comparing AHI_{PG} with $AHI_{M\ CPAP}$ Trec (−0.3 events/hour; limits of agreement, −1.8 to 1.1 events/hour) and $AHI_{M\ CPAP}$ TST (−0.3 events/hour; limits of agreement, −1.7 to 1.0 events/hour).

Discrepancies between PG and CPAP were mainly observed in three patients. In patient 3, $AHI_{A\ CPAP}$ was higher than $AHI_{PG,}$ due to a great difference between the time spent with CPAP and PG TST. In patient 5, artifacts on the respiratory inductance plethysmography impeded the characterization of apneas on PG, and therefore apneas were not scored on PG, leading to a higher number of automatic but also manually scored apneas on CPAP. In patient 14, a majority of central-like events without OD and lasting <20 s were present and not scored on PG, while on CPAP, as it was not possible to characterize the apneas, they were manually scored as obstructive apneas, leading to a high $AI_{M\ CPAP}$ when compared to PG. Of note, apneas were scored as hypopneas on the automatic CPAP scoring.

4. Discussion

The present study is the first to compare the automatic scoring of residual respiratory events by the built-in software of CPAP devices with a manual scoring on the CPAP tracings, integrating SpO_2, and with an in-lab PG in children on long-term, constant CPAP. The main finding was that manual scoring integrating SpO_2 seems very useful, even though the scoring is still not perfect with CPAP devices, due in part to a default of apnea characterization.

A limited number of studies have compared the scoring of respiratory events by the algorithms of current generation CPAP devices with manual scoring on PSG [9–15]. Good agreements have been reported between AHI scored on PSG and $AHI_{A\ CPAP}$ during constant or autotitrating CPAP, with a tendency to a stronger correlation for apnea than for hypopnea. Contrary to these findings, the current study found no correlation between AI_{PG} and $AI_{A\ CPAP}$ or between HI_{PG} and $HI_{A\ CPAP}$. This may be explained by the very low AI_{PG} in the patients (<1 event/hour) except in two patients, and by a high number of falsely scored hypopneas by the CPAP device (Stellar™) in the youngest patient of the series.

A number of factors may explain the differences between respiratory events detected automatically by the CPAP software and those manually scored on PG. First, the respiratory events scored automatically by the CPAP device represented the number of detected events per hour of CPAP therapy time, whereas the respiratory events on PG were only scored during sleep (with the limitation that wakefulness cannot be scored with PG as compared to PSG). However, when the number of events for the Trec or TST was corrected, surprisingly, the only difference was that AHI_{PG} did not correlate anymore with $AHI_{A\ CPAP}$ TST. Second, the scoring of respiratory events by CPAP devices did not comply with the AASM guidelines. Moreover, this scoring has been designed for adult patients, with the duration of the events set at 10 s instead of two respiratory cycles for children. Also, a respiratory event was defined by an arbitrary percentage of flow reduction. This may also explain why the CPAP software did not score some events. Also, one common limitation of the CPAP scoring was the false scoring of a sigh as an apnea. Third, even if it was possible to integrate an optional SpO_2 signal in the CPAP software, the CPAP scoring did not integrate the changes in SpO_2, which may have explained the discrepancies in the scoring of hypopneas. Finally, the software of the different CPAP devices was still not able to correctly distinguish obstructive from central apneas, which may have overestimated the number of apneas scored by CPAP. For all of these reasons, it was decided to manually score all the respiratory events on the CPAP software in the present study. The results showed that the manual scoring of respiratory events, taking in account SpO_2 changes, markedly reduced the differences of AHI, AI and HI values between the CPAP and PG scoring.

The scoring of respiratory events, and in particular hypopneas, by the CPAP device could be improved by integrating OD in the scoring of respiratory events. The addition of a thoracic and/or abdominal movement signal could help to characterize apneas. Moreover, combining actimetry or even pulse wave plethysmography to the CPAP device, in order to detect movements or artifacts on the SpO_2 recording, could be another window for improvement, even though some movements may be visible on the CPAP software. Finally, it could be very interesting to have the possibility of discarding selected time periods on the CPAP software, in order to remove artifacts or periods of movements from the scoring.

The present study had several limitations. First, the number of patients was small and the AHI values were low. Indeed, because

Table 3
Correlations between the indexes of respiratory events obtained with in-lab PG and the built-in software of the CPAP devices.

	$AHI_{A\ CPAP}$	$AHI_{A\ CPAP}$ Trec	$AHI_{A\ CPAP}$ TST	$AHI_{M\ CPAP}$ Trec	$AHI_{M\ CPAP}$ TST
AHI_{PG}	r = 0.667 $p = 0.007$	r = 0.569 $p = 0.027$	r = 0.509 $p = 0.053$	r = 0.915 $p < 0.001$	r = 0.933 $p < 0.001$
	$AI_{A\ CPAP}$	$AI_{A\ CPAP}$ Trec	$AI_{A\ CPAP}$ TST	$AI_{M\ CPAP}$ Trec	$AI_{M\ CPAP}$ TST
AI_{PG}	r = 0.502 $p = 0.067$	r = 0.443 $p = 0.098$	r = 0.355 $p = 0.194$	r = 0.928 $p < 0.001$	r = 0.940 $p < 0.001$
	$HI_{A\ CPAP}$	$HI_{A\ CPAP}$ Trec	$HI_{A\ CPAP}$ TST	$HI_{M\ CPAP}$ Trec	$HI_{M\ CPAP}$ TST
HI_{PG}	r = −0.109 $p = 0.710$	r = −0.086 $p = 0.761$	r = −0.093 $p = 0.742$	r = 0.983 $p < 0.001$	r = 0.985 $p < 0.001$

PG: polygraphy; CPAP: continuous positive airway pressure; AHI_{PG}: polygraphic apnea-hypopnea index; AI_{PG}: polygraphic apnea index; HI_{PG}: polygraphic hypopnea index; $AHI_{A\ CPAP}$: automatic apnea-hypopnea index assessed by CPAP software; $AI_{A\ CPAP}$: automatic apnea index assessed by CPAP software; $HI_{A\ CPAP}$: automatic hypopnea index assessed by CPAP software; $AHI_{M\ CPAP}$: manual apnea-hypopnea index calculated using CPAP software; $AI_{M\ CPAP}$: manual apnea index calculated using CPAP software; $HI_{M\ CPAP}$: manual hypopnea index calculated using CPAP software; Trec: recording time; TST: total sleep time.

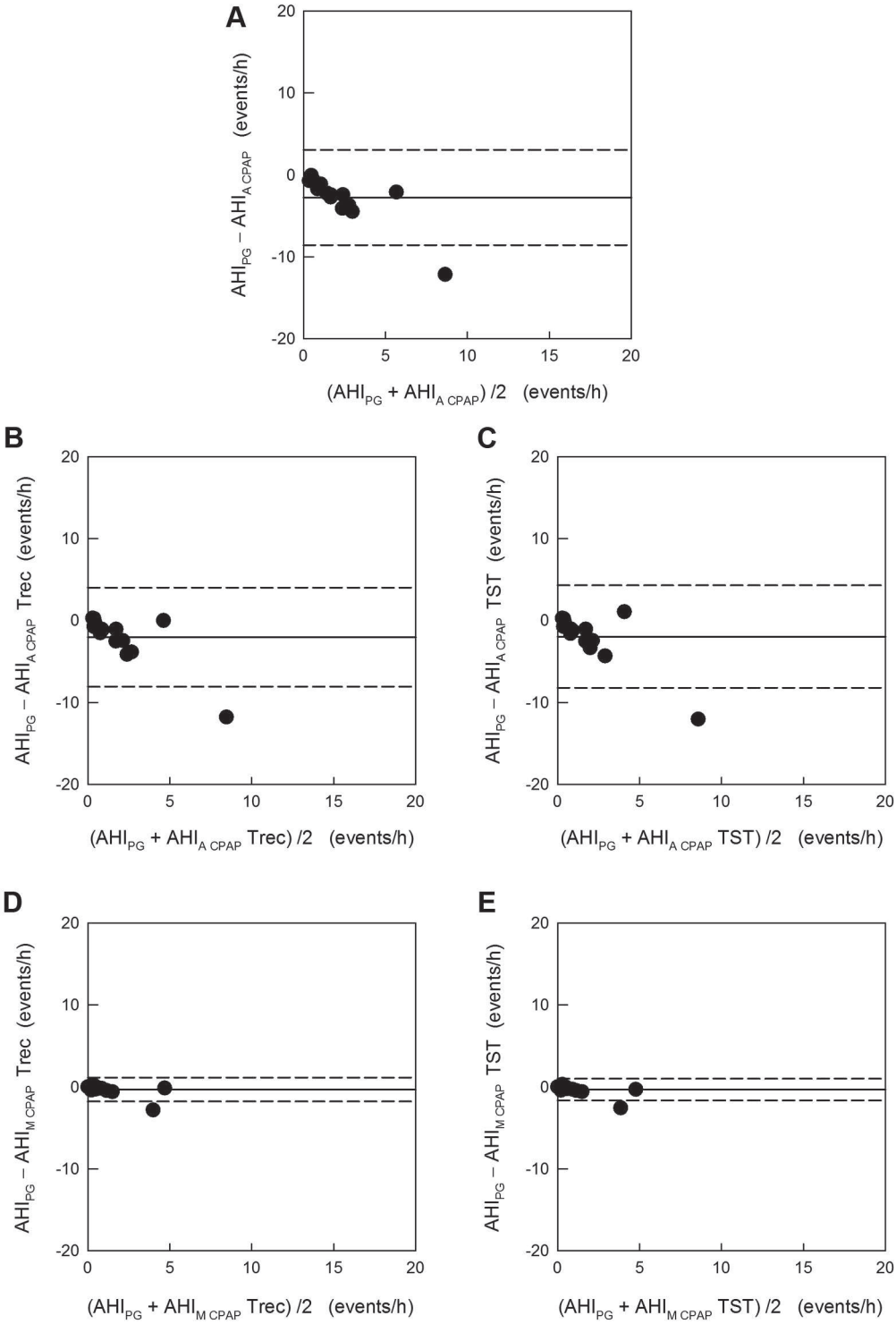

Fig. 5. Bland–Altman plots of apnea-hypopnea indexes with the differences between polygraphic scoring and automatic CPAP scoring (A), automatic CPAP scoring for the recording time (B), automatic CPAP scoring for TST (C), manual CPAP scoring for the recording time (D), and manual CPAP scoring for the TST (E). The continuous line represents the bias (mean of the difference) and the dashed lines represent the limits of agreement. Note that the difference between the two methods tended to greatly reduce with the manual CPAP scoring. CPAP, continuous positive airway pressure; OD, oxygen desaturation; PG, polygraphy; PW, pulse wave plethysmography; SpO_2, arterial oxygen saturation; TST, total sleep time.

the PGs were performed on stable patients on long-term CPAP therapy, the residual AHI_{PG} values were low [20]. One possibility to have higher residual AHI may be to perform the study during a titration study, which was not feasible at the time of the present study. A second limitation was that young children could not be studied, as airflow cannot be detected by the CPAP internal pneumotachograph below a minimal threshold. This minimal airflow threshold, reported as a minimal weight by the manufacturer, varies according to the CPAP device. A third limitation was that PG was performed instead of PSG, as in routine clinical management. In children, PG has been shown to underestimate the AHI when compared to PSG [21], mainly because of an incorrect

estimation of TST. However, sleep and wakefulness can be quite accurately determined in children using cardiorespiratory and videotape recordings [22], reducing the discrepancy between PSG and PG. In the present study, PG was combined with cardiorespiratory and videotape recordings. This had the 'advantage' that with PG, central apnea or hypopnea associated with micro-arousal was not scored, as with the CPAP software. A fourth limitation was that several CPAP devices were used, exclusively from the ResMed brand, having different detection algorithms. Finally, the average window for the SpO_2 signal integrated in the CPAP software was unknown and may have been different compared to that of in-lab PG. Moreover, it is well known that two pulse oximeters, even though from the same brand, may give variable inter-subject SpO_2 data.

In conclusion, the manual scoring of respiratory events by CPAP devices with the addition of an integrated SpO_2 signal may be helpful to assess CPAP efficacy. However, there is room for improvement for this scoring by the CPAP devices. Confirmation of the present results in children having higher residual AHI and using other CPAP devices is necessary.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2017.05.019.

References

[1] Kaditis AG, Alonso Alvarez ML, Boudewyns A, et al. Obstructive sleep disordered breathing in 2- to 18-year-old children: diagnosis and management. Eur Respir J 2016;47:69–94.
[2] Kushida CA, Chediak A, Berry RB, et al. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. J Clin Sleep Med 2008;4:157–71.
[3] Mador MJ. Is the CPAP estimate of the apnea-hypopnea index on therapy clinically useful? Sleep Breath 2013;17:15–6.
[4] Bradley PA, Mortimore IL, Douglas NJ. Comparison of polysomnography with ResCare Autoset in the diagnosis of the sleep apnoea/hourypopnoea syndrome. Thorax 1995;50:1201–3.
[5] Gugger M, Mathis J, Bassetti C. Accuracy of an intelligent CPAP machine with in-built diagnostic abilities in detecting apnoeas: a comparison with polysomnography. Thorax 1995;50:1199–201.
[6] Desai H, Patel A, Patel P, et al. Accuracy of autotitrating CPAP to estimate the residual Apnea-Hypopnea Index in patients with obstructive sleep apnea on treatment with autotitrating CPAP. Sleep Breath 2009;13:383–90.
[7] Prasad B, Carley DW, Herdegen JJ. Continuous positive airway pressure device-based automated detection of obstructive sleep apnea compared to standard laboratory polysomnography. Sleep Breath 2010;14:101–7.
[8] Ueno K, Kasai T, Brewer G, et al. Evaluation of the apnea-hypopnea index determined by the S8 auto-CPAP, a continuous positive airway pressure device, in patients with obstructive sleep apnea-hypopnea syndrome. J Clin Sleep Med 2010;6:146–51.
[9] Berry RB, Kushida CA, Kryger MH, et al. Respiratory event detection by a positive airway pressure device. Sleep 2012;35:361–7.
[10] Denotti AL, Wong KKH, Dungan II GC, et al. Residual sleep-disordered breathing during autotitrating continuous positive airway pressure therapy. Eur Respir J 2012;39:1391–7.
[11] Huang HCC, Hillman DR, McArdle N. Control of OSA during automatic positive airway pressure titration in a clinical case series: predictors and accuracy of device download data. Sleep 2012;35:1277–83.
[12] Ikeda Y, Kasai T, Kawana F, et al. Comparison between the apnea-hypopnea indices determined by the REMstar auto M series and those determined by standard in-laboratory polysomnography in patients with obstructive sleep apnea. Intern Med 2012;51:2877–85.
[13] Cilli A, Uzun R, Bilge U. The accuracy of autotitrating CPAP-determined residual apnea-hypopnea index. Sleep Breath 2013;17:189–93.
[14] Nigro CA, González S, Arce A, et al. Accuracy of a novel auto-CPAP device to evaluate the residual apnea-hypopnea index in patients with obstructive sleep apnea. Sleep Breath 2015;19:569–78.
[15] Stepnowsky C, Zamora T, Barker R, et al. Accuracy of positive airway pressure device—measured apneas and hypopneas: role in treatment followup. Sleep Disord 2013. http://dx.doi.org/10.1155/2013/314589.
[16] Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American Academy of sleep medicine. J Clin Sleep Med 2012;8:597–619.
[17] Uliel S, Tauman R, Greenfeld M, et al. Normal polysomnographic respiratory values in children and adolescents. Chest 2004;125:872–8.
[18] Haupt ME, Goodman DM, Sheldon SH. Sleep related expiratory obstructive apnea in children. J Clin Sleep Med 2012;8:673–9.
[19] Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurements. Lancet 1986;327:307–10.
[20] Amaddeo A, Caldarelli V, Fernandez-Bolanos M, et al. Polygraphic respiratory events during sleep in children treated with home continuous positive airway pressure: description and clinical consequences. Sleep Med 2015;16:107–12.
[21] Tan HL, Gozal D, Ramirez HM, et al. Overnight polysomnography versus respiratory polygraphy in the diagnosis of pediatric obstructive sleep apnea. Sleep 2014;37:255–60.
[22] Morielli A, Ladan S, Ducharme FM, et al. Can sleep and wakefulness be distinguished in children by cardiorespiratory and videotape recordings? Chest 1996;109:680–7.

14. Bibliography

1. Kaditis, A. G. *et al.* Obstructive sleep disordered breathing in 2- to 18-year-old children: diagnosis and management. *Eur. Respir. J.* **47,** 69–94 (2016).
2. Marcus, C. L. *et al.* Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* **130,** e714–e755 (2012).
3. Bonuck, K. A. *et al.* Prevalence and Persistence of Sleep Disordered Breathing Symptoms in Young Children: A 6-Year Population-Based Cohort Study. *Sleep* **34,** 875–884 (2011).
4. Bixler, E. O. *et al.* Sleep disordered breathing in children in a general population sample: prevalence and risk factors. *Sleep* **32,** 731–736 (2009).
5. Brockmann, P. E., Urschitz, M. S., Schlaud, M. & Poets, C. F. Primary snoring in school children: prevalence and neurocognitive impairments. *Sleep Breath.* **16,** 23–29 (2012).
6. Hunter, S. J. *et al.* Effect of Sleep-disordered Breathing Severity on Cognitive Performance Measures in a Large Community Cohort of Young School-aged Children. *Am. J. Respir. Crit. Care Med.* **194,** 739–747 (2016).
7. Smith, D. L., Gozal, D., Hunter, S. J. & Kheirandish-Gozal, L. Frequency of snoring, rather than apnea–hypopnea index, predicts both cognitive and behavioral problems in young children. *Sleep Med.* **34,** 170–178 (2017).
8. Guilleminault, C., Winkle, R., Korobkin, R. & Simmons, B. Children and nocturnal snoring: evaluation of the effects of sleep related respiratory resistive load and daytime functioning. *Eur. J. Pediatr.* **139,** 165–171 (1982).
9. Darien, I. *American Academy of Sleep Medicine. International Classification of Sleep Disorders.* (American Academy of Sleep Medicine, 2014).
10. Lumeng, J. C. & Chervin, R. D. Epidemiology of pediatric obstructive sleep apnea. *Proc. Am. Thorac. Soc.* **5,** 242–252 (2008).
11. Kaditis, A. G. *et al.* ERS statement on obstructive sleep disordered breathing in 1- to 23-month-old children. *Eur. Respir. J.* **50,** (2017).
12. Robin P. La chute de la base de la langue considérée comme une nouvelle cause de gène dans la respiration naso-pharyngienne. *Bull Acad Natl Med Paris* **89: 37-41,** 37–41 (1923).
13. Anderson, I. C. W. *et al.* Prevalence and severity of obstructive sleep apnea and snoring in infants with Pierre Robin sequence. *Cleft Palate-Craniofacial J. Off. Publ. Am. Cleft Palate-Craniofacial Assoc.* **48,** 614–618 (2011).
14. Renault, F., Flores-Guevara, R., Soupre, V., Vazquez, M.-P. & Baudon, J.-J. Neurophysiological brainstem investigations in isolated Pierre Robin sequence. *Early Hum. Dev.* **58,** 141–152 (2000).
15. MacLean, J. E., Fitzsimons, D., Fitzgerald, D. A. & Waters, K. A. The spectrum of sleep-disordered breathing symptoms and respiratory events in infants with cleft lip and/or palate. *Arch. Dis. Child.* **97,** 1058–1063 (2012).
16. Moraleda-Cibrián, M. *et al.* Obstructive Sleep Apnea Pretreatment and Posttreatment in Symptomatic Children with Congenital Craniofacial Malformations. *J. Clin. Sleep Med. JCSM Off. Publ. Am. Acad. Sleep Med.* **11,** 37–43 (2015).
17. Baugh, A. D., Wooten, W., Chapman, B., Drake, A. F. & Vaughn, B. V. Sleep characteristics in Goldenhar Syndrome. *Int. J. Pediatr. Otorhinolaryngol.* **79,** 356–358 (2015).
18. Akre, H., Øverland, B., Åsten, P., Skogedal, N. & Heimdal, K. Obstructive sleep apnea in Treacher Collins syndrome. *Eur. Arch. Otorhinolaryngol.* **269,** 331–337 (2012).
19. Plomp, R. G. *et al.* Obstructive sleep apnoea in Treacher Collins syndrome: prevalence, severity and cause. *Int. J. Oral Maxillofac. Surg.* **41,** 696–701 (2012).
20. Alsaadi, M. M., Iqbal, S. M., Elgamal, E. A., Salih, M. A. & Gozal, D. Sleep-disordered breathing in children with craniosynostosis. *Sleep Breath.* **17,** 389–393 (2013).
21. Al-Saleh, S. *et al.* Sleep-related disordered breathing in children with syndromic

craniosynostosis. *J. Cranio-Maxillo-fac. Surg. Off. Publ. Eur. Assoc. Cranio-Maxillo-fac. Surg.* **39,** 153–157 (2011).
22. Fan, Z., Ahn, M., Roth, H. L., Li, L. & Vaughn, B. V. Sleep Apnea and Hypoventilation in Patients with Down Syndrome: Analysis of 144 Polysomnogram Studies. *Children* **4,** (2017).
23. de Miguel-Díez, J., Villa-Asensi, J. R. & Alvarez-Sala, J. L. Prevalence of sleep-disordered breathing in children with Down syndrome: polygraphic findings in 108 children. *Sleep* **26,** 1006–1009 (2003).
24. Alexander, M. *et al.* Morbidity and medication in a large population of individuals with Down syndrome compared to the general population. *Dev. Med. Child Neurol.* **58,** 246–254 (2016).
25. Fitzgerald, D. A., Paul, A. & Richmond, C. Severity of obstructive apnoea in children with Down syndrome who snore. *Arch. Dis. Child.* **92,** 423–425 (2007).
26. Lin, H.-Y. *et al.* Polysomnographic characteristics in patients with Prader-Willi syndrome. *Pediatr. Pulmonol.* **42,** 881–887 (2007).
27. Pavone, M. *et al.* Sleep disordered breathing in patients with Prader-Willi syndrome: A multicenter study. *Pediatr. Pulmonol.* **50,** 1354–1359 (2015).
28. Cohen, M., Hamilton, J. & Narang, I. Clinically Important Age-Related Differences in Sleep Related Disordered Breathing in Infants and Children with Prader-Willi Syndrome. *PLoS ONE* **9,** (2014).
29. Afsharpaiman, S., Sillence, D. O., Sheikhvatan, M., Ault, J. E. & Waters, K. Respiratory events and obstructive sleep apnea in children with achondroplasia: investigation and treatment outcomes. *Sleep Breath. Schlaf Atm.* **15,** 755–761 (2011).
30. Tenconi, R. *et al.* Sleep-disordered breathing and its management in children with achondroplasia. *Am. J. Med. Genet. A.* **173,** 868–878 (2017).
31. Moreau, J. *et al.* Obstructive sleep apnea syndrome after hematopoietic stem cell transplantation in children with mucopolysaccharidosis type I. *Mol. Genet. Metab.* **116,** 275–280 (2015).
32. Lin, H.-Y. *et al.* Polysomnographic characteristics in patients with mucopolysaccharidoses. *Pediatr. Pulmonol.* **45,** 1205–1212 (2010).
33. Pinard, J.-M. *et al.* Sleep-disordered breathing in children with congenital muscular dystrophies. *Eur. J. Paediatr. Neurol.* **16,** 619–624 (2012).
34. Suresh, S., Wales, P., Dakin, C., Harris, M.-A. & Cooper, D. (Gus) M. Sleep-related breathing disorder in Duchenne muscular dystrophy: Disease spectrum in the paediatric population. *J. Paediatr. Child Health* **41,** 500–503 (2005).
35. Guilleminault, C. *et al.* Sleep-disordered breathing in Ehlers-Danlos syndrome: a genetic model of OSA. *CHEST J.* **144,** 1503–1511 (2013).
36. Gaisl, T. *et al.* Obstructive sleep apnoea and quality of life in Ehlers-Danlos syndrome: a parallel cohort study. *Thorax* **72,** 729–735 (2017).
37. Gangopadhyay, N., Mendonca, D. & Woo, A. Pierre Robin Sequence. *Semin. Plast. Surg.* **26,** 076–082 (2012).
38. Izumi, K., Konczal, L. L., Mitchell, A. L. & Jones, M. C. Underlying genetic diagnosis of Pierre Robin sequence: retrospective chart review at two children's hospitals and a systematic literature review. *J. Pediatr.* **160,** 645–650.e2 (2012).
39. Botto, L. D. *et al.* A population-based study of the 22q11.2 deletion: phenotype, incidence, and contribution to major birth defects in the population. *Pediatrics* **112,** 101–107 (2003).
40. Issekutz, K. A., Graham, J. M., Prasad, C., Smith, I. M. & Blake, K. D. An epidemiological analysis of CHARGE syndrome: preliminary results from a Canadian study. *Am. J. Med. Genet. A.* **133A,** 309–317 (2005).
41. Conte, C. *et al.* Novel mutations of TCOF1 gene in European patients with treacher Collins syndrome. *BMC Med. Genet.* **12,** 125 (2011).
42. Tan, H.-L., Kheirandish-Gozal, L., Abel, F. & Gozal, D. Craniofacial Syndromes and Sleep-Related Breathing Disorders. *Sleep Med. Rev.* **27,** 74–88 (2016).

43. CDC. Data and Statistics | Down Syndrome | Birth Defects | NCBDDD | CDC. *Centers for Disease Control and Prevention* (2017). Available at: https://www.cdc.gov/ncbddd/birthdefects/downsyndrome/data.html. (Accessed: 25th November 2017)
44. Reference, G. H. Ehlers-Danlos syndrome. *Genetics Home Reference* Available at: https://ghr.nlm.nih.gov/condition/ehlers-danlos-syndrome. (Accessed: 26th November 2017)
45. Ehrhart, F. *et al.* Rett syndrome – biological pathways leading from MECP2 to disorder phenotypes. *Orphanet J. Rare Dis.* **11,** (2016).
46. RESERVED, I. U.--A. R. Orphanet: Achondroplasia. Available at: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=15. (Accessed: 26th November 2017)
47. Khan, S. A. *et al.* Epidemiology of mucopolysaccharidoses. *Mol. Genet. Metab.* **121,** 227–240 (2017).
48. Caron, C. J. J. M. *et al.* Obstructive sleep apnoea in craniofacial microsomia: analysis of 755 patients. *Int. J. Oral Maxillofac. Surg.* **46,** 1330–1337 (2017).
49. Kennedy, W. P. *et al.* 22q11.2 Deletion syndrome and obstructive sleep apnea. *Int. J. Pediatr. Otorhinolaryngol.* **78,** 1360–1364 (2014).
50. Trider, C.-L. *et al.* Understanding obstructive sleep apnea in children with CHARGE syndrome. *Int. J. Pediatr. Otorhinolaryngol.* **76,** 947–953 (2012).
51. Julliand, S. *et al.* Lung function, diagnosis, and treatment of sleep-disordered breathing in children with achondroplasia. *Am. J. Med. Genet. A.* **158A,** 1987–1993 (2012).
52. John, Â. *et al.* Sleep abnormalities in untreated patients with mucopolysaccharidosis type VI. *Am. J. Med. Genet. A.* **155,** 1546–1551 (2011).
53. Berry, R. B. *et al.* Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J. Clin. Sleep Med. JCSM Off. Publ. Am. Acad. Sleep Med.* **8,** 597–619 (2012).
54. Javaheri, S. Sleep disorders in systolic heart failure: a prospective study of 100 male patients. The final report. *Int. J. Cardiol.* **106,** 21–28 (2006).
55. Eckert, D. J., Jordan, A. S., Merchia, P. & Malhotra, A. Central sleep apnea: Pathophysiology and treatment. *Chest* **131,** 595–607 (2007).
56. Poets, C. F. Apnea of prematurity: What can observational studies tell us about pathophysiology? *Sleep Med.* **11,** 701–707 (2010).
57. Abu-Shaweesh, J. M. & Martin, R. J. Neonatal apnea: what's new? *Pediatr. Pulmonol.* **43,** 937–944 (2008).
58. Verhulst, S. L. *et al.* Reference values for sleep-related respiratory variables in asymptomatic European children and adolescents. *Pediatr. Pulmonol.* **42,** 159–167 (2007).
59. Traeger, N. *et al.* Polysomnographic values in children 2-9 years old: additional data and review of the literature. *Pediatr. Pulmonol.* **40,** 22–30 (2005).
60. Rand, C. M., Carroll, M. S. & Weese-Mayer, D. E. Congenital central hypoventilation syndrome: a neurocristopathy with disordered respiratory control and autonomic regulation. *Clin. Chest Med.* **35,** 535–545 (2014).
61. Weese-Mayer, D. E. *et al.* An Official ATS Clinical Policy Statement: Congenital Central Hypoventilation Syndrome. *Am. J. Respir. Crit. Care Med.* **181,** 626–644 (2010).
62. Weese-Mayer, D. E., Marazita, M. L., Rand, C. M. & Berry-Kravis, E. M. Congenital Central Hypoventilation Syndrome. in *GeneReviews(®)* (eds. Adam, M. P. et al.) (University of Washington, Seattle, 1993).
63. Kritzinger, F. E., Al-Saleh, S. & Narang, I. Descriptive analysis of central sleep apnea in childhood at a single center. *Pediatr. Pulmonol.* **46,** 1023–1030 (2011).
64. Losurdo, A. *et al.* Sleep disordered breathing in children and adolescents with Chiari malformation type I. *J. Clin. Sleep Med. JCSM Off. Publ. Am. Acad. Sleep Med.* **9,** 371–377 (2013).

65. Terán-Pérez, G. *et al.* Polysomnographic features in infants with early diagnosis of congenital hypothyroidism. *Brain Dev.* **32,** 332–337 (2010).
66. Badr, M. S., Toiber, F., Skatrud, J. B. & Dempsey, J. Pharyngeal narrowing/occlusion during central sleep apnea. *J. Appl. Physiol. Bethesda Md 1985* **78,** 1806–1815 (1995).
67. Eckert, D. J., Jordan, A. S., Merchia, P. & Malhotra, A. Central Sleep Apnea. *Chest* **131,** 595–607 (2007).
68. Dayyat, E., Kheirandish-Gozal, L. & Gozal, D. Childhood Obstructive Sleep Apnea: One or Two Distinct Disease Entities? *Sleep Med. Clin.* **2,** 433–444 (2007).
69. Bhattacharjee, R. *et al.* Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. *Am. J. Respir. Crit. Care Med.* **182,** 676–683 (2010).
70. Chen, C.-C. J. J., Spanò, G. & Edgin, J. O. The impact of sleep disruption on executive function in Down syndrome. *Res. Dev. Disabil.* **34,** 2033–2039 (2013).
71. Carberry, J. C., Jordan, A. S., White, D. P., Wellman, A. & Eckert, D. J. Upper Airway Collapsibility (Pcrit) and Pharyngeal Dilator Muscle Activity are Sleep Stage Dependent. *Sleep* **39,** 511–521 (2016).
72. Isono, S. Developmental changes of pharyngeal airway patency: implications for pediatric anesthesia. *Paediatr. Anaesth.* **16,** 109–122 (2006).
73. Nishimura, M. *et al.* Longitudinal analyses of respiratory chemosensitivity in normal subjects. *Am. Rev. Respir. Dis.* **143,** 1278–1281 (1991).
74. Marcus, C. L., Glomb, W. B., Basinski, D. J., Davidson, S. L. & Keens, T. G. Developmental pattern of hypercapnic and hypoxic ventilatory responses from childhood to adulthood. *J. Appl. Physiol. Bethesda Md 1985* **76,** 314–320 (1994).
75. Katz, E. S. & White, D. P. Genioglossus activity during sleep in normal control subjects and children with obstructive sleep apnea. *Am. J. Respir. Crit. Care Med.* **170,** 553–560 (2004).
76. Arens, R. & Marcus, C. L. Pathophysiology of upper airway obstruction: a developmental perspective. *Sleep* **27,** 997–1019 (2004).
77. Gleadhill, I. C. *et al.* Upper airway collapsibility in snorers and in patients with obstructive hypopnea and apnea. *Am. Rev. Respir. Dis.* **143,** 1300–1303 (1991).
78. Marcus, C. L. *et al.* Upper Airway Dynamic Responses in Children with the Obstructive Sleep Apnea Syndrome. *Pediatr. Res.* **57,** 99–107 (2005).
79. Isono, S., Tanaka, A., Ishikawa, T. & Nishino, T. Developmental changes in collapsibility of the passive pharynx during infancy. *Am. J. Respir. Crit. Care Med.* **162,** 832–836 (2000).
80. Marcus, C. L. Pathophysiology of childhood obstructive sleep apnea: current concepts. *Respir. Physiol.* **119,** 143–154 (2000).
81. Vogler, R. C., Ii, F. J. & Pilgram, T. K. Age-specific size of the normal adenoid pad on magnetic resonance imaging. *Clin. Otolaryngol. Allied Sci.* **25,** 392–395 (2000).
82. Van Holsbeke, C. *et al.* Functional respiratory imaging as a tool to assess upper airway patency in children with obstructive sleep apnea. *Sleep Med.* **14,** 433–439 (2013).
83. Nolan, J. & Brietzke, S. E. Systematic review of pediatric tonsil size and polysomnogram-measured obstructive sleep apnea severity. *Otolaryngol.--Head Neck Surg. Off. J. Am. Acad. Otolaryngol.-Head Neck Surg.* **144,** 844–850 (2011).
84. Lee, C.-H., Hsu, W.-C., Chang, W.-H., Lin, M.-T. & Kang, K.-T. Polysomnographic findings after adenotonsillectomy for obstructive sleep apnoea in obese and non-obese children: a systematic review and meta-analysis. *Clin. Otolaryngol.* (2016).
85. Marcus, C. L. *et al.* A Randomized Trial of Adenotonsillectomy for Childhood Sleep Apnea. *N. Engl. J. Med.* **368,** 2366–2376 (2013).
86. Flores-Mir, C. *et al.* Craniofacial morphological characteristics in children with obstructive sleep apnea syndrome: a systematic review and meta-analysis. *J. Am. Dent. Assoc. 1939* **144,** 269–277 (2013).
87. Kalampouka, E. *et al.* Family history of adenotonsillectomy as a risk factor for tonsillar

hypertrophy and snoring in childhood. *Pediatr. Pulmonol.* **49,** 366–371 (2014).
88. Alexopoulos, E. I. *et al.* Parental History of Adenotonsillectomy Is Associated with Obstructive Sleep Apnea Severity in Children with Snoring. *J. Pediatr.* **164,** 1352–1357 (2014).
89. Lundkvist, K., Sundquist, K., Li, X. & Friberg, D. Familial risk of sleep-disordered breathing. *Sleep Med.* **13,** 668–673 (2012).
90. Redline, S. *et al.* Risk factors for sleep-disordered breathing in children. Associations with obesity, race, and respiratory problems. *Am. J. Respir. Crit. Care Med.* **159,** 1527–1532 (1999).
91. Spilsbury, J. C., Storfer-Isser, A., Rosen, C. L. & Redline, S. Remission and incidence of obstructive sleep apnea from middle childhood to late adolescence. *Sleep* **38,** 23–29 (2015).
92. Silvestri, J. M. *et al.* Polysomnography in obese children with a history of sleep-associated breathing disorders. *Pediatr. Pulmonol.* **16,** 124–129 (1993).
93. Marcus, C. L. *et al.* Evaluation of pulmonary function and polysomnography in obese children and adolescents. *Pediatr. Pulmonol.* **21,** 176–183 (1996).
94. Verhulst, S. L. *et al.* Sleep-disordered breathing in overweight and obese children and adolescents: prevalence, characteristics and the role of fat distribution. *Arch. Dis. Child.* **92,** 205–208 (2007).
95. Corbo, G. M. *et al.* Snoring in 9- to 15-year-old children: risk factors and clinical relevance. *Pediatrics* **108,** 1149–1154 (2001).
96. Kohler, M. *et al.* Obesity and risk of sleep related upper airway obstruction in Caucasian children. *J. Clin. Sleep Med. JCSM Off. Publ. Am. Acad. Sleep Med.* **4,** 129–136 (2008).
97. Bin-Hasan, S. *et al.* Prevalence of obstructive sleep apnea among obese toddlers and preschool children. *Sleep Breath. Schlaf Atm.* (2017). doi:10.1007/s11325-017-1576-4
98. Tong, Y. *et al.* MR Image Analytics to Characterize the Upper Airway Structure in Obese Children with Obstructive Sleep Apnea Syndrome. *PLoS ONE* **11,** (2016).
99. Arens, R. *et al.* Upper airway structure and body fat composition in obese children with obstructive sleep apnea syndrome. *Am. J. Respir. Crit. Care Med.* **183,** 782–787 (2011).
100. Naimark, A. & Cherniack, R. M. Compliance of the respiratory system and its components in health and obesity. *J. Appl. Physiol.* **15,** 377–382 (1960).
101. Sher, A. E., Shprintzen, R. J. & Thorpy, M. J. Endoscopic observations of obstructive sleep apnea in children with anomalous upper airways: predictive and therapeutic value. *Int. J. Pediatr. Otorhinolaryngol.* **11,** 135–146 (1986).
102. Donnelly, L. F., Shott, S. R., LaRose, C. R., Chini, B. A. & Amin, R. S. Causes of persistent obstructive sleep apnea despite previous tonsillectomy and adenoidectomy in children with down syndrome as depicted on static and dynamic cine MRI. *AJR Am. J. Roentgenol.* **183,** 175–181 (2004).
103. Horton, W. A., Hall, J. G. & Hecht, J. T. Achondroplasia. *Lancet Lond. Engl.* **370,** 162–172 (2007).
104. Tabachnik, E., Muller, N. L., Bryan, A. C. & Levison, H. Changes in ventilation and chest wall mechanics during sleep in normal adolescents. *J. Appl. Physiol.* **51,** 557–564 (1981).
105. Kubin, L., Davies, R. O. & Pack, A. I. Control of Upper Airway Motoneurons During REM Sleep. *News Physiol. Sci. Int. J. Physiol. Prod. Jointly Int. Union Physiol. Sci. Am. Physiol. Soc.* **13,** 91–97 (1998).
106. White, J. E., Drinnan, M. J., Smithson, A. J., Griffiths, C. J. & Gibson, G. J. Respiratory muscle activity and oxygenation during sleep in patients with muscle weakness. *Eur. Respir. J.* **8,** 807–814 (1995).
107. Wing, Y. *et al.* A controlled study of sleep related disordered breathing in obese children. *Arch. Dis. Child.* **88,** 1043–1047 (2003).
108. Sogut, A. *et al.* Prevalence of obstructive sleep apnea syndrome and associated symptoms in 3--11-year-old Turkish children. *Pediatr. Pulmonol.* **39,** 251–256 (2005).
109. Goodwin, J. L., Vasquez, M. M., Silva, G. E. & Quan, S. F. Incidence and Remission of Sleep Disordered Breathing and Related Symptoms in 6-17 Year Old Children-the Tucson

Children's Assessment of Sleep Apnea Study (TuCASA). *J. Pediatr.* **157,** 57–61 (2010).
110. Weinstock, T. G. *et al.* Predictors of Obstructive Sleep Apnea Severity in Adenotonsillectomy Candidates. *SLEEP* (2014). doi:10.5665/sleep.3394
111. Gozal, D., Wang, M. & Pope, D. W. Objective sleepiness measures in pediatric obstructive sleep apnea. *Pediatrics* **108,** 693–697 (2001).
112. Sinha, D. & Guilleminault, C. Sleep disordered breathing in children. (2010).
113. ADENOID FACIES. Available at: http://me.hawkelibrary.com/new/main.php?g2_itemId=1094. (Accessed: 3rd December 2017)
114. Brodsky, L. Modern assessment of tonsils and adenoids. *Pediatr. Clin. North Am.* **36,** 1551–1569 (1989).
115. Friedman, M., Ibrahim, H. & Bass, L. Clinical staging for sleep-disordered breathing. *Otolaryngol.--Head Neck Surg. Off. J. Am. Acad. Otolaryngol.-Head Neck Surg.* **127,** 13–21 (2002).
116. Chervin, R. D. *et al.* Inattention, hyperactivity, and symptoms of sleep-disordered breathing. *Pediatrics* **109,** 449–456 (2002).
117. Chervin, R. D., Dillon, J. E., Bassetti, C., Ganoczy, D. A. & Pituch, K. J. Symptoms of sleep disorders, inattention, and hyperactivity in children. *Sleep* **20,** 1185–1192 (1997).
118. O'Brien, L. M. *et al.* Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention-deficit/hyperactivity disorder. *Pediatrics* **111,** 554–563 (2003).
119. Gottlieb, D. J. *et al.* Sleep-disordered breathing symptoms are associated with poorer cognitive function in 5-year-old children. *J. Pediatr.* **145,** 458–464 (2004).
120. Melendres, M. C. S., Lutz, J. M., Rubin, E. D. & Marcus, C. L. Daytime sleepiness and hyperactivity in children with suspected sleep-disordered breathing. *Pediatrics* **114,** 768–775 (2004).
121. Quan, S. F., Archbold, K., Gevins, A. S. & Goodwin, J. L. Long-Term Neurophysiologic Impact of Childhood Sleep Disordered Breathing on Neurocognitive Performance. *Southwest J. Pulm. Crit. Care* **7,** 165–175 (2013).
122. de Carvalho, L. B. C. *et al.* Symptoms of sleep disorders and objective academic performance. *Sleep Med.* **14,** 872–876 (2013).
123. Chervin, R. D., Dillon, J. E., Archbold, K. H. & Ruzicka, D. L. Conduct problems and symptoms of sleep disorders in children. *J. Am. Acad. Child Adolesc. Psychiatry* **42,** 201–208 (2003).
124. O'Brien, L. M. *et al.* Aggressive behavior, bullying, snoring, and sleepiness in schoolchildren. *Sleep Med.* **12,** 652–658 (2011).
125. Landau, Y. E. *et al.* Impaired behavioral and neurocognitive function in preschool children with obstructive sleep apnea. *Pediatr. Pulmonol.* **47,** 180–188 (2012).
126. Bourke, R. *et al.* Cognitive and academic functions are impaired in children with all severities of sleep-disordered breathing. *Sleep Med.* **12,** 489–496 (2011).
127. Brooks, L. J. *et al.* Relationship between sleep, sleep apnea, and neuropsychological function in children with Down syndrome. *Sleep Breath. Schlaf Atm.* **19,** 197–204 (2015).
128. Piteo, A. M. *et al.* Snoring and cognitive development in infancy. *Sleep Med.* **12,** 981–987 (2011).
129. Weiss, R. *et al.* Obesity and the metabolic syndrome in children and adolescents. *N. Engl. J. Med.* **350,** 2362–2374 (2004).
130. Ip, M. S. M. *et al.* Obstructive sleep apnea is independently associated with insulin resistance. *Am. J. Respir. Crit. Care Med.* **165,** 670–676 (2002).
131. Punjabi, N. M. *et al.* Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am. J. Respir. Crit. Care Med.* **165,** 677–682 (2002).
132. Tauman, R., O'Brien, L. M., Ivanenko, A. & Gozal, D. Obesity rather than severity of sleep-disordered breathing as the major determinant of insulin resistance and altered lipidemia in snoring

children. *Pediatrics* **116,** e66-73 (2005).
133. Kaditis, A. G. *et al.* Obstructive sleep-disordered breathing and fasting insulin levels in nonobese children. *Pediatr. Pulmonol.* **40,** 515–523 (2005).
134. de la Eva, R. C., Baur, L. A., Donaghue, K. C. & Waters, K. A. Metabolic correlates with obstructive sleep apnea in obese subjects. *J. Pediatr.* **140,** 654–659 (2002).
135. Waters, K. A. *et al.* Follow-up on metabolic markers in children treated for obstructive sleep apnea. *Am. J. Respir. Crit. Care Med.* **174,** 455–460 (2006).
136. Verhulst, S. L. *et al.* Sleep-disordered breathing and uric acid in overweight and obese children and adolescents. *Chest* **132,** 76–80 (2007).
137. Van Hoorenbeeck, K. *et al.* Weight loss and sleep-disordered breathing in childhood obesity: effects on inflammation and uric acid. *Obes. Silver Spring Md* **20,** 172–177 (2012).
138. Verhulst, S. L. *et al.* Sleep-disordered breathing and systemic inflammation in overweight children and adolescents. *Int. J. Pediatr. Obes. IJPO Off. J. Int. Assoc. Study Obes.* **3,** 234–239 (2008).
139. Li, A. M. *et al.* Ambulatory blood pressure in children with obstructive sleep apnoea: a community based study. *Thorax* **63,** 803–809 (2008).
140. Chan, J. Y. S. *et al.* Cardiac remodelling and dysfunction in children with obstructive sleep apnoea: a community based study. *Thorax* **64,** 233–239 (2009).
141. DelRosso, L. M., King, J. & Ferri, R. Systolic Blood Pressure Elevation in Children with Obstructive Sleep Apnea Is Improved with Positive Airway Pressure Use. *J. Pediatr.* (2017). doi:10.1016/j.jpeds.2017.11.043
142. Tauman, R., Lavie, L., Greenfeld, M. & Sivan, Y. Oxidative Stress in Children with Obstructive Sleep Apnea Syndrome. *J. Clin. Sleep Med. JCSM Off. Publ. Am. Acad. Sleep Med.* **10,** 677–681 (2014).
143. Gozal, D., Kheirandish-Gozal, L., Serpero, L. D., Sans Capdevila, O. & Dayyat, E. Obstructive sleep apnea and endothelial function in school-aged nonobese children: effect of adenotonsillectomy. *Circulation* **116,** 2307–2314 (2007).
144. Kheirandish-Gozal, L., Bhattacharjee, R., Kim, J., Clair, H. B. & Gozal, D. Endothelial progenitor cells and vascular dysfunction in children with obstructive sleep apnea. *Am. J. Respir. Crit. Care Med.* **182,** 92–97 (2010).
145. Duman, D., Naiboglu, B., Esen, H. S., Toros, S. Z. & Demirtunc, R. Impaired right ventricular function in adenotonsillar hypertrophy. *Int. J. Cardiovasc. Imaging* **24,** 261–267 (2008).
146. Tal, A., Leiberman, A., Margulis, G. & Sofer, S. Ventricular dysfunction in children with obstructive sleep apnea: radionuclide assessment. *Pediatr. Pulmonol.* **4,** 139–143 (1988).
147. Amonoo-Kuofi, K. *et al.* Adenotonsillectomy for sleep-disordered breathing in children with syndromic craniosynostosis. *J. Craniofac. Surg.* **20,** 1978–1980 (2009).
148. Melacini, P. *et al.* Cardiac and respiratory involvement in advanced stage Duchenne muscular dystrophy. *Neuromuscul. Disord. NMD* **6,** 367–376 (1996).
149. Sisk, E. A., Heatley, D. G., Borowski, B. J., Leverson, G. E. & Pauli, R. M. Obstructive sleep apnea in children with achondroplasia: surgical and anesthetic considerations. *Otolaryngol.--Head Neck Surg. Off. J. Am. Acad. Otolaryngol.-Head Neck Surg.* **120,** 248–254 (1999).
150. Tasker, R. C. *et al.* Distinct patterns of respiratory difficulty in young children with achondroplasia: a clinical, sleep, and lung function study. *Arch. Dis. Child.* **79,** 99–108 (1998).
151. Lefaivre, J. F. *et al.* Down syndrome: identification and surgical management of obstructive sleep apnea. *Plast. Reconstr. Surg.* **99,** 629–637 (1997).
152. Jacobs, I. N., Gray, R. F. & Todd, N. W. Upper airway obstruction in children with Down syndrome. *Arch. Otolaryngol. Head Neck Surg.* **122,** 945–950 (1996).
153. MESOLELLA, M. *et al.* Management of otolaryngological manifestations in mucopolysaccharidoses: our experience. *Acta Otorhinolaryngol. Ital.* **33,** 267–272 (2013).
154. Li, A. M., Yin, J., Chan, D., Hui, S. & Fok, T. F. Sleeping energy expenditure in paediatric patients with obstructive sleep apnoea syndrome. *Hong Kong Med. J. Xianggang Yi Xue Za Zhi* **9,**

353–356 (2003).
155. Marcus, C. L. *et al.* Determinants of growth in children with the obstructive sleep apnea syndrome. *J. Pediatr.* **125,** 556–562 (1994).
156. Van Cauter, E., Plat, L. & Copinschi, G. Interrelations between sleep and the somatotropic axis. *Sleep* **21,** 553–566 (1998).
157. Nieminen, P. *et al.* Growth and biochemical markers of growth in children with snoring and obstructive sleep apnea. *Pediatrics* **109,** e55 (2002).
158. Gkouskou, K. K. *et al.* Dietary habits of preschool aged children with tonsillar hypertrophy, pre- and post-operatively. *Eur. Rev. Med. Pharmacol. Sci.* **14,** 1025–1030 (2010).
159. Roemmich, J. N. Increases in Overweight After Adenotonsillectomy in Overweight Children With Obstructive Sleep-Disordered Breathing Are Associated With Decreases in Motor Activity and Hyperactivity. *PEDIATRICS* **117,** e200–e208 (2006).
160. Scholle, S., Wiater, A. & Scholle, H. C. Normative values of polysomnographic parameters in childhood and adolescence: Cardiorespiratory parameters. *Sleep Med.* **12,** 988–996 (2011).
161. Marcus, C. L., OMLlN, K. J., Basinki, D. J. & Bailey, S. L. Normal Polysomnographic Values for Children. *Am Rev Respir Dis* **146,** 1235–1239 (1992).
162. Roland, P. S. *et al.* Clinical practice guideline: polysomnography for sleep-disordered breathing prior to tonsillectomy in children. *Otolaryngol. Neck Surg.* **145,** S1–S15 (2011).
163. Amin, R. *et al.* Activity-adjusted 24-hour ambulatory blood pressure and cardiac remodeling in children with sleep disordered breathing. *Hypertens. Dallas Tex 1979* **51,** 84–91 (2008).
164. Chervin, null, Hedger, null, Dillon, null & Pituch, null. Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. *Sleep Med.* **1,** 21–32 (2000).
165. Drake, C. *et al.* The pediatric daytime sleepiness scale (PDSS): sleep habits and school outcomes in middle-school children. *Sleep* **26,** 455–458 (2003).
166. Villa, M. P. *et al.* Sleep clinical record: an aid to rapid and accurate diagnosis of paediatric sleep disordered breathing. *Eur. Respir. J.* **41,** 1355–1361 (2013).
167. Brouillette, R. T. *et al.* Nocturnal pulse oximetry as an abbreviated testing modality for pediatric obstructive sleep apnea. *Pediatrics* **105,** 405–412 (2000).
168. Nixon, G. M. *et al.* Planning adenotonsillectomy in children with obstructive sleep apnea: the role of overnight oximetry. *Pediatrics* **113,** e19-25 (2004).
169. Pavone, M. *et al.* Night-to-night consistency of at-home nocturnal pulse oximetry testing for obstructive sleep apnea in children. *Pediatr. Pulmonol.* **48,** 754–760 (2013).
170. Coverstone, A. M. *et al.* Overnight Pulse Oximetry for Evaluation of Sleep Apnea among Children with Trisomy 21. *J. Clin. Sleep Med. JCSM Off. Publ. Am. Acad. Sleep Med.* **10,** 1309–1315 (2014).
171. Hornero, R. *et al.* Nocturnal Oximetry-based Evaluation of Habitually Snoring Children. *Am. J. Respir. Crit. Care Med.* (2017). doi:10.1164/rccm.201705-0930OC
172. Tsai, C.-M. *et al.* Usefulness of desaturation index for the assessment of obstructive sleep apnea syndrome in children. *Int. J. Pediatr. Otorhinolaryngol.* **77,** 1286–1290 (2013).
173. Verhulst, S. L., Schrauwen, N., De Backer, W. A. & Desager, K. N. First night effect for polysomnographic data in children and adolescents with suspected sleep disordered breathing. *Arch. Dis. Child.* **91,** 233–237 (2006).
174. Katz, E. S. *et al.* Night-to-night variability of polysomnography in children with suspected obstructive sleep apnea. *J. Pediatr.* **140,** 589–594 (2002).
175. American Academy of Sleep Medicine; 2007. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specification.* (Iber C, editor.).
176. Berry, R. B. *et al.* The AASM manual for the scoring of sleep and associated events. *Rules Terminol. Tech. Specif. Darien Ill. Am. Acad. Sleep Med.* (2012).
177. Pautrat, J. *et al.* Carbon dioxide levels during polygraphy in children with sleep-disordered breathing. *Sleep Breath. Schlaf Atm.* **19,** 149–157 (2015).

178. Delerme, S. *et al.* Concordance between transcutaneous and arterial measurements of carbon dioxide in an ED. *Am. J. Emerg. Med.* **30,** 1872–1876 (2012).
179. Ozyuvaci, E. *et al.* Comparison of transcutaneous, arterial and end-tidal measurements of carbon dioxide during laparoscopic cholecystectomy in patients with chronic obstructive pulmonary disease. *J. Int. Med. Res.* **40,** 1982–1987 (2012).
180. Marcus, C. L. *et al.* Feasibility of Comprehensive, Unattended Ambulatory Polysomnography in School-Aged Children. *J. Clin. Sleep Med. JCSM Off. Publ. Am. Acad. Sleep Med.* **10,** 913–918 (2014).
181. Goodwin, J. L. *et al.* Feasibility of using unattended polysomnography in children for research--report of the Tucson Children's Assessment of Sleep Apnea study (TuCASA). *Sleep* **24,** 937–944 (2001).
182. Marcus, C. L., Keens, T. G. & Ward, S. L. Comparison of nap and overnight polysomnography in children. *Pediatr. Pulmonol.* **13,** 16–21 (1992).
183. Lloberes, P. *et al.* Diagnosis and treatment of sleep apnea-hypopnea syndrome. Spanish Society of Pulmonology and Thoracic Surgery. *Arch. Bronconeumol.* **47,** 143–156 (2011).
184. Thurnheer, R. *et al.* Respiratory polygraphy in sleep apnoea diagnosis. Report of the Swiss respiratory polygraphy registry and systematic review of the literature. *Swiss Med. Wkly.* **137,** 97–102 (2007).
185. Tan, H.-L., Gozal, D., Ramirez, H. M., Bandla, H. P. R. & Kheirandish-Gozal, L. Overnight Polysomnography versus Respiratory Polygraphy in the Diagnosis of Pediatric Obstructive Sleep Apnea. *SLEEP* (2014). doi:10.5665/sleep.3392
186. Geddes, L. A., Voelz, M., James, S. & Reiner, D. Pulse arrival time as a method of obtaining systolic and diastolic blood pressure indirectly. *Med. Biol. Eng. Comput.* **19,** 671–672 (1981).
187. Sforza, E., Jouny, C. & Ibanez, V. Cardiac activation during arousal in humans: further evidence for hierarchy in the arousal response. *Clin. Neurophysiol.* **111,** 1611–1619 (2000).
188. Argod, J., Pépin, J. L., Smith, R. P. & Lévy, P. Comparison of esophageal pressure with pulse transit time as a measure of respiratory effort for scoring obstructive nonapneic respiratory events. *Am. J. Respir. Crit. Care Med.* **162,** 87–93 (2000).
189. Pitson, D. J., Sandell, A., van den Hout, R. & Stradling, J. R. Use of pulse transit time as a measure of inspiratory effort in patients with obstructive sleep apnoea. *Eur. Respir. J.* **8,** 1669–1674 (1995).
190. Argod, J., Pépin, J. L. & Lévy, P. Differentiating obstructive and central sleep respiratory events through pulse transit time. *Am. J. Respir. Crit. Care Med.* **158,** 1778–1783 (1998).
191. Foo, J. Y. A. *et al.* Use of pulse transit time to distinguish respiratory events from tidal breathing in sleeping children. *Chest* **128,** 3013–3019 (2005).
192. Pépin, J.-L. *et al.* Pulse transit time improves detection of sleep respiratory events and microarousals in children. *Chest* **127,** 722–730 (2005).
193. Li, A. M., Au, C. T., Ho, C., Fok, T. F. & Wing, Y. K. Blood pressure is elevated in children with primary snoring. *J. Pediatr.* **155,** 362–368.e1 (2009).
194. Koltai, P. J., Solares, C. A., Mascha, E. J. & Xu, M. Intracapsular partial tonsillectomy for tonsillar hypertrophy in children. *The Laryngoscope* **112,** 17–19 (2002).
195. Isaacson, G. Pediatric intracapsular tonsillectomy with bipolar electrosurgical scissors. *Ear. Nose. Throat J.* **83,** 702, 704–706 (2004).
196. Friedman, M., Wilson, M., Lin, H.-C. & Chang, H.-W. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. *Otolaryngol.-Head Neck Surg.* **140,** 800–808 (2009).
197. Wilson, K., Lakheeram, I., Morielli, A., Brouillette, R. & Brown, K. Can assessment for obstructive sleep apnea help predict postadenotonsillectomy respiratory complications? *Anesthesiology* **96,** 313–322 (2002).
198. Ye, J. *et al.* Postoperative respiratory complications of adenotonsillectomy for obstructive

sleep apnea syndrome in older children: prevalence, risk factors, and impact on clinical outcome. *J. Otolaryngol. - Head Neck Surg. J. Oto-Rhino-Laryngol. Chir. Cervico-Faciale* **38,** 49–58 (2009).
199. Biavati, M. J., Manning, S. C. & Phillips, D. L. Predictive factors for respiratory complications after tonsillectomy and adenoidectomy in children. *Arch. Otolaryngol. Head Neck Surg.* **123,** 517–521 (1997).
200. Tait, A. R. *et al.* Risk factors for perioperative adverse respiratory events in children with upper respiratory tract infections. *Anesthesiology* **95,** 299–306 (2001).
201. Mitchell, R. B. Adenotonsillectomy for obstructive sleep apnea in children: outcome evaluated by pre- and postoperative polysomnography. *The Laryngoscope* **117,** 1844–1854 (2007).
202. O'Brien, L. M., Sitha, S., Baur, L. A. & Waters, K. A. Obesity increases the risk for persisting obstructive sleep apnea after treatment in children. *Int. J. Pediatr. Otorhinolaryngol.* **70,** 1555–1560 (2006).
203. Ye, J. *et al.* Outcome of adenotonsillectomy for obstructive sleep apnea syndrome in children. *Ann. Otol. Rhinol. Laryngol.* **119,** 506–513 (2010).
204. Mitchell, R. B. & Kelly, J. Outcome of adenotonsillectomy for obstructive sleep apnea in children under 3 years. *Otolaryngol.--Head Neck Surg. Off. J. Am. Acad. Otolaryngol.-Head Neck Surg.* **132,** 681–684 (2005).
205. Brietzke, S. E. & Gallagher, D. The effectiveness of tonsillectomy and adenoidectomy in the treatment of pediatric obstructive sleep apnea/hypopnea syndrome: a meta-analysis. *Otolaryngol.--Head Neck Surg. Off. J. Am. Acad. Otolaryngol.-Head Neck Surg.* **134,** 979–984 (2006).
206. Imanguli, M. & Ulualp, S. O. Risk factors for residual obstructive sleep apnea after adenotonsillectomy in children. *The Laryngoscope* **126,** 2624–2629 (2016).
207. Kay, D. J. & Goldsmith, A. J. Laryngomalacia: a classification system and surgical treatment strategy. *Ear. Nose. Throat J.* **85,** 328–331, 336 (2006).
208. Olney, D. R., Greinwald, J. H., Smith, R. J. & Bauman, N. M. Laryngomalacia and its treatment. *The Laryngoscope* **109,** 1770–1775 (1999).
209. Landry, A. M. & Thompson, D. M. Laryngomalacia: disease presentation, spectrum, and management. *Int. J. Pediatr.* **2012,** 753526 (2012).
210. Ayari, S. *et al.* Management of laryngomalacia. *Eur. Ann. Otorhinolaryngol. Head Neck Dis.* **130,** 15–21 (2013).
211. Richter, G. T. & Thompson, D. M. The surgical management of laryngomalacia. *Otolaryngol. Clin. North Am.* **41,** 837–864, vii (2008).
212. Farhood, Z. *et al.* Objective Outcomes of Supraglottoplasty for Children With Laryngomalacia and Obstructive Sleep Apnea: A Meta-analysis. *JAMA Otolaryngol.-- Head Neck Surg.* **142,** 665–671 (2016).
213. Lee, C.-F., Hsu, W.-C., Lee, C.-H., Lin, M.-T. & Kang, K.-T. Treatment outcomes of supraglottoplasty for pediatric obstructive sleep apnea: A meta-analysis. *Int. J. Pediatr. Otorhinolaryngol.* **87,** 18–27 (2016).
214. Reinhard, A., Gorostidi, F., Leishman, C., Monnier, P. & Sandu, K. Laser supraglottoplasty for laryngomalacia; a 14 year experience of a tertiary referral center. *Eur. Arch. Oto-Rhino-Laryngol. Off. J. Eur. Fed. Oto-Rhino-Laryngol. Soc. EUFOS Affil. Ger. Soc. Oto-Rhino-Laryngol. - Head Neck Surg.* **274,** 367–374 (2017).
215. Morovic, C. G. & Monasterio, L. Distraction osteogenesis for obstructive apneas in patients with congenital craniofacial malformations. *Plast. Reconstr. Surg.* **105,** 2324–2330 (2000).
216. Verlinden, C. R. A., van de Vijfeijken, S. E. C. M., Jansma, E. P., Becking, A. G. & Swennen, G. R. J. Complications of mandibular distraction osteogenesis for congenital deformities: a systematic review of the literature and proposal of a new classification for complications. *Int. J. Oral Maxillofac. Surg.* **44,** 37–43 (2015).
217. Denny, A. D., Talisman, R., Hanson, P. R. & Recinos, R. F. Mandibular distraction osteogenesis in very young patients to correct airway obstruction. *Plast. Reconstr. Surg.* **108,** 302–311 (2001).

218. Tahiri, Y., Viezel-Mathieu, A., Aldekhayel, S., Lee, J. & Gilardino, M. The Effectiveness of Mandibular Distraction in Improving Airway Obstruction in the Pediatric Population: *Plast. Reconstr. Surg.* **133,** 352e–359e (2014).
219. Gürsoy, S., Hukki, J. & Hurmerinta, K. Five-Year Follow-Up of Maxillary Distraction Osteogenesis on the Dentofacial Structures of Children With Cleft Lip and Palate. *J. Oral Maxillofac. Surg.* **68,** 744–750 (2010).
220. Tibesar, R. J. *et al.* Distraction osteogenesis of the mandible for airway obstruction in children: Long-term results. *Otolaryngol. Head Neck Surg.* **143,** 90–96 (2010).
221. Strome, M. Obstructive sleep apnea in Down syndrome children: a surgical approach. *The Laryngoscope* **96,** 1340–1342 (1986).
222. Kosko, J. R. & Derkay, C. S. Uvulopalatopharyngoplasty: treatment of obstructive sleep apnea in neurologically impaired pediatric patients. *Int. J. Pediatr. Otorhinolaryngol.* **32,** 241–246 (1995).
223. Kerschner, J. E., Lynch, J. B., Kleiner, H., Flanary, V. A. & Rice, T. B. Uvulopalatopharyngoplasty with tonsillectomy and adenoidectomy as a treatment for obstructive sleep apnea in neurologically impaired children. *Int. J. Pediatr. Otorhinolaryngol.* **62,** 229–235 (2002).
224. Truong, M. T., Woo, V. G. & Koltai, P. J. Sleep endoscopy as a diagnostic tool in pediatric obstructive sleep apnea. *Int. J. Pediatr. Otorhinolaryngol.* **76,** 722–727 (2012).
225. Durr, M. L., Meyer, A. K., Kezirian, E. J. & Rosbe, K. W. Drug-induced sleep endoscopy in persistent pediatric sleep-disordered breathing after adenotonsillectomy. *Arch. Otolaryngol. Head Neck Surg.* **138,** 638–643 (2012).
226. Shott, S. R. & Donnelly, L. F. Cine magnetic resonance imaging: evaluation of persistent airway obstruction after tonsil and adenoidectomy in children with Down syndrome. *The Laryngoscope* **114,** 1724–1729 (2004).
227. Maris, M. *et al.* Drug-induced sedation endoscopy in surgically naive children with Down syndrome and obstructive sleep apnea. *Sleep Med.* **24,** 63–70 (2016).
228. Prosser, J. D. *et al.* Polysomnographic outcomes following lingual tonsillectomy for persistent obstructive sleep apnea in down syndrome. *The Laryngoscope* **127,** 520–524 (2017).
229. Thottam, P. J., Govil, N., Duvvuri, U. & Mehta, D. Transoral robotic surgery for sleep apnea in children: Is it effective? *Int. J. Pediatr. Otorhinolaryngol.* **79,** 2234–2237 (2015).
230. Patel, P. A., Shetye, P., Warren, S. M., Grayson, B. H. & McCarthy, J. G. Five-Year Follow-Up of Midface Distraction in Growing Children with Syndromic Craniosynostosis. *Plast. Reconstr. Surg.* **140,** 794e–803e (2017).
231. Meling, T. R., Hans-Erik, H., Per, S. & Due-Tonnessen, B. J. Le Fort III distraction osteogenesis in syndromal craniosynostosis. *J. Craniofac. Surg.* **17,** 28–39 (2006).
232. Saltaji, H. *et al.* Le Fort III distraction osteogenesis versus conventional Le Fort III osteotomy in correction of syndromic midfacial hypoplasia: a systematic review. *J. Oral Maxillofac. Surg. Off. J. Am. Assoc. Oral Maxillofac. Surg.* **72,** 959–972 (2014).
233. Arnaud, E. & Di Rocco, F. Faciocraniosynostosis: monobloc frontofacial osteotomy replacing the two-stage strategy? *Childs Nerv. Syst. ChNS Off. J. Int. Soc. Pediatr. Neurosurg.* **28,** 1557–1564 (2012).
234. Mahadevan, M., Barber, C., Salkeld, L., Douglas, G. & Mills, N. Pediatric tracheotomy: 17 year review. *Int. J. Pediatr. Otorhinolaryngol.* **71,** 1829–1835 (2007).
235. Carr, M. M., Poje, C. P., Kingston, L., Kielma, D. & Heard, C. Complications in pediatric tracheostomies. *The Laryngoscope* **111,** 1925–1928 (2001).
236. Fricke, B. L. *et al.* Comparison of lingual tonsil size as depicted on MR imaging between children with obstructive sleep apnea despite previous tonsillectomy and adenoidectomy and normal controls. *Pediatr. Radiol.* **36,** 518–523 (2006).
237. Donnelly, L. F., Shott, S. R., LaRose, C. R., Chini, B. A. & Amin, R. S. Causes of persistent obstructive sleep apnea despite previous tonsillectomy and adenoidectomy in children with down

syndrome as depicted on static and dynamic cine MRI. *AJR Am. J. Roentgenol.* **183,** 175–181 (2004).
238. Bravo, G., Ysunza, A., Arrieta, J. & Pamplona, M. C. Videonasopharyngoscopy is useful for identifying children with Pierre Robin sequence and severe obstructive sleep apnea. *Int. J. Pediatr. Otorhinolaryngol.* **69,** 27–33 (2005).
239. Cormack, R. S. & Lehane, J. Difficult tracheal intubation in obstetrics. *Anaesthesia* **39,** 1105–1111 (1984).
240. Lam, D. J. *et al.* Assessment of pediatric obstructive sleep apnea using a drug-induced sleep endoscopy rating scale. *The Laryngoscope* **126,** 1492–1498 (2016).
241. Boudewyns, A., Verhulst, S., Maris, M., Saldien, V. & Van de Heyning, P. Drug-induced sedation endoscopy in pediatric obstructive sleep apnea syndrome. *Sleep Med.* **15,** 1526–1531 (2014).
242. Boudewyns, A., Saldien, V., Van de Heyning, P. & Verhulst, S. Drug-induced sedation endoscopy in surgically naïve infants and children with obstructive sleep apnea: impact on treatment decision and outcome. *Sleep Breath.* (2017). doi:10.1007/s11325-017-1581-7
243. Slaats, M. *et al.* Predicting the effect of treatment in paediatric OSA by clinical examination and functional respiratory imaging. *Pediatr. Pulmonol.* **52,** 799–805 (2017).
244. Villa, M. P. *et al.* Rapid maxillary expansion in children with obstructive sleep apnea syndrome: 12-month follow-up. *Sleep Med.* **8,** 128–134 (2007).
245. Vale, F. *et al.* Efficacy of Rapid Maxillary Expansion in the Treatment of Obstructive Sleep Apnea Syndrome: A Systematic Review With Meta-analysis. *J. Evid.-Based Dent. Pract.* **17,** 159–168 (2017).
246. Huynh, N. T., Desplats, E. & Almeida, F. R. Orthodontics treatments for managing obstructive sleep apnea syndrome in children: A systematic review and meta-analysis. *Sleep Med. Rev.* **25,** 84–94 (2016).
247. Sharples, L. *et al.* Clinical effectiveness and cost-effectiveness results from the randomised controlled Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea-hypopnoea (TOMADO) and long-term economic analysis of oral devices and continuous positive airway pressure. *Health Technol. Assess. Winch. Engl.* **18,** 1–296 (2014).
248. Vecchierini, M.-F. *et al.* A custom-made mandibular repositioning device for obstructive sleep apnoea-hypopnoea syndrome: the ORCADES study. *Sleep Med.* **19,** 131–140 (2016).
249. Schwartz, M., Acosta, L., Hung, Y.-L., Padilla, M. & Enciso, R. Effects of CPAP and mandibular advancement device treatment in obstructive sleep apnea patients: a systematic review and meta-analysis. *Sleep Breath. Schlaf Atm.* (2017). doi:10.1007/s11325-017-1590-6
250. Verhulst, S. L., Franckx, H., Van Gaal, L., De Backer, W. & Desager, K. The Effect of Weight Loss on Sleep-disordered Breathing in Obese Teenagers. *Obesity* **17,** 1178–1183 (2009).
251. Siegfried, W., Siegfried, A., Rabenbauer, M. & Hebebrand, J. Snoring and Sleep Apnea in Obese Adolescents: Effect of Long-term Weight Loss-Rehabilitation. *Sleep Breath. Schlaf Atm.* **3,** 83–88 (1999).
252. Kalra, M. *et al.* Obstructive sleep apnea in extremely overweight adolescents undergoing bariatric surgery. *Obes. Res.* **13,** 1175–1179 (2005).
253. Taylor, S. J. A., Rennie, K. & Jon, C. Clinical outcomes of an inpatient pediatric obesity treatment program in the USA. *Int. J. Adolesc. Med. Health* (2017). doi:10.1515/ijamh-2016-0141
254. Brouillette, R. T. *et al.* Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea. *J. Pediatr.* **138,** 838–844 (2001).
255. Kheirandish-Gozal, L. & Gozal, D. Intranasal budesonide treatment for children with mild obstructive sleep apnea syndrome. *Pediatrics* **122,** e149-155 (2008).
256. Goldbart, A. D., Greenberg-Dotan, S. & Tal, A. Montelukast for children with obstructive sleep apnea: a double-blind, placebo-controlled study. *Pediatrics* **130,** e575-580 (2012).
257. Kheirandish-Gozal, L., Bhattacharjee, R., Bandla, H. P. R. & Gozal, D. Antiinflammatory therapy outcomes for mild OSA in children. *Chest* **146,** 88–95 (2014).

258. Kheirandish, L., Goldbart, A. D. & Gozal, D. Intranasal steroids and oral leukotriene modifier therapy in residual sleep-disordered breathing after tonsillectomy and adenoidectomy in children. *Pediatrics* **117,** e61-66 (2006).
259. Al-Ghamdi, S. A. *et al.* Do systemic corticosteroids effectively treat obstructive sleep apnea secondary to adenotonsillar hypertrophy? *The Laryngoscope* **107,** 1382–1387 (1997).
260. Kureshi, S. A. *et al.* Pilot study of nasal expiratory positive airway pressure devices for the treatment of childhood obstructive sleep apnea syndrome. *J. Clin. Sleep Med. JCSM Off. Publ. Am. Acad. Sleep Med.* **10,** 663–669 (2014).
261. Guilleminault, C. *et al.* Critical role of myofascial reeducation in pediatric sleep-disordered breathing. *Sleep Med.* **14,** 518–525 (2013).
262. Sullivan, C. E., Issa, F. G., Berthon-Jones, M. & Eves, L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet Lond. Engl.* **1,** 862–865 (1981).
263. Girbal, I. C. *et al.* Non-invasive ventilation in complex obstructive sleep apnea – A 15-year experience of a pediatric tertiary center. *Rev. Port. Pneumol.* **20,** 146–151 (2014).
264. McDougall, C. M., Adderley, R. J., Wensley, D. F. & Seear, M. D. Long-term ventilation in children: longitudinal trends and outcomes. *Arch. Dis. Child.* **98,** 660–665 (2013).
265. Edwards, E. A., Hsiao, K. & Nixon, G. M. Paediatric home ventilatory support: the Auckland experience. *J. Paediatr. Child Health* **41,** 652–658 (2005).
266. Racca, F. *et al.* Long-term home ventilation of children in Italy: a national survey. *Pediatr. Pulmonol.* **46,** 566–572 (2011).
267. Pavone, M., Verrillo, E., Caldarelli, V., Ullmann, N. & Cutrera, R. Non-invasive positive pressure ventilation in children. *Early Hum. Dev.* **89 Suppl 3,** S25-31 (2013).
268. Hull, J. *et al.* British Thoracic Society guideline for respiratory management of children with neuromuscular weakness. *Thorax* **67 Suppl 1,** i1-40 (2012).
269. Katz, S. L. *et al.* Nocturnal hypoventilation: predictors and outcomes in childhood progressive neuromuscular disease. *Arch. Dis. Child.* **95,** 998–1003 (2010).
270. Ogna, A. *et al.* Nocturnal hypoventilation in neuromuscular disease: prevalence according to different definitions issued from the literature. *Sleep Breath. Schlaf Atm.* **20,** 575–581 (2016).
271. White, J. E., Drinnan, M. J., Smithson, A. J., Griffiths, C. J. & Gibson, G. J. Respiratory muscle activity and oxygenation during sleep in patients with muscle weakness. *Eur. Respir. J.* **8,** 807–814 (1995).
272. Steier, J. *et al.* Sleep-disordered breathing in unilateral diaphragm paralysis or severe weakness. *Eur. Respir. J.* **32,** 1479–1487 (2008).
273. Aboussouan, L. S. Sleep-disordered Breathing in Neuromuscular Disease. *Am. J. Respir. Crit. Care Med.* **191,** 979–989 (2015).
274. Sood, N., Paradowski, L. J. & Yankaskas, J. R. Outcomes of intensive care unit care in adults with cystic fibrosis. *Am. J. Respir. Crit. Care Med.* **163,** 335–338 (2001).
275. Ellaffi, M. *et al.* One-year outcome after severe pulmonary exacerbation in adults with cystic fibrosis. *Am. J. Respir. Crit. Care Med.* **171,** 158–164 (2005).
276. Texereau, J. *et al.* Determinants of mortality for adults with cystic fibrosis admitted in Intensive Care Unit: a multicenter study. *Respir. Res.* **7,** 14 (2006).
277. Fauroux, B. *et al.* Practice of noninvasive ventilation for cystic fibrosis: a nationwide survey in France. *Respir. Care* **53,** 1482–1489 (2008).
278. Waters, K. A., Everett, F. M., Bruderer, J. W. & Sullivan, C. E. Obstructive sleep apnea: the use of nasal CPAP in 80 children. *Am. J. Respir. Crit. Care Med.* **152,** 780–785 (1995).
279. Marcus, C. L. *et al.* Use of nasal continuous positive airway pressure as treatment of childhood obstructive sleep apnea. *J. Pediatr.* **127,** 88–94 (1995).
280. Khirani, S. *et al.* Continuous positive airway pressure titration in infants with severe upper airway obstruction or bronchopulmonary dysplasia. *Crit. Care Lond. Engl.* **17,** R167 (2013).
281. Guilleminault, C., Pelayo, R., Clerk, A., Leger, D. & Bocian, R. C. Home nasal continuous

positive airway pressure in infants with sleep-disordered breathing. *J. Pediatr.* **127,** 905–912 (1995).
282. Essouri, S. *et al.* Noninvasive positive pressure ventilation in infants with upper airway obstruction: comparison of continuous and bilevel positive pressure. *Intensive Care Med.* **31,** 574–580 (2005).
283. Chihara, Y. *et al.* Flexible positive airway pressure improves treatment adherence compared with auto-adjusting PAP. *Sleep* **36,** 229–236 (2013).
284. Marcus, C. L. *et al.* Adherence to and effectiveness of positive airway pressure therapy in children with obstructive sleep apnea. *Pediatrics* **117,** e442-451 (2006).
285. Marcus, C. L. *et al.* Randomized, Double-Blind Clinical Trial of Two Different Modes of Positive Airway Pressure Therapy on Adherence and Efficacy in Children. *J. Clin. Sleep Med.* (2012). doi:10.5664/jcsm.1656
286. Koontz, K. L., Slifer, K. J., Cataldo, M. D. & Marcus, C. L. Improving pediatric compliance with positive airway pressure therapy: the impact of behavioral intervention. *Sleep* **26,** 1010–1015 (2003).
287. Rains, J. C. Treatment of obstructive sleep apnea in pediatric patients. Behavioral intervention for compliance with nasal continuous positive airway pressure. *Clin. Pediatr. (Phila.)* **34,** 535–541 (1995).
288. DiFeo, N. *et al.* Predictors of positive airway pressure therapy adherence in children: a prospective study. *J. Clin. Sleep Med. JCSM Off. Publ. Am. Acad. Sleep Med.* **8,** 279–286 (2012).
289. Nixon, G. M., Mihai, R., Verginis, N. & Davey, M. J. Patterns of continuous positive airway pressure adherence during the first 3 months of treatment in children. *J. Pediatr.* **159,** 802–807 (2011).
290. Ramirez, A. *et al.* Interfaces for long-term noninvasive positive pressure ventilation in children. *Intensive Care Med.* **38,** 655–662 (2012).
291. Young, H. K. *et al.* Outcome of noninvasive ventilation in children with neuromuscular disease. *Neurology* **68,** 198–201 (2007).
292. Mellies, U. *et al.* Long-term noninvasive ventilation in children and adolescents with neuromuscular disorders. *Eur. Respir. J.* **22,** 631–636 (2003).
293. Simonds, A. K., Ward, S., Heather, S., Bush, A. & Muntoni, F. Outcome of paediatric domiciliary mask ventilation in neuromuscular and skeletal disease. *Eur. Respir. J.* **16,** 476–481 (2000).
294. Chatwin, M., Bush, A. & Simonds, A. K. Outcome of goal-directed non-invasive ventilation and mechanical insufflation/exsufflation in spinal muscular atrophy type I. *Arch. Dis. Child.* **96,** 426–432 (2011).
295. Moran, F., Bradley, J. M. & Piper, A. J. Non-invasive ventilation for cystic fibrosis. *Cochrane Database Syst. Rev.* **2,** CD002769 (2017).
296. Force, P. A. P. T. T., Medicine, A. A. of S. & others. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. *J. Clin. Sleep Med. JCSM Off. Publ. Am. Acad. Sleep Med.* **4,** 157 (2008).
297. Pasquina, P. *et al.* What Does Built-In Software of Home Ventilators Tell Us? An Observational Study of 150 Patients on Home Ventilation. *Respiration* **83,** 293–299 (2012).
298. airsense10-autoset.pdf.
299. Khirani, S. *et al.* Can the analysis of built-in software of CPAP devices replace polygraphy in children? *Sleep Med.* **37,** 46–53 (2017).
300. Paiva, R. *et al.* Carbon dioxide monitoring during long-term noninvasive respiratory support in children. *Intensive Care Med.* **35,** 1068–1074 (2009).
301. Janssens, J.-P., Borel, J.-C., Pépin, J.-L. & SomnoNIV Group. Nocturnal monitoring of home non-invasive ventilation: the contribution of simple tools such as pulse oximetry, capnography, built-in ventilator software and autonomic markers of sleep fragmentation. *Thorax* **66,** 438–445 (2011).

302. Contal, O. *et al.* Monitoring of noninvasive ventilation by built-in software of home bilevel ventilators: a bench study. *Chest* **141,** 469–476 (2012).
303. Gonzalez-Bermejo, J. *et al.* Proposal for a systematic analysis of polygraphy or polysomnography for identifying and scoring abnormal events occurring during non-invasive ventilation. *Thorax* **67,** 546–552 (2012).
304. Edwards, B. A., Malhotra, A. & Sands, S. A. Adapting our approach to treatment-emergent central sleep apnea. *Sleep* **36,** 1121–1122 (2013).
305. Fauroux, B. *et al.* Facial side effects during noninvasive positive pressure ventilation in children. *Intensive Care Med.* **31,** 965–969 (2005).
306. Vandenbussche, N. L., Overeem, S., van Dijk, J. P., Simons, P. J. & Pevernagie, D. A. Assessment of respiratory effort during sleep: Esophageal pressure versus noninvasive monitoring techniques. *Sleep Med. Rev.* **24,** 28–36 (2015).
307. Chervin, R. D. & Aldrich, M. S. Effects of esophageal pressure monitoring on sleep architecture. *Am. J. Respir. Crit. Care Med.* **156,** 881–885 (1997).
308. Staats, B. A., Bonekat, H. W., Harris, C. D. & Offord, K. P. Chest wall motion in sleep apnea. *Am. Rev. Respir. Dis.* **130,** 59–63 (1984).
309. Luo, Y.-M. *et al.* Distinguishing obstructive from central sleep apnea events: diaphragm electromyogram and esophageal pressure compared. *CHEST J.* **135,** 1133–1141 (2009).
310. Boudewyns, A. *et al.* Assessment of respiratory effort by means of strain gauges and esophageal pressure swings: a comparative study. *Sleep* **20,** 168–170 (1997).
311. Meslier, N. *et al.* Validation of a suprasternal pressure transducer for apnea classification during sleep. *Sleep* **25,** 753–757 (2002).
312. Delessert, A. *et al.* Pulse wave amplitude drops during sleep are reliable surrogate markers of changes in cortical activity. *Sleep* **33,** 1687–1692 (2010).
313. Karmakar, C., Khandoker, A., Penzel, T., Schöbel, C. & Palaniswami, M. Detection of respiratory arousals using photoplethysmography (PPG) signal in sleep apnea patients. *IEEE J. Biomed. Health Inform.* **18,** 1065–1073 (2014).
314. Haba-Rubio, J. *et al.* Obstructive sleep apnea syndrome: effect of respiratory events and arousal on pulse wave amplitude measured by photoplethysmography in NREM sleep. *Sleep Breath.* **9,** 73–81 (2005).
315. Collins, B., Powitzky, R., Robledo, C., Rose, C. & Glade, R. Airway management in pierre robin sequence: patterns of practice. *Cleft Palate-Craniofacial J. Off. Publ. Am. Cleft Palate-Craniofacial Assoc.* **51,** 283–289 (2014).
316. Khansa, I. *et al.* Airway and Feeding Outcomes of Mandibular Distraction, Tongue-Lip Adhesion, and Conservative Management in Pierre Robin Sequence: A Prospective Study. *Plast. Reconstr. Surg.* **139,** 975e–983e (2017).
317. Schaefer, R. B. & Gosain, A. K. Airway management in patients with isolated Pierre Robin sequence during the first year of life. *J. Craniofac. Surg.* **14,** 462–467 (2003).
318. Denny, A. D., Talisman, R., Hanson, P. R. & Recinos, R. F. Mandibular distraction osteogenesis in very young patients to correct airway obstruction. *Plast. Reconstr. Surg.* **108,** 302–311 (2001).
319. Gómez, O. J., Barón, O. I. & Peñarredonda, M. L. Pierre Robin Sequence: An Evidence-Based Treatment Proposal. *J. Craniofac. Surg.* (2017). doi:10.1097/SCS.0000000000004178
320. Rathé, M. *et al.* Pierre Robin sequence: Management of respiratory and feeding complications during the first year of life in a tertiary referral centre. *Int. J. Pediatr. Otorhinolaryngol.* **79,** 1206–1212 (2015).
321. Leboulanger, N. *et al.* Physiologic and clinical benefits of noninvasive ventilation in infants with Pierre Robin sequence. *Pediatrics* **126,** e1056-1063 (2010).
322. Fauroux, B., Boffa, C., Desguerre, I., Estournet, B. & Trang, H. Long-term noninvasive mechanical ventilation for children at home: a national survey. *Pediatr. Pulmonol.* **35,** 119–125 (2003).

323. Rose, L. *et al.* Home Mechanical Ventilation in Canada: A National Survey. *Respir. Care* (2015). doi:10.4187/respcare.03609