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Development and application of a physiological ventilation device test bench, capable of reproducing automatically respiratory profiles registered with ventilation polygraph

Shuo Liu

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Development and application of a physiological ventilation device test bench, capable of reproducing automatically respiratory profiles registered with ventilation polygraph

Thèse de doctorat de l'Université Paris-Saclay
Préparée à l'Université Paris-Sud

École doctorale ED566: Sciences du sport,
de la motricité et du mouvement humain (SSMMH)

Thèse présentée et soutenue à Orsay, le 13 Décembre 2019, par

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Abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnea hypopnea index
AHI _{flow}	Apnea hypopnea index calculated only based on airflow analysis
AHI _{PAP}	Apnea hypopnea index determined by positive airway pressure devices
AHI _{PG}	Apnea hypopnea index determined by polygraph device
AI	Apnea index
AI _{PAP}	Apnea index determined by positive airway pressure devices
AI _{PG}	Apnea index determined by polygraph device
AMPD	Automatic multiscale-based peak detection
APAP	Auto-titrating (Auto-adjusting) positive airway pressure
BiPAP	Bilevel positive airway pressure
CAI	Central apnea index
CA	Central apnea
CPAP	Continuous positive airway pressure
CSA	Central sleep apnea
HI	Hypopnea index
HI _{flow}	Hypopnea index calculated only based on airflow analysis
HI _{PAP}	Hypopnea index determined by positive airway pressure devices
HI _{PG}	Hypopnea index determined by polygraph device
IAH	Index d'apnée-hypopnée
IA	Index d'apnée
IH	Index d'hypopnée
MAI	Mixed apnea index
MA	Mixed apnea
OAI	Obstructive apnea index
OA	Obstructive apnea
OSA	Obstructive sleep apnea
PAP	Positive airway pressure
PPC	Pression positive continue
PPV	Positive predictive value
P _{ch}	Sealed chamber pressure in Starling resistor
P _{crit}	Critical pressure of Starling resistor
P _{ds}	Pressure at the downstream segment
P _{us}	Pressure at the upstream segment
P _{tm}	Transmural pressure of Starling resistor
RIP	Respiratory inductance plethysmography
SDB	Sleep disordered breathing
Std	Standard deviation
TTL	Transistor-to-transistor logic
V _n '	Patient's nasal airflow



Résumé

Le syndrome d'apnée obstructive du sommeil représente un problème de santé publique, en affectant environ 6% à 17% de la population adulte. Le traitement de référence de cette maladie reste la ventilation nocturne par l'envoi d'une pression positive continue (PPC) fixe ou autopilotée dans les voies aériennes supérieures du patient afin de les maintenir ouvertes. L'efficacité traitement de PPC autopilotée dépend des algorithmes et technologies implémentés qui détectent les événements respiratoires et qualifient leur mécanisme (lié à l'obstruction des voies aériennes supérieures ou à une altération de la commande centrale de respiration), qui sont protégés par les fabricants et perçus comme une boîte noire par le public. En pratique, le fonctionnement des machines est observé par enregistrement de la ventilation de patients sous traitement. Il paraît cependant difficile de comparer les différentes machines à cause des variabilités respiratoires inter- et intra-patient. Ainsi, des bancs d'essai ont été développés pour compenser ce manque en simulant des débits respiratoires et éventuellement des obstructions de voies aériennes supérieures, représentant des patients apnéiques. Les scénarios respiratoires simulés sont composés par une répétition des événements respiratoires extraits de patients ou conçus artificiellement. Avec les bancs d'essai précédents, la simulation d'un profil respiratoire entier enregistré par poly(somno)graphie peut sembler laborieuse parce que elle n'est pas automatisée.

L'objectif de cette thèse consiste à développer un banc d'essai physiologique, capable de reproduire automatiquement le profil respiratoire enregistré par polygraphie, en tenant compte des caractéristiques obstructives et centrales des événements respiratoires.

Un algorithme a ainsi été développé pour analyser les signaux polygraphiques et calculer la pression de l'effort musculaire de respiration et les résistances de voies aériennes supérieures pour piloter sur banc respectivement le poumon artificiel et la résistance de Starling qui



modélisait les obstructions dans les voies aériennes supérieures. Le profil respiratoire simulé avec ce nouveau banc physiologique a révélé une similitude satisfaisante avec celui des patients concernant des paramètres temporels, d'amplitude du débit respiratoire et la capacité à reproduire des événements respiratoires de différentes natures. Ensuite, cette approche innovante a été validée avec simulation de 15 scénarios respiratoires d'une heure, issus de 12 patients apnéiques (modérés ou sévères), exprimant tous types d'événements (i.e. obstructif, central et mixte). La performance de simulation du banc d'essai a été prouvée robuste face aux profils respiratoires testés. La capacité de simulation a finalement permis d'investiguer la précision de l'index d'apnée-hypopnée (IAH) résiduel déterminé par PPC, en comparant les IAH déterminés par 4 dispositifs de PPC (AirSense 10, DreamStation Auto, S.Box et Prisma 20A) avec ceux obtenus en polygraphies diagnostiques des patients présentant des événements centraux et obstructifs. Les résultats ont montré que toutes les PPC testées ont eu un accord meilleur en index d'apnée qu'en index d'hypopnée (IH) avec la polygraphie. En plus, elles ont montré une tendance à la sous-estimation de l'IH par rapport à la polygraphie avec un degré variant en fonction du fabricant.

Ce nouveau banc d'essai physiologique permet de facilement simuler le profil respiratoire d'un patient spécifique à partir des données polygraphiques. Il pourrait être un outil utile pour la compréhension et la comparaison des appareils ventilatoires ainsi qu'un pas vers la personnalisation du traitement.



Summary

Obstructive sleep apnea (OSA) represents a public health problem, affecting about 6% to 17% of adult population. So far, the reference treatment for moderate-to-severe OSA remains nocturnal ventilation via a Positive Airway Pressure (PAP) device delivering a either fixed or auto-titrating pressure to patient's upper airway in order to maintain it open. The treatment efficiency of auto-titrating PAP (APAP) depends greatly on the algorithms and technologies implemented for detecting and characterizing disordered breathing events (linked to upper airway obstruction or central command impairment). However, they are often protected by manufacturers and resembling a black box to the public. From clinical studies, device functioning can be indirectly observed by recording patient ventilation under APAP. However, it is difficult to compare treatment efficiencies of different PAP devices because of intra- and inter-patient breathing profile variability. Thus respiratory simulation benches have been developed to resolve this problem, by reproducing respiratory scenarios artificially designed and composed of a repetitive string of typical obstructive and central events extracted from patients' recordings. All of them seem to have a limitation in reproducing entirely a specific patient breathing profile for its poly(somno)graph recordings in an automatic manner.

The aim of this thesis consists to develop a physiological bench which reproduces automatically the breathing profile registered in the polygraph recordings of patients diagnosed with sleep apnea syndrome, taking into account sleep disordered breathing (SDB) of central and obstructive mechanisms.

To achieve this, a specific algorithm was developed for analyzing polygraph signals and calculating the respiratory muscular effort pressure and upper airway resistance required for controlling bench hardware, mainly constituted by an active lung simulator and a Starling



resistor modeling upper airway resistance. The respiratory profile simulated on this new bench showed a satisfying similarity to the one of patient in both temporal and intensity parameters of airflow, at the same time reproducing patient's SDB events of central and obstructive mechanisms. Then this novel approach was validated by simulating on bench 15 one-hour breathing scenarios, sampled from polygraph recordings of 12 patients diagnosed with moderate-to-severe sleep apnea syndrome. The apnea index (AI) of these polygraph samples presented a wide spectrum from 1.4 to 76.7 events/hour, containing all types (i.e. obstructive, central and mixed) of apneas. The bench simulation performance was proved robust for all the breathing phenotypes sampled. Finally, the accuracy of residual apnea hypopnea indices determined by 4 PAP devices (AirSense 10, DreamStation Auto, S.Box and Prisma 20A) of different manufacturers, was also investigated in comparison with polygraph scorings, through this physiological bench, simulating 25 breathing scenarios of 1-hour issuing from patients with predominant central sleep apnea syndrome. All PAP devices had shown a better agreement in AI than hypopnea index (HI) with polygraph scorings. They tended to underestimate HI with a severity dependent to manufacturer.

This new physiological bench facilitates simulating any apneic patient breathing profile from its polygraph recordings in an automatic manner. It can serve as a tool for learning about ventilation devices' behaviors and helping clinicians in choosing an optimal ventilation device adapted to the specific breathing characteristics of their patients.



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Publications related to this research:

Patent:

An application of the patent (Fr1858334) about simulating a patient breathing profile through a test bench has been submitted to National Institute of Industrial Property (France), on September 16th 2018, by Michel Petitjean, Sébastien Hardy, Yann Retory, Amélie Sagniez, Shuo Liu. It is in course of examination.

Posters or oral presentations:

Shuo Liu, Yann Retory, Amélie Sagniez, Sébastien Hardy, François Cottin, Gabriel Roisman, Michel Petitjean. Sleep disordered breathing (SDB): respiration simulation on a bench integrating polygraph data. *European Respiratory Journal* 2018 52: PA2255; DOI: 10.1183/13993003.congress-2018.PA2255. It has been presented at ERS 2018, September 17th, 2018, Paris, France in a poster discussion format.

Shuo Liu, Yann Retory, Amélie Sagniez, Sébastien Hardy, François Cottin, Gabriel Roisman, Michel Petitjean. Syndrome d'apnée du sommeil: simulation respiratoire sur un banc intégrant des signaux physiologiques issus de polygraphie ventilatoire nocturne. *Journée annuelle de la Fédération Demeny-Vaucanson*, Orsay, Novembre 20th, 2018.

Yann Retory, Shuo Liu, Sébastien Hardy, François Cottin, Gabriel Roisman, Michel Petitjean. Evaluation of AHI agreement between PAP algorithms and polygraph in CSA patients. It has been presented at ERS 2019, September 30th, 2019, Madrid, Spain.

Yann Retory, Shuo Liu, Sébastien Hardy, François Cottin, Gabriel Roisman, Michel Petitjean. Evaluation de l'index d'apnées-hypopnées des machines de Pression Positive Continue sur un banc d'essai physiologique. It has been presented at SFRMS 2019, November 21-22, 2019, Lille France.

Articles:

Shuo Liu, Yann Retory, Amélie Sagniez, Sébastien Hardy, François Cottin, Gabriel Roisman, Michel Petitjean. New physiological bench test reproducing nocturnal breathing pattern of patients with sleep disordered breathing. Edited by Heming Wang. *PLOS ONE* 14 (12): e0225766. <https://doi.org/10.1371/journal.pone.0225766>.



The manuscripts of two other articles about the validation (title: Validation of a new physiological bench test reproducing nocturnal breathing profile of patients with sleep apnea) and application (title: Bench test evaluation of apnea-hypopnea-index agreement between positive air pressure devices and polygraph in predominant central sleep apnea patients) of this new physiological bench have been prepared. At the time of this thesis defense, we are waiting for the publication of the precedent article, which explains the methodology used. We will submit these two articles after the thesis defense.

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Introduction

Obstructive sleep apnea (OSA) is a highly prevalent disease, affecting about 6% to 17% in adult population (Baltzan et al. 2006). It is a kind of sleep disordered breathing (SDB), characterized by repetitive narrowing or closure of the upper airway during sleep (Remmers, deGroot, Sauerland, & Anch, 1978). This leads to intermittent arterial oxygen desaturations, and increased activation of the sympathetic nervous system, which may result in complications in cardiovascular diseases (Jean-Louis et al. 2008), as well as arterial hypertension (Nieto F et al. 2000) in the long term.

The reference treatment for patients affected by moderate to severe OSA is nocturnal ventilation, which delivers a positive airway pressure (PAP) to patient's upper airways through a nasal or facial mask. This pressure can overcome the increased closing force from the upper airways during sleep and maintain them open. This treatment modality has been developed for about 40 years (Sullivan et al. 1981). Initially, pressure delivered by PAP devices was fixed. Then they are becoming more and more intelligent thanks to the emergence of new technologies and great advances in computing power. They are able to detect and characterize patient's various disordered breathing events in real time: apneas and hypopneas of obstructive and central mechanisms, snoring, inspiratory flow limitations. Then the pressure delivered is adapted instantaneously in function of patient's upper airways status. It is so-called APAP (auto-adjusting positive airway pressure) mode.

Each manufacturer possesses its own technology and algorithm to detect and characterize disordered breathing events. Their details are often undisclosed to the public and protected by manufacturers through patents. Most of the time, device functioning can be retrospectively



and indirectly observed by recording patient ventilation under PAP treatment. However, it is difficult to evaluate and compare the algorithms of miscellaneous PAP devices objectively under the same controlled conditions. That is why there have been some work developing respiratory simulation benches to evaluate APAP algorithms, as reported in the literature (Farré et al. 2002b; Abdenbi 2004; Coller, Stanley, and Parthasarathy 2005; Rigau et al. 2006; Hirose et al. 2008; Netzel, Hein, and Hein 2014; Zhu et al. 2015; Isetta et al. 2016). These benches simulate apneic patient breathing profile by using a representative disordered breathing scenario composed of a repetitive string of several typical respiratory events artificially designed or issued from real patients' breathing recordings. According to these benches' test results, we could know about the treatment efficiencies of various APAP algorithms for the specific bench simulated breathing scenario. However, it is always difficult to conclude from them an appropriate APAP algorithm for an individual patient, due to differences between patients' breathing profiles and bench simulated ones. Furthermore, manufacturers tend to provide personalized therapy which is adapted to each patient's pathophysiological characteristics in the next few years. All of these contexts put forward the demand of a physiological bench, which can mimic each patient's disordered breathing profiles in a more detailed manner.

In this prospect, my thesis aims to develop a physiological bench, which is able to reproduce automatically breathing profiles registered in polygraph recordings, issuing from diagnostic examination of sleep apnea syndrome.



Chapter I. Sleep Apnea Syndrome

Sleep apnea syndrome is a kind of disordered breathing disease occurring during sleep, characterized by frequent respiratory pauses, namely apneas, which lead to intermittent arterial oxygen desaturations, increased activations of the sympathetic nervous system, resulting in cardiovascular complications in the long-term. The reasons for apneas can be related to two different mechanisms: due to a closed upper airway, i.e. the obstructive sleep apnea syndrome (OSAS); or due to the absence of central command to breathing, i.e. the central sleep apnea syndrome (CSAS). It has been also observed that there can be an overlap between OSAS and CSAS in certain patients. In this chapter, we will talk about the pathophysiological factors inducing sleep apneas as well as the treatment strategies at present.

1.1 Obstructive sleep apnea syndrome

1.1.1 Pathophysiology

Human upper airway is a structure performing multiple functional tasks: speech, swallowing, air passage during breathing. It consists of numerous muscles and soft tissues but lacks rigid supports. The pharynx which extends from hard palate to larynx is the softest part in the upper airway. It's also collapsible. The collapses of pharynx during sleep can cause the breathing disorder obstructive sleep apnea (OSA), which is defined by recurrent episodes of upper airway obstruction. The clinical consequences of this disease include daytime hypersomnolence, neurocognitive dysfunction, cardiovascular disease, metabolic dysfunction (Reichmuth et al. 2005), respiratory failure and *cor pulmonale* (Sidney Burwell et al. 1956). The major relevant risk factors are



found to be obesity, male gender, postmenopausal status and age (Jordan and McEvoy 2003; Young, Peppard, and Gottlieb 2002).

Patency of the pharynx during sleep is maintained by the balance between anatomically imposed mechanical loads and compensatory neuromuscular responses. So the pathogenesis of OSA is believed to combine both the increased upper airway mechanical loads and defects in neuromuscular mechanisms (Mezzanotte, Tangel, and White 1992). Firstly, the increased upper airway mechanical loads can be related to alterations in upper airway anatomy, including structural changes like tonsillar hypertrophy (Moser and Rajagopal 1987), retrognathia (Lyberg, Krogstad, and Djupesland 1989), variations in craniofacial structures (Watanabe et al. 2002), the increased amounts of peripharyngeal fat due to obesity (Shelton et al. 1993), etc. It has also been demonstrated that the caliber of the upper airway during the absence of neuromuscular activity is reduced in patients with OSA compared to normal subjects (Isono et al. 1997), which predisposes the upper airway to more easily collapse. Of noteworthy, only anatomically increased mechanical loads on the upper airway might not be sufficient to produce pharyngeal collapse during sleep (Patil, Schneider, Marx, et al. 2007). They should be counterbalanced by the action of pharyngeal dilator muscles, which is regulated by wake vs sleep state dependent mechanisms, local mechanical responses to negative pressure as well as ventilatory control mechanisms. Compared to wakeful state, the activation of dilator muscles during sleep is reduced, due to the loss of wakefulness stimulus. Furthermore, if there is a dysfunction in upper airway sensory pathways or ventilatory control mechanisms, for example a high loop gain, the risk to develop OSA would then increase, in addition to increased mechanical loads on the upper airway.

In order to better understand the physics of upper airway collapse, Starling resistor is widely used to model the upper airway (Figure 1-1) (Patil, Schneider, Schwartz, et al. 2007). In



analogy to human upper airway, the critical pressure (P_{crit}) surrounding the collapsible tube represents upper airway mechanical loads; the pressure at the upstream segment (P_{us}) can be considered as nasal pressure; and the pressure at the downstream segment (P_{ds}) represents tracheal pressure. Depending on the relationships between P_{us} , P_{crit} and P_{ds} , different inspiratory airflow patterns are observed. Indeed, when P_{crit} is significantly lower than P_{us} and P_{ds} , the pharynx is at the minimal resistance (Zone 3 in Figure 1-1), and the airflow through the tube follows the principles of an Ohmic resistor. While P_{ds} falls below P_{crit} during inspiration (Zone 2 in Figure 1-1), local collapse occurs in pharynx. At this time, the shape of inspiratory airflow becomes flattened. Its amplitude has only a linear relationship with the difference between P_{us} and P_{crit} and would remain constant regardless of drop in P_{ds} . Finally, when P_{crit} becomes greater than both P_{us} and P_{ds} (Zone 1 in Figure 1-1), the pharynx would occlude totally. P_{crit} of human upper airway can be measured by lowering nasal pressure until inspiratory airflow ceases. It has then been sectioned to define a spectrum of upper airway obstruction from normal breathing ($P_{crit} < -10$ cm H₂O), to snoring (-10 cm H₂O $\leq P_{crit} < -5$ cm H₂O), to obstructive hypopneas (-5 cm H₂O $\leq P_{crit} < 0$ cm H₂O) and to apneas ($P_{crit} \geq 0$ cm H₂O) (Gleadhill et al. 1991; Smith et al. 1988).



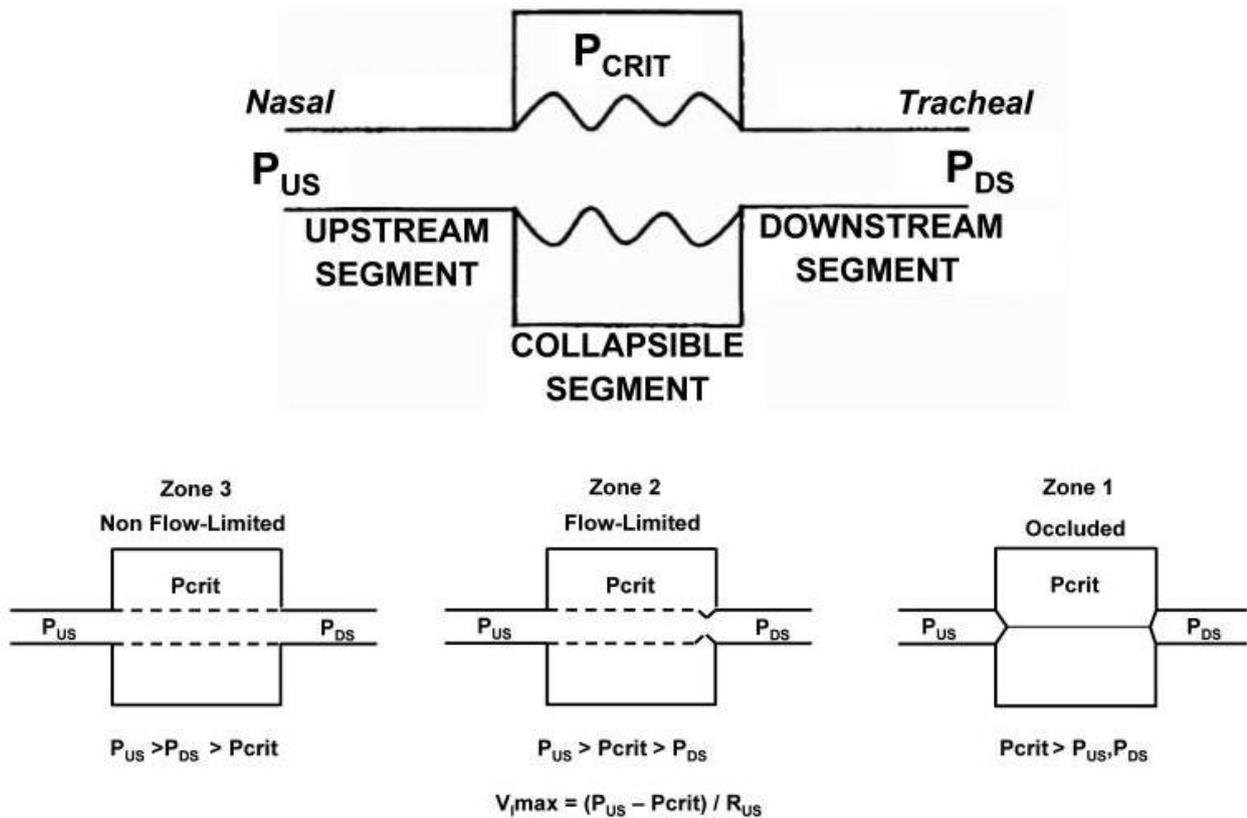


Figure 1-1: Explanation of physics in upper airway collapse via a Starling resistor model (Patil, Schneider, Schwartz, et al., 2007).

1.1.2 Treatment

- **Positive airway pressure treatment**

Positive airway pressure (PAP) is the treatment of choice for patients with moderate-to-severe obstructive sleep apnea (Malhotra and White 2002). This treatment is firstly proposed and described by Sullivan et al. in 1981 (Sullivan et al. 1981). It consists of delivering an effective positive air pressure via a nasal or facial mask to patient's upper airway in order to compensate the hypotonic dilator muscle activities at the pharynx during sleep. Randomized controlled trials have demonstrated that PAP can effectively reduce the apnea-hypopnea index and improve subjective and objective sleepiness. In some studies, it has also been shown that PAP treatment in long



term can alleviate the neurocognitive sequelae, reduce the risks in cardiovascular complications (Levy et al. 2011) and improve the quality of life. Manufacturers of PAP devices often provide several pressure modalities available so that physicians can make choice between them and adapt the treatment strategy to each patient's characteristics. The principle pressure modalities are described as follows.

1) Continuous positive airway pressure

Pressure delivered in continuous positive airway pressure (CPAP) mode is set to be constant. This pressure's value is prescribed by a clinical professional, and corresponds to the effective treatment pressure determined via a pressure titration process.

CPAP treatment is efficient in reducing obstructive disordered breathing events; however, poor adherence could limit its effectiveness. According to literature, the percentage of non-adherent patients (nightly use < 4 hours/night) varies from 29% to 83% (Weaver and Grunstein 2008). The adherence is related to many factors: patient characteristics, disease severity, interface technology, patients' experience related to the initial exposure to CPAP as well as psychological and social variables (Weaver and Grunstein 2008). The pattern of adherence has been proved to be established very early, within the first week of treatment, and it predicts the long-term use (Weaver et al. 1997). A systematic approach to PAP treatment including education, objective adherence monitoring, early intervention for side effects, telephone and clinic support, is thought to be essential for the prospect of optimizing patients' adherence (Kakkar and Berry 2007).

2) Auto-adjusting positive airway pressure

Rather than using a constant pressure during the whole night, certain PAP device provides also the option of adapting treatment pressure to patients' instantaneous breathing status,



based on obstructive events' detection, namely auto-adjusting positive airway pressure (APAP) mode. Briefly, the device increases the air pressure when it detects that upper airway resistance augments significantly, in order to prevent the other upcoming obstructive breathing events. Once the patient returns to normal breathing state, PAP device will decrease air pressure gradually for maximizing patients' comfort. Indeed, APAP mode is invented for obtaining an optimal treatment pressure automatically, which is adapted to patients' instantaneous needs and vary in function of body posture, sleep stage, previous drug or alcohol intake.

Besides, APAP could also serve as a tool of pressure titration in order to find an optimal constant pressure for CPAP mode. It is shown that automatic pressure titration with APAP is as effective as manual titration, for patients with moderate to severe obstructive sleep apnea (Fietze et al. 2007). Compared to in-laboratory manual titration accompanied by a technician, automatic pressure titration can be effectuated at home. Thus it costs less expensive and is more accessible to the public.

Treatment efficacy and adherence are similar between CPAP and APAP. Some subsets of patients prefer APAP to CPAP (Galetke et al. 2008). For patients with cardiovascular complications, they are recommended to be treated with CPAP or another mode called bilevel positive airway pressure described below, rather than APAP (Patruno et al. 2007), because APAP mode requests more frequently sympathetic nervous system activities than CPAP (Patruno et al. 2014).

3) Bilevel positive airway pressure

The pressure delivered by bilevel positive airway pressure (BiPAP) mode is also always positive, except that the pressure level at expiration is lower than that at inspiration. This favors



patient's spontaneous expiration. BiPAP is able to improve the adherence of some patients who are intolerant to CPAP mode.

1.2. Central sleep apnea syndrome

1.2.1 Pathophysiology

Central sleep apnea (CSA) is characterized by airflow cessation with an absence of respiratory muscular effort during sleep. It manifests in multiple pathologies: high altitude-induced periodic breathing, idiopathic CSA, narcotic-induced central apnea, obesity hypoventilation syndrome and Cheyne-Stokes breathing (Eckert et al. 2007). It is classified into 2 groups based on wakefulness CO_2 level: hypercapnic CSA versus non-hypercapnic CSA (Bradley et al. 1986). The precedent is due to impaired central drive (for example, congenital central hypoventilation syndrome, obesity hypoventilation syndrome) or impaired respiratory motor control (for example, narcotic-induced CSA). The underlying factor inducing non hypercapnic CSA is unstable ventilatory drive during sleep. During sleep, ventilatory drive becomes more vulnerable compared to awakening, due to the loss of wakefulness stimulus and behavioral inputs. It is modulated by chemical control. Chemoreceptors of H^+ , PaO_2 and PaCO_2 detect indirectly or directly blood CO_2 and O_2 concentration change, thus regulating the ventilatory drive. While the concentration of H^+ and PaCO_2 increases, hyperventilation will be triggered to excrete excessive CO_2 . However, if the PaCO_2 decreases to a level below the apnea threshold, the ventilatory drive is then inhibited and a central sleep apnea takes place. This ventilatory output responding to a given change in PaO_2 or PaCO_2 (i.e. chemosensitivity) can vary greatly between individuals and with disease status as well. Individuals with high chemosensitivity are more likely at risk of unstable breathing, thus



presenting central sleep apnea syndrome. (Solin et al. 2000) The same CSA risk validates for individuals having a longer delay in the negative feedback loop controlling ventilation (Hall et al. 1996) or minimal difference between the apnea threshold and sleeping eucapnic PaCO₂. (Xie et al. 2002) The transition from wakefulness to sleep unstabilizes the breathing control, thus generates CSA as well.

In some patients, we can find an overlap between CSA and OSA. As the activation of upper airway dilator muscles is also controlled by central pattern generator neurons, patients with predominantly CSA and an anatomically narrowed upper airway are logically more predisposed to upper airway collapse compared to normal subjects. Furthermore, some OSA patients could develop treatment-emergent CSA during PAP therapy. This may be explained that the improved CO₂ excretion efficiency render the hypocapnic patient vulnerable to crossing the apnea threshold. Moreover, activation of stretch reflexes that may inhibit ventilation secondary to increased lung volume effects of CPAP (especially if over titrated) could contribute as well.

1.2.2 Treatment

Treatment approaches vary greatly in function of the pathophysiologic factors contributing to various forms of CSA. For patients affected by obesity hypoventilation syndrome, weight loss seems effective. However, it might not be easy to achieve. CSA can be induced by narcotic medication. In this case, dose reduction is likely to improve AHI quickly. O₂ therapy seems to be effective to stabilize the respiratory control in non-hypercapnic CSA patients with heightened chemo-sensitivity. The non-invasive ventilation remains a major approach for reducing SDB events and improve the quality of life for patients with severe hypercapnic CSA.



CPAP ventilation is proved efficient for some patients with idiopathic CSA (Hoffstein & Slutsky, 1987). The mechanism is not clear, and might be related to prevention of inhibitory reflex arising during airway obstruction, and potentially the increased lung volume, O₂ storage. It improves hemodynamics and SDB in heart failure patients. Furthermore, the combination of CPAP and increased CO₂ could also be highly effective in treating idiopathic CSA (Hommura et al. 1997) and mixed central and obstructive SDB (Thomas, Daly, and Weiss 2005).

Similarly, BiPAP may be effective in some CSA patients, however, deleterious to certain by inducing hypocapnia (Johnson and Johnson 2005). When used with a backup rate, it may lead to significant improvements in ventilation during sleep and a marked reduction in Paco₂ in patients with obesity hypoventilation syndrome (Storre et al. 2006).

Adaptive servo-ventilation is used to treat CSA patients especially with Cheyne-Stokes respiration or coexisting OSA and CSA. It can normalize patient breathing airflow by adapting the pressure support in function of hypoventilation and central apneas. At the same time, it applies also an auto-adjusting positive expiratory airway pressure to overcome upper airway obstruction. It showed efficacy in reducing SDB severity, improving cardiac function in patients with SDB and heart failure. (Sharma et al. 2012) However, adaptive servo-ventilation is not recommended for patients fulfilling the SERVE-HF inclusion criteria (i.e. predominant CSA and chronic systolic heart failure with substantially reduced left ventricular ejection fraction $\leq 45\%$) (Cowie et al. 2015). For these patients with severe impaired heart condition, the improved cardiac function can attenuate CSA as well.



Chapter II. State of the art of evaluating algorithms implemented in Auto-adjusting Positive Airway Pressure devices

PAP is the treatment of choice for patients with moderate-to-severe OSA. In order to improve treatment comfort and optimize pressure in function of within-night and night-to-night variations in patient's upper airway collapsibility, auto-adjusting positive airway pressure (APAP) is increasingly being used.

Nowadays, a great variety of APAP devices from different manufacturers is commercialized at market. They use different technologies and algorithms to detect disordered breathing events and characterize their related mechanisms. Because the pressure responses required are different between obstructive and central SDB. The air pressure needs to be elevated after detecting obstructive events, in order to enlarge patient's narrowed upper airway and to prevent the next upcoming obstructive events, whereas the pressure ought not to increase, following the detection of central events, otherwise, it could interrupt patients' sleep and generate the unnecessary discomfort.

As these algorithms implemented for APAP functioning mode are undisclosed to the public, they seem like a black box to the public and cannot be evaluated directly. Most of the time their functioning can be retrospectively and indirectly observed by recording patient ventilation under APAP treatment. However, it is difficult to compare the treatment efficiencies of APAP devices from different manufacturers objectively by means of clinical studies. Since the conditions of testing different APAP devices are never the same due to the within-night and night-to-



night breathing variations within a real patient and these of inter-patients. Moreover, clinical trials could be time-consuming, expensive, and sometimes manufacturer-dependent in order to validate a novel functioning mode in a new generation of devices. This is why some attempts of respiratory simulation benches have been reported in literature, trying to evaluate miscellaneous devices with respiratory scripts composed of obstructive or central SDB.

2.1 State of the art of evaluating PAP algorithms with a bench

In the literature, there are several studies evaluating APAP algorithms with a bench test method (Farré et al. 2002; Abdenbi et al. 2004; Coller et al. 2005; Lofaso et al. 2006; Rigau et al. 2006; Hirose et al. 2008; Netzel et al. 2014; Zhu et al. 2015; Isette et al. 2016). With time passing and new technologies arriving, the test bench also evolved in a more and more complete and physiological manner.

The first bench evaluating APAP algorithm in the literature was proposed by Farré et al. in 2002. They used a computer controlled pump to reproduce the disordered breathing airflow patterns registered in patients with OSA. The breathing patterns generated could be programmed to be independent or dependent on the pressure delivered by APAP devices. In the latter mode, the severity of disordered breathing patterns was gradually alleviated with increased pressure delivered from APAP devices. As some APAP devices were beginning to be able to distinguish between SDB of obstructive and central mechanisms by using the forced oscillation technique (FOT), pressure pulses etc., Rigau et al. improved this model by adding a servo-controlled valve at the upstream of flow generator in 2006, in order to mimic upper airway obstruction. Instead of using a servo-controlled valve, some researchers replaced it with a Starling resistor (Abdenbi et al. 2004; Coller et al. 2005; Hirose et al. 2008; Netzel et al. 2014; Zhu et al. 2015) to simulate upper airway



obstruction. It consists of an elastic tube mounted inside a sealed chamber filled with air, whose pressure is controllable. The APAP device circuit is connected to the elastic tube of Starling resistor. The degree of collapse of the elastic tube depends on the transmural pressure applied, which is defined as the difference between the pressure inside the elastic tube and the pressure of the sealed chamber. Therefore, by varying the chamber pressure, different degrees of obstruction are created in the elastic tube. Furthermore, the Starling resistor has an advantage of varying its resistance automatically in response to the pressure changes sent from APAP devices.

There are also various available options about the hardware used to simulate pulmonary function. Except flow pump, it could be a mechanical lung simulator like a Michigan lung simulator or an active lung simulator in advanced like ASL5000 (IngMar Medical, Pittsburgh, USA). The mimicked pulmonary movement in Michigan lung simulator is driven indirectly via a ventilator providing 2 different levels of pressure. The simulated pulmonary compliance is then regulated through a spring. On the contrary, the breathing airflow generated by an active lung simulator is controlled based on the physical model that the user has entered and parameterized through the interface of its related software. The user can enter respiratory muscular effort pressure, pulmonary compliance, airway resistance as inputs. Then the active lung simulator analyzes and calculates automatically the breathing airflow needed to be generated through the movement of a piston, in function of parameters entered previously as well as the instantaneous pressure measured at the output of the piston, which is influenced by the pressure sent from APAP device and the instantaneous resistance of the upper airway simulator.



2.2 Objective of this PhD project

As the bench tests mentioned above mimic the sleep disordered breathing profile of patients with SAOS or SACS by using a respiratory script composed of a repetitive string of several typical SDB events, it is difficult to generalize the knowledge about treatment efficiency differences between APAP algorithms acquired during bench tests to an individual patient. Because the characteristics of disordered breathing patterns could vary a lot from a patient to another and within a same patient as well, according to the sleep stage, sleep position, previous drug or alcohol intake etc. Moreover, APAP manufacturers are also adjusting their algorithm responses as a more and more detailed function of patient personal SDB characteristics to improve treatment performance. Thus, bench test models need to evolve in a physiological manner as well. Indeed, in 2016, Isetta et al. mimicked a full night of one female OSA phenotype on their bench, taking into account the influence of sleep positions and sleep stages (REM, Non-REM and awake) to the upper airway collapsibility. However, a predetermined database of disordered breathing patterns as well as non-automatic bench integration represents a limitation in simulating a specific patient with their bench test model.

The aim of this PhD project is to develop a new physiological bench test model, which enables reproducing automatically the SDB profiles of apneic patients registered by polygraphs, taking into account their cycle-by-cycle disordered breathing of central and obstructive mechanisms. This bench model can then be used to help validate new functioning modes developed by manufacturers for some specific subgroups of patients, as well as select an optimal therapy device for any individual patient, adapted to its personal SDB patterns.



2.3 Bench hardware

The bench hardware used in this project is the same as that published in the thesis of Kaixian ZHU, which mainly consists of an active lung simulator ASL5000 (IngMar Medical, Ltd. 2013) and a Starling resistor.

2.3.1 Active lung simulator ASL5000

Figure below describes the functional concept of the lung simulation ASL5000. The inspiratory and expiratory airflow is generated by the movement of a piston. This is calculated mathematically via a host computer depending on the ventilatory model and the pulmonary setting parameters (like resistance, compliance) that the user has chosen and entered in the related software interface, as well as the pressure measured at the output of air. This pressure could be the pressure delivered from an external ventilator.



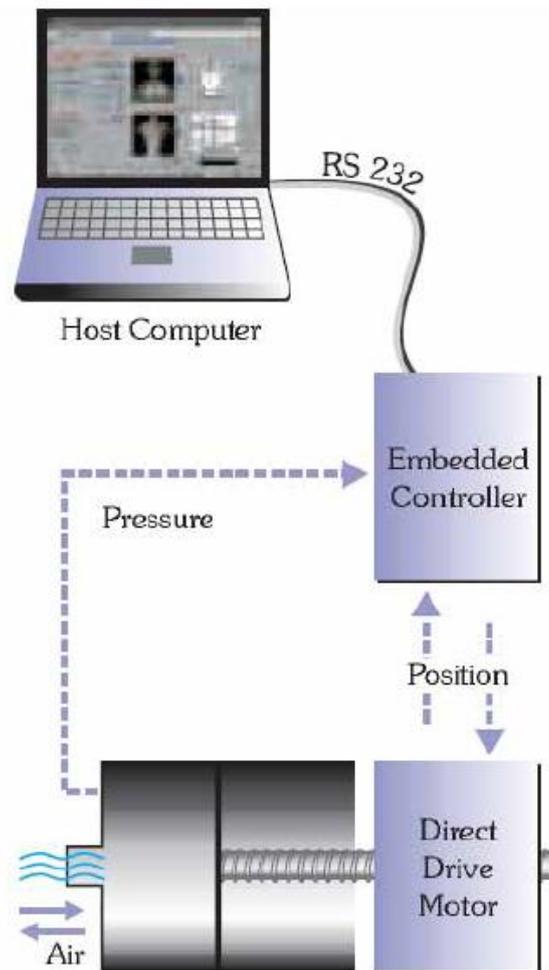


Figure 2-1: Functional concept of active lung simulator ASL 5000 (IngMar Medical, Ltd. 2013).

The ventilatory model used in this thesis corresponds to a single-compartment model (Figure 2-2), which mimics the ventilatory function via a single compliance (C) and a single resistance (R) connected in series. The C includes both the lung compliance and the chest wall compliance. The R represents the airway resistance at a normal state. Then the piston's movement is governed with the equation below:

$$P_{aw} - \Delta P_{mus} = V/C + R*(dV/dt),$$

where P_{aw} is the air pressure measured at the output of ventilatory model, thus the output of piston as well. ΔP_{mus} corresponds to patient's muscular effort pressure for breathing, defined by



the user (the inspiratory muscular effort pressure is set to be negative.). V and dV/dt are respectively instantaneous pulmonary volume and breathing airflow (inspiratory airflow values are thus positive).

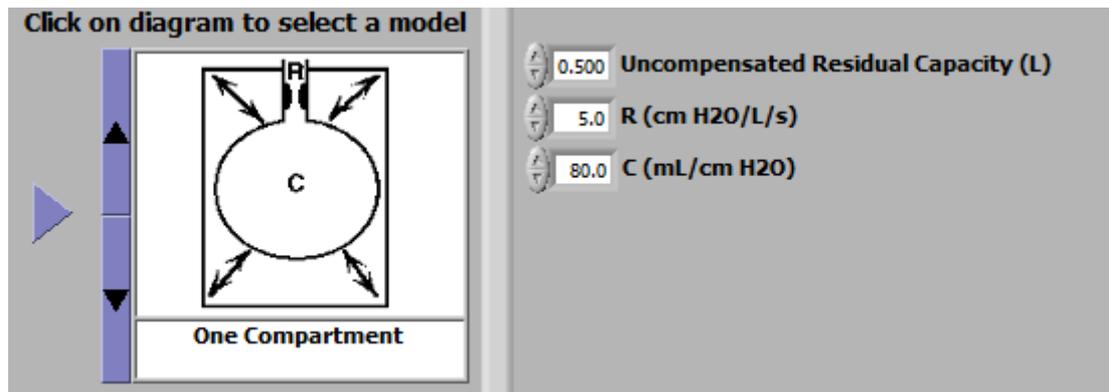


Figure 2-2: Single compartment model set in active lung simulator ASL 5000 (IngMar Medical, Ltd. 2013).

To feature this lung model to reproduce a specific patient's ventilatory function, we will need to set the parameters C , R and the breathing muscular effort. As apneic patients in general have a normal pulmonary compliance and this parameter does not influence directly PAP devices' responses to patients' SDB patterns, we have set C equal to 80 mL/cmH₂O for all patients. As we use an external simulator, i.e. Starling resistor, to mimic a patient's recurrent upper airway obstruction, this R is set to 7.25 cmH₂O/L/s. The most important input should be patient breathing muscular effort, which determines the breathing airflow amplitude, period etc. The data frequency need to be 512 Hz. The method used by us to estimate it from patient polygraph recordings is described in chapter III. The interface window used for uploading patient breathing muscular effort data files is illustrated in figure 2-3.

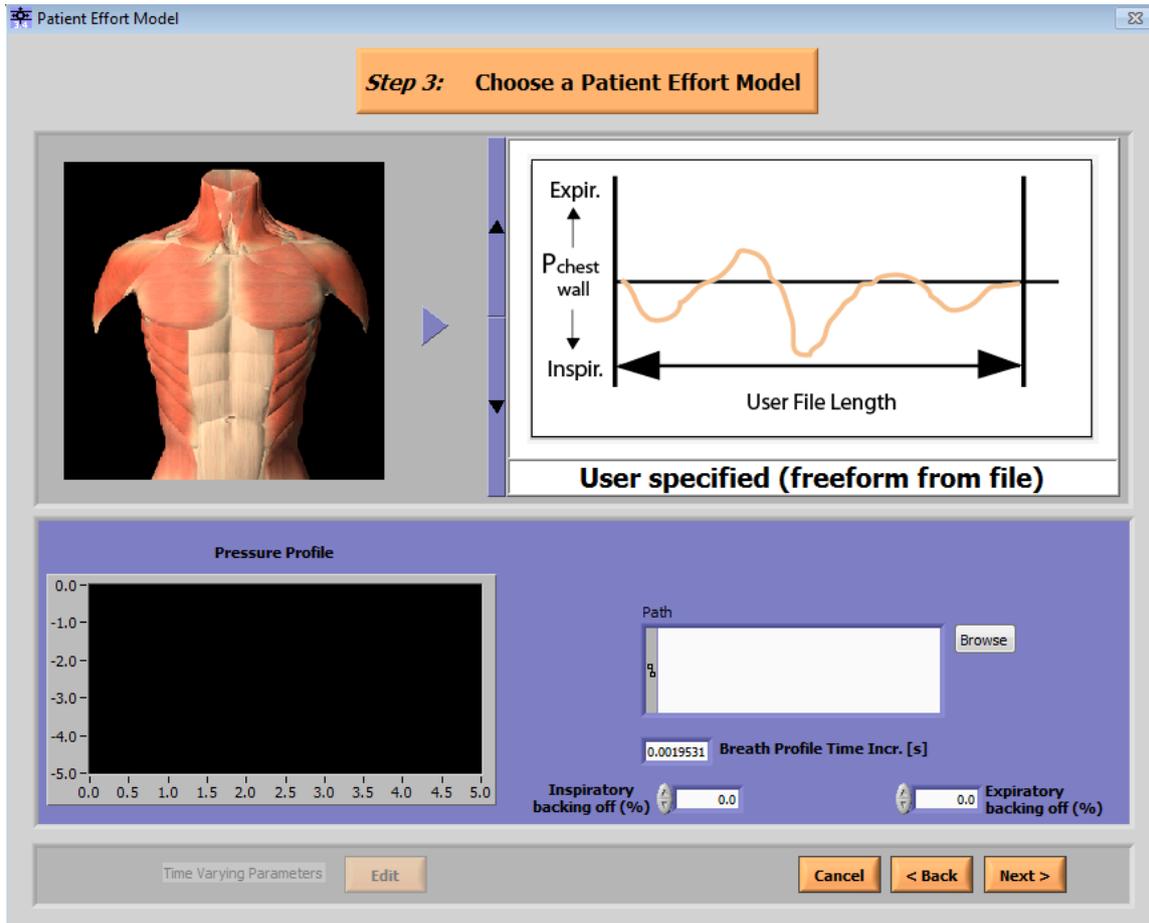


Figure 2-3: File-based patient breathing muscular effort in active lung simulator ASL 5000 (IngMar Medical, Ltd. 2013).

2.3.2 Starling resistor

The Starling resistor used in this thesis has been described in thesis of Kaixian ZHU. It is composed of compliant rubber tube (120 mm long between two 15-mm external diameter connectors at each side of the cylinder) interposed within a cylindrical transparent chamber (180 mm long, 28 mm internal diameter) (Figure 2-4). The opening degree of the rubber tube is mainly regulated via modifying the chamber pressure or the upstream pressure of rubber tube.

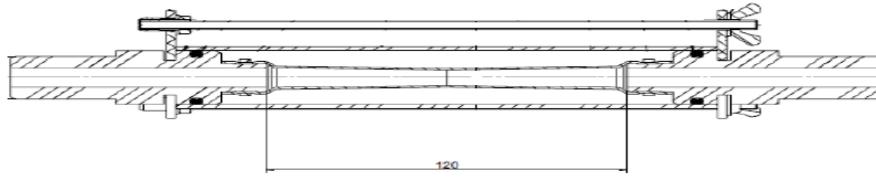


Figure 2-4: Cross-section of Starling resistor used in this thesis (Kaixian ZHU's thesis, 2016).

Chapter III. A novel physiological bench test reproducing patient sleep disordered breathing profiles by using polygraph data

With emergence of big data and artificial intelligence, APAP devices can probably adapt pressure responses in function of each patient's own disordered breathing phenotypes in the near future. At that time, bench tests will be required to reproduce more easily the breathing profile of any apneic patient for being able to find an optimal ventilation device for him or her. To anticipate this new potential demand, we wonder to know whether it is feasible that a bench can be constructed in a manner, capable of reproducing automatically a patient's SDB profile from its available medical data, for example, the polygraph recordings, which are performed during the diagnostic examination of Sleep Apnea Syndrome (SAS). This is why this study has been carried out.



3.1 Article:

New physiological bench test reproducing nocturnal breathing pattern of patients
with sleep disordered breathing

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New physiological bench test reproducing nocturnal breathing pattern of patients
with sleep disordered breathing

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Abstract

Previous studies have shown that Automatic Positive Airway Pressure devices display different behaviors when connected to a bench using theoretical respiratory cycle scripts. However, these scripts are limited and do not simulate physiological behavior during the night. Our aim was to develop a physiological bench that is able to simulate patient breathing airflow by integrating polygraph data. We developed an algorithm analyzing polygraph data and transformed this information into digital inputs required by the bench hardware to reproduce a patient breathing profile on bench. The inputs are respectively the simulated respiratory muscular effort pressure input for an artificial lung and the sealed chamber pressure to regulate the Starling resistor. We did simulations on our bench for a total of 8 hours and 59 minutes for a breathing profile from the demonstration recording of a Nox T3 Sleep Monitor. The simulation performance results showed that in terms of relative peak-valley amplitude of each breathing cycle, simulated bench airflow was biased by only $1.48\% \pm 6.80\%$ compared to estimated polygraph nasal airflow for a total of 6,479 breathing cycles. For total respiratory cycle time, the average bias \pm one standard deviation was 0.000 ± 0.288 seconds. For patient apnea events, our bench simulation had a sensitivity of 84.7% and a positive predictive value equal to 90.3%, considering 149 apneas detected both in polygraph nasal simulated bench airflows. Our new physiological bench would allow personalizing APAP device selection to each patient by taking into account individual characteristics of a sleep breathing profile.

Introduction

Obstructive sleep apnea (OSA) is a sleep disordered breathing (SDB), characterized by repetitive narrowing or closure of the upper airway during sleep [1]. This leads to intermittent arterial oxygen desaturations [2], and also to increased activations of the sympathetic



nervous system, which may result in complications in cardiovascular diseases [3], as well as arterial hypertension [4]. Patients affected by OSA have symptoms like heavy snoring, excessive diurnal somnolence, and difficulty in concentration and memory, all of which significantly reduce their quality of life. Depending on severity, moderate and severe syndromes are largely treated by using continuous positive air pressure (CPAP) devices to maintain open airways, and prevent the occurrence of adverse breathing events during sleep at night. These treatments have proven to be efficient by drastically reducing the number of breathing events [5]. Moreover, they have a clearly beneficial impact on diurnal activities by significantly reducing sleepiness [5]. However, one of the key issues in treating a SDB patient with CPAP is the choices of medical device available on the market and of the ventilation mode (constant positive airway pressure or automatic positive airway pressure (APAP)). APAP mode relies on the use of a dedicated algorithm driving the response of the device to breathing events such as apneas or a significant reduction of respiratory flow. These algorithms are different from one device to another [6–13] and several setting options [14–16] can be chosen by users. Because the algorithms are protected by patents, they are like a black box to the public [17] and cannot be evaluated directly. Most of the time, device functioning can be retrospectively and indirectly observed by recording patient ventilation under APAP [18,19]. This is why there has been some work to develop respiratory benches, as reported in the literature [6–13], to evaluate miscellaneous devices. Some benches consist of a lung simulator to mimic the patient's respiratory airflow [6]. Other benches are additionally connected to an upper airway simulator by use of either an obstruction valve [9,13] or a Starling resistor [7,8,10–12], whose resistances are conditioned to pressure changes from APAP devices in different manners. The mechanical impedance in an obstruction valve is controlled via a predefined computer program, in function of the instantaneous pressure of the APAP. On the contrary, the resistance of Starling resistor reacts mechanically and automatically to the pressure changes. Bench hardware can be



programmed to simulate the artificially composed respiratory scenarios, which generally contain a string of repetitive disordered breathing events, i.e. obstructive and central apneas, obstructive and central hypopneas, inspiratory flow limitation, snoring. Various APAP devices are then connected to the bench simulation. Their pressure responses to the SDB events are recorded, assessed and compared. However, all these benches use airflow from a limited database of breathing airflow short segments recorded in patients and/or artificially designed. Thus, the respiratory scenarios simulated on bench cannot represent completely the physiological variability and chronology of human breathing. This is why it is difficult to generalize the bench-observed treatment efficiencies to one individual patient. Furthermore, as APAP manufacturers are adjusting their algorithm responses as a more and more detailed function of patient physiological breathing behaviors, this also underlines the needs to adapt the bench testing in a physiological manner. Based on these contexts, Isetta *et al.* mimicked a full night of one female OSA phenotype on their bench [13]. However, there still existed a distinction between bench simulated breathing profile and the one of a specific patient. Thus, a physiological bench, which could replicate automatically any apneic patient breathing profile by using its polygraph recordings, should solve this problem. Thus, the aim of our study was to develop a new approach for bench testing, which enables the automatic reproduction of a patient nasal breathing phenotype, taking into account the central and obstructive characteristics of each respiratory cycle. To accomplish this, the secondary aim was to develop an algorithm that is able to process a patient's night polygraph data, and to calculate the digital inputs required to control the hardware of the bench simulation device.

Material and methods

Bench test system design

Our bench system is composed of two parts: signal processing and bench simulation.



Our work mainly focused on designing an algorithm that is able to integrate polygraph data as inputs, and to return as outputs the necessary digital inputs to control our bench hardware. This hardware consists of an artificial lung using a piston to mimic patient pulmonary motion during respiration, driven by simulated respiratory muscular effort pressure (ΔP_{mus}) and a Starling resistor that mimics upper airway obstruction by varying its resistance. Our algorithm calculates the level of upper airway obstruction as well as the pressure intensity of the respiratory muscular effort to be simulated in each breathing cycle of a patient by analyzing polygraph data in a way that is most in line with AASM rules [20].

Specifically, to simulate a targeted polygraph nasal airflow (\dot{V}_{source}) on our bench (Fig 1), the resistance of a Starling resistor was increased during an obstructive respiratory event, and set to minimum during periods of normal breathing as well as central breathing events. The ΔP_{mus} used to command our artificial lung was calculated based on the breathing airflow issuing from a central ventilation command. We noted this estimated non-obstructed nasal airflow, without any obstruction occurring in the upper airways, as \dot{V}_{cc} .



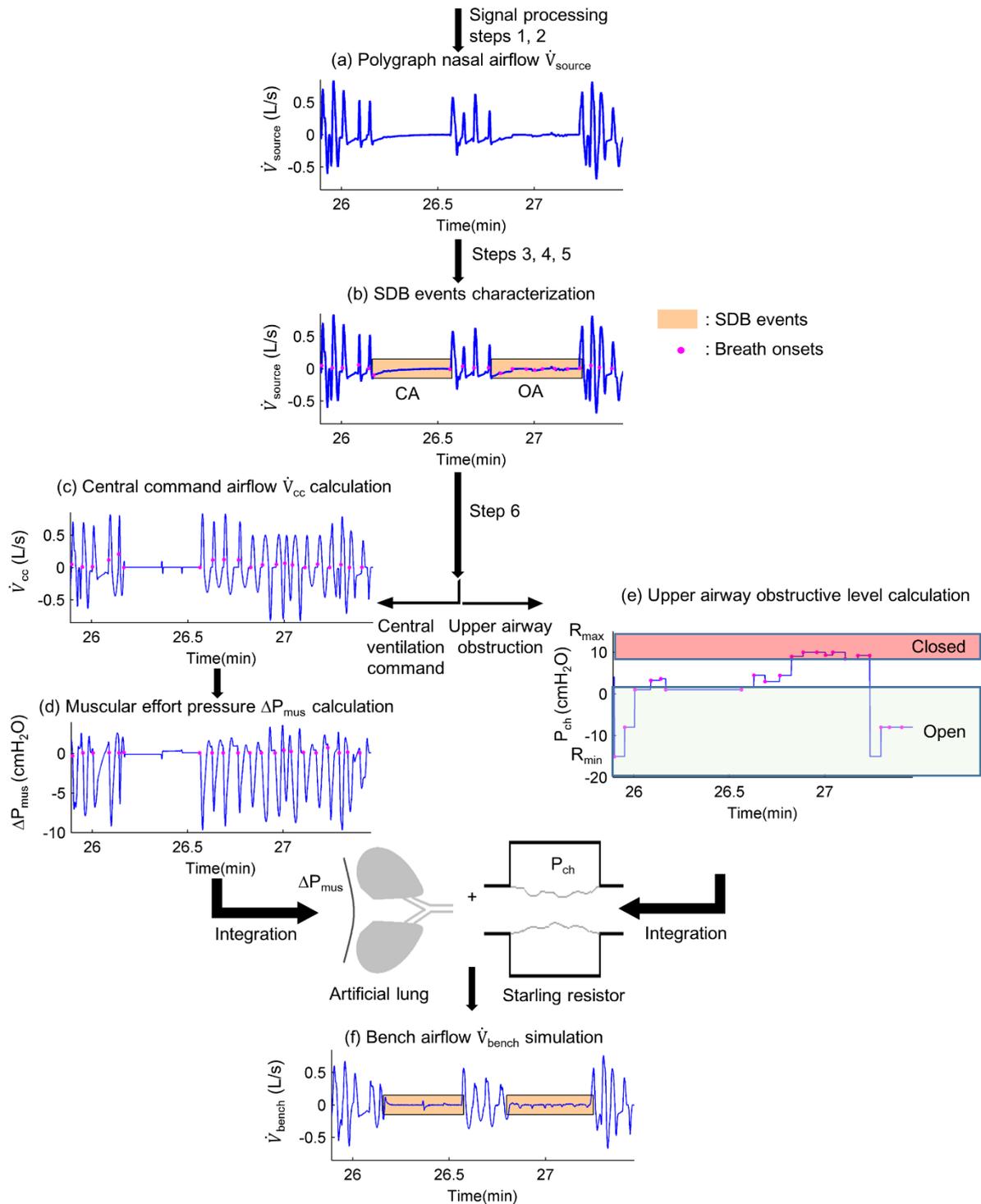


Fig 1. Signal processing overview from polygraph data to its breathing profile simulated on bench.

The signal processing steps or steps refer to the main steps described in polygraph signal processing section.

- (a) Polygraph nasal airflow, steps 1 and 2: nasal airflow (\dot{V}_{source}) of period without movement artifact is derived from polygraph raw signals. It represents the target breathing airflow, which is aimed to be simulated on bench.
- (b) Sleep disordered breathing events characterization, steps 3, 4 and 5: breathing onset positions (*) and sleep disordered breathing (SDB) events (orange frames) are identified. SDB events can be obstructive apneas (OA), central apneas (CA), obstructive hypopneas, central hypopneas.
- (c) Central command airflow calculation, step 6: the estimated non-obstructed nasal airflow issuing from central ventilation command (\dot{V}_{cc}) is calculated by combining information of \dot{V}_{source} and SDB events characterization. During normal breathing periods or central SDB events, \dot{V}_{cc} is directly assumed identical to \dot{V}_{source} , whereas during obstructive breathing events, the amplitude of \dot{V}_{cc} is hypothesized to be equal to \dot{V}_{source} amplitude of the pre-event 2-minute baseline.
- (d) Muscular effort pressure calculation, step 6: the respiratory muscular effort pressure (ΔP_{mus}) is calculated by taking into account \dot{V}_{cc} as well as the lung compliance and airway resistance set in the active lung simulator.
- (e) Upper airway obstructive level calculation, step 6: the sealed chamber pressure (P_{ch}) used to regulate Starling resistor for each breathing cycle is calculated as a function of \dot{V}_{cc} and \dot{V}_{source} .
- (f) Bench airflow simulation: the bench-simulated airflow (\dot{V}_{bench}) is obtained by controlling the active lung simulator and the Starling resistor with ΔP_{mus} and P_{ch} .

Bench Hardware

As shown in Fig 2, the bench hardware used in our study to reproduce the polygraph breathing profile was derived from a setup described in a previous study from our



laboratory [12]. The hardware consisted mainly of an active lung simulator ASL 5000 (IngMar Medical, Pittsburgh, USA) and a Starling resistor, in which a rubber tube could collapse as a function of transmural pressure. The transmural pressure is the difference between the intraluminal pressure at the upper stream (P_{us}) and the extra-luminal pressure, which corresponds to the sealed chamber pressure (P_{ch}). In detail, P_{us} was set to 4 cmH₂O, as the minimal default pressure sent by APAP devices. Then, the obstructive state in the rubber tube of the Starling resistor was altered by varying P_{ch} via a pressure control system, which supplied continuous positive or negative pressures. The adjustment of obstruction level in the Starling resistor was triggered once at the beginning of each breathing cycle via a transistor-transistor logic (TTL) signal sent by the active lung simulator.

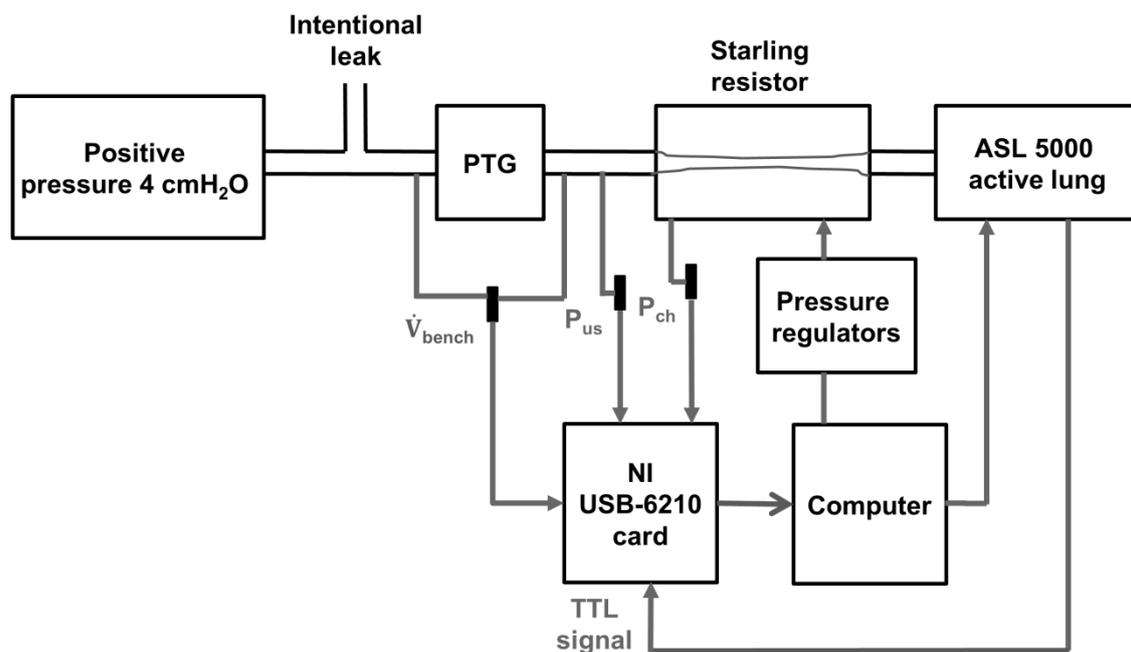


Fig 2. Bench hardware diagram. PTG: pneumotachograph; \dot{V}_{bench} : bench airflow measured by a pneumotachograph; P_{us} : pressure at upstream of Starling resistor; P_{ch} : sealed chamber pressure in

Starling resistor; TTL signal: transistor-transistor logic signal.

To simulate ventilatory function, we used a single-compartment model in the active lung simulator, in which a patient's lung was modeled as a single compliance C and a single resistor R connected in series, representing respectively lung compliance and airway resistance with $C = 80$ mL/cmH₂O and $R = 7.25$ cmH₂O/(L/s). In our case, because we used a Starling resistor to mimic the upper airway pathophysiology, the airway resistance set in the active lung simulator did not take into account upper airway resistance. The digital input used to command each breathing cycle in active lung simulator was ΔP_{mus} . There is a relationship between ΔP_{mus} and non-obstructed breathing airflow \dot{V}_{cc} , dominated by the equation

$$\Delta P_{\text{mus}} = -\frac{V_{\text{cc}}}{C} - R * \dot{V}_{\text{cc}}, \quad (1)$$

in which V_{cc} represents pulmonary instantaneous volume, thus $V_{\text{cc}} = \int \dot{V}_{\text{cc}} dt$.

The flow produced on the bench (\dot{V}_{bench}) was monitored by a pneumotachograph located between the source of positive pressure 4 cmH₂O and the Starling resistor (Fig 2).

All signals measured on the bench were sampled via a NI USB-6210 card (data acquisition card, National Instruments, USA) and a custom-developed LabVIEW (National Instruments) program at a rate of 20 Hz. Then, they were stored in a personal computer for further offline analysis.

Polygraph Signal Processing



The polygraph data used in our study issued from a one-night demonstration recording by a Nox T3 Sleep Monitor (Nox Medical, Reykjavik, Iceland). On our bench, we reproduced a total of 8 hours and 59 minutes of this breathing profile by integrating polygraph recordings. The corresponding apnea-hypopnea index (AHI) of this recording was 22.6 events/h with apnea index (AI) = 15.5 events/h and hypopnea index (HI) = 7.1 events/h. The signals used in our study were respectively an acceleration signal sampled at 20 Hz, nasal pressure sampled at 200 Hz, thoracic and abdominal Respiratory Inductance Plethysmography (RIP thorax and RIP abdomen) sampled at 25 Hz, RIP flow at 25Hz, pulse oximetry (SpO_2) sampled at 3 Hz, and audio volume sampled at 100 Hz.

We developed an algorithm with Matlab (MATLAB, Signal Processing Toolbox and Statistics Toolbox Release 2013b, The MathWorks, Inc., Natick, Massachusetts, United States) which allowed for interpretation of polygraph signals and calculation of the digital inputs that needed to be integrated into the bench hardware. Concretely, the ΔP_{mus} to drive the artificial lung and the P_{ch} to regulate the obstructive level in the Starling resistor were used for bench simulation. Fig 3 describes the six main signal-processing steps implemented in the algorithm. Each step is then depicted in detail in the following subsections.



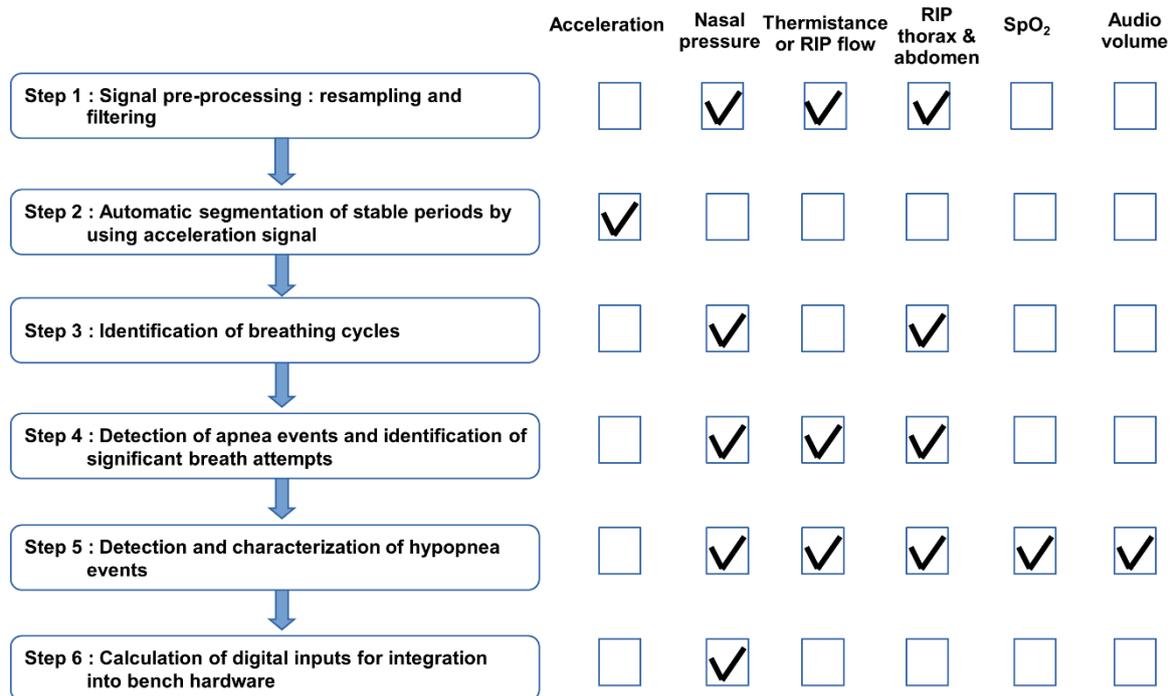


Fig 3. Main steps in polygraph signal processing. The checked signals next to each signal-processing step mean that they were directly associated with this step.

Step 1: Signal pre-processing: resampling and filtering

Nasal pressure, RIP flow, audio volume, RIP thorax and abdomen were first down-sampled at 20 Hz to homogenize the whole signal data for further analyses. Then nasal pressure, RIP flow, RIP thorax and RIP abdomen were smoothed by a Savitzky-Golay filter [21]. In our conditions, the filter was constructed by fitting successive sub-sets of adjacent data points in 1 second with a third-degree polynomial function. According to AASM rules [20], the nasal airflow modulation with time \dot{V}_{source} (20 Hz) was estimated as the square-root transformation of nasal pressure.

Step 2: Automatic segmentation of stable periods by using acceleration signal

The aim of this second step was to avoid body motion artifacts in the respiratory signals. We chose to exclude periods with a high probability of artifact occurrence by using the 3D



accelerometer signal (Fig 4(a)), which reflected body movement at night during recording. This signal was the calculation of the Euclidean norm of 3-axis acceleration.

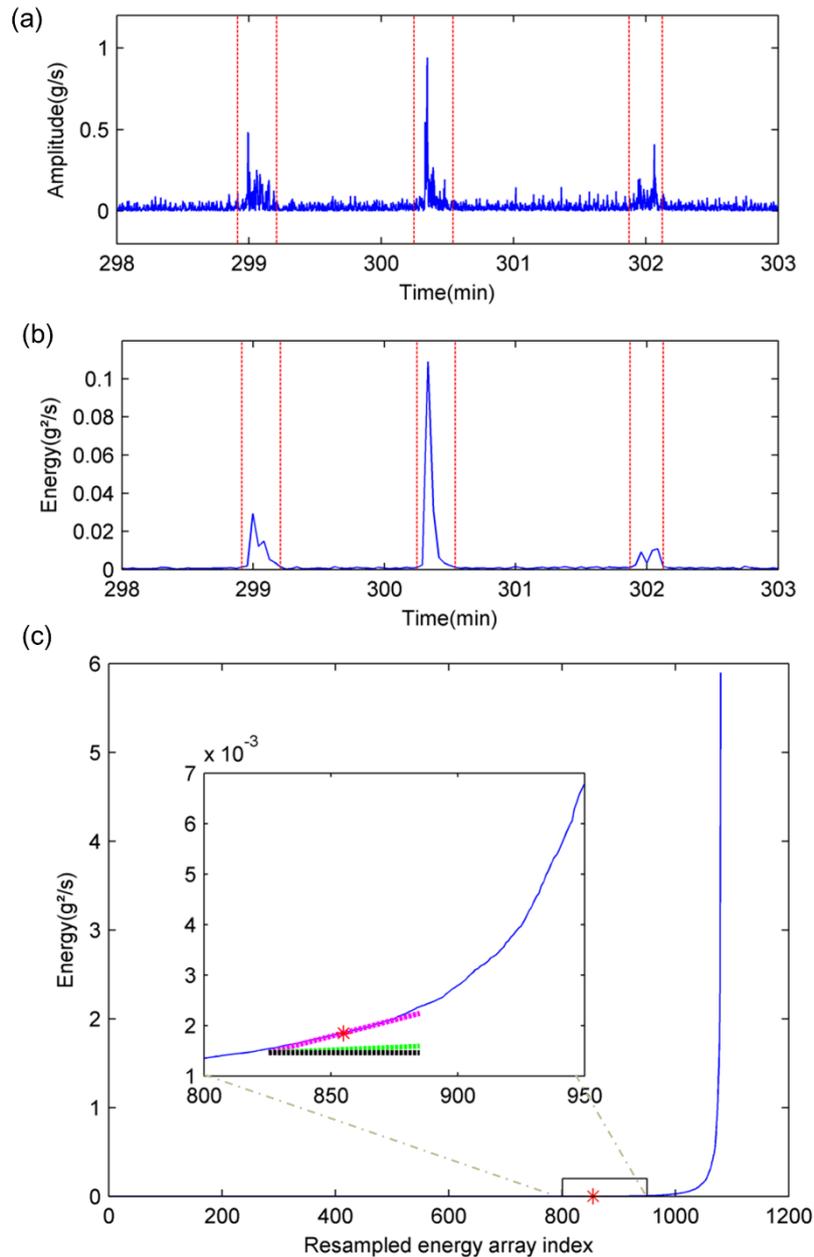


Fig 4. Segmentation of stable periods by analyzing acceleration signal. (a): Example of acceleration signal (20 Hz) obtained from polygraph. This signal corresponds to the

Euclidean norm of three-axis accelerations measured by the accelerometer installed in the polygraph device. (b): Energy signal - calculated in frames of 5 seconds with 50% overlap. (c): Determination of frame energy threshold in the resampled increasing frame energy array, represented by the blue line. The magenta line is the current linear regression line, which fits into six consecutive points in the resampled increasing frame energy array. The green line's slope is the average value of all previously calculated slopes. The black line is a reference horizontal line. The slope of the magenta line is greater than 5.8 times that of the green line. The energy value of the red asterisk corresponds to the median energy of the six consecutive points fitted by the magenta line. Thus, the amplitude of the red asterisk is determined as the frame energy threshold.

Stable periods were characterized by low acceleration amplitude segments, in comparison to periods with movement in the 3D accelerometer signal. To automatically identify stable periods, our method was based on setting up an adaptive threshold in the energy signal of 3D acceleration. The energy signal (Fig 4(b)) was calculated in a frame of 5 seconds with an overlap of 50%, as shown in equation (2), in which $S_k(i)$ was the 3D accelerometer signal contained in the k^{th} frame of 100 data samples, and E_k represented the energy of the signal in the k^{th} frame.

$$E_k = \sum_{i=1}^{100} |S_k(i)|^2 \quad (2)$$

To determine an appropriate energy threshold discriminating between high and low energy frames, the energy array was sorted by an ascending order in the first step. Then, in order to decrease the required computing power, the energy array was down-sampled to obtain a new energy array composed by 1080 samples (Fig 4(c)). To detect the change onset point in the sorted and down-sampled energy array, we chose to detect the slope change position. Thus, we



calculated the slopes of every six consecutive energy points with a 50% overlap by performing a linear regression (Fig 4(c)). We obtained a slope array of 359 values. We assumed that the patient should spend at least 25% of the recording time sleeping with negligible body movement. Accordingly, the slope change position needed to be situated after index 90 ($359 \times 25\% = 90$) of the slope array. To find the slope change position, we divided each slope value situating from index 90 by the average of its previous slope values. If this ratio was greater than 5.8, a number that was empirically determined, the corresponding slope was then considered as the change position in slopes. Consequently, the energy threshold was determined as the median of the 6 consecutive energy values, from which the corresponding slope was calculated.

At the end, stable frames were combined if they overlapped and were lower than the calculated energy threshold. All considered signals in the remaining steps of the process were mostly extracted from these stable periods. Nevertheless, we allowed short periods of movement less than 2 minutes to maintain congruity of the polygraph signals.

Step 3: Identification of breathing cycles

The proper identification of each breathing onset from \dot{V}_{source} is mandatory to simulate corresponding respiratory cycles (Fig 5). As breathing onset positions are difficult to determine directly from \dot{V}_{source} during highly-reduced breathing periods, it is necessary to apply a methodology to identify breathing onsets depending on the amplitudes of the nasal airflow excursion signal. Firstly, we calculated the excursion of \dot{V}_{source} . We detected inspiratory peaks and expiratory valleys in a three-minute moving window by using an automatic multiscale-based peak detection (AMPD) algorithm developed by Scholkmann *et al.* [22]. The 3-minute window was chosen in consideration of both computational time and algorithm performance. Indeed, the AMPD algorithm has



an $O(n^3)$ complexity (n : signal length contained in a window), meaning that the smaller the window size is, the shorter the computational time will be. However, it should also contain enough breathing cycles so that the AMPD algorithm can capture the periodic pattern. In average, a 3-minute window contained about 45 ($T_{\text{tot}} = 4\text{s}$) to 72 ($T_{\text{tot}} = 2.5\text{s}$) breathing cycles, of which the amount was comparable to examples cited in Scholkmann et al's paper [21]. Moreover, we also checked whether there were any missed cycle detections, by detecting oscillation around zero values with respect to amplitude threshold and a temporal threshold compatible with a respiratory cycle. These thresholds were established based on knowledge related to the mean amplitude and total respiratory cycle time (T_{tot}) of previous respiratory cycles without obstruction. Thus, the upper envelope and lower envelope of \dot{V}_{source} were obtained by interpolating peaks and valleys, respectively. Excursion was calculated as the difference between the upper envelope and lower envelope. Based on the excursion values, breathing onsets were then determined with two distinct methods. Considering periods with high excursion values, breathing onset positions were determined as the inflection point in \dot{V}_{source} between expiratory minimal and inspiratory maximal values respecting the order of two consecutive cycles. However, our algorithm relied on RIP signals to infer breathing onset positions for low nasal airflow excursion periods.



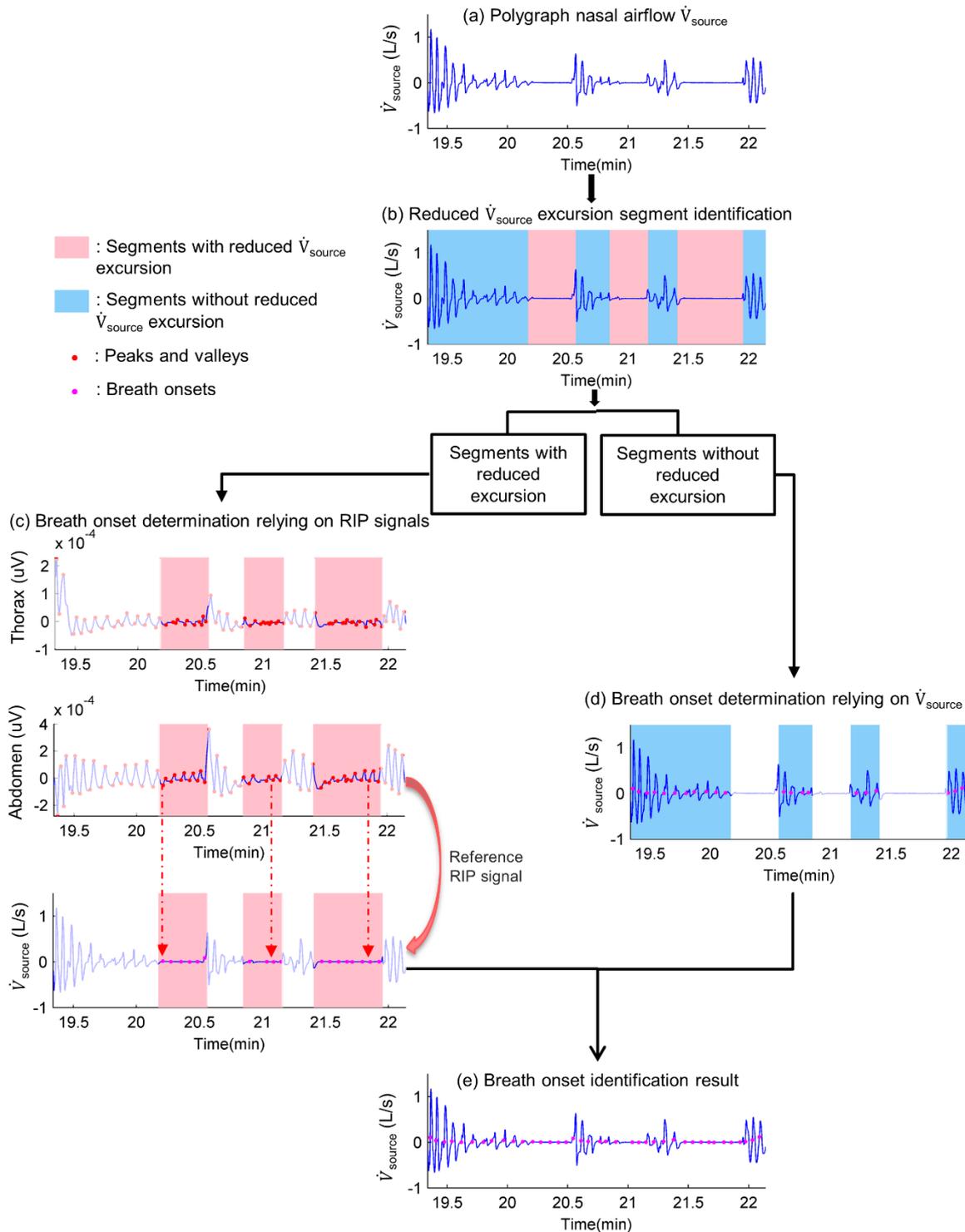


Fig 5. Identification of breath onset positions in polygraph nasal airflow.

(a) Polygraph nasal airflow: an example of polygraph nasal airflow (\dot{V}_{source}), of which we need to identify breath onset positions.

- (b) Reduced excursion segments identification: \dot{V}_{source} is segmented in function of its excursion: periods with reduced excursion (pink shade) and periods without reduced excursion (blue shade).
- (c) Breath onset determination relying on Respiratory Inductance Plethysmography (RIP) signals: during periods with reduced \dot{V}_{source} excursion, as breath onset positions are difficult to be directly determined from \dot{V}_{source} , the reference RIP signal's valleys temporal coordinates are used to indicate the corresponding breath onset positions in \dot{V}_{source} . The choice between RIP thorax and RIP abdomen to be the reference RIP signal is determined by criterion of possessing a higher relative amplitude modulation compared to the other one.
- (d) Breath onset determination relying on \dot{V}_{source} : in segments without reduced \dot{V}_{source} excursion, breathing onsets can be directly determined as the inflection point in \dot{V}_{source} between expiratory minimal and inspiratory maximal values.
- (e) Breath onset identification result: all breath onsets in \dot{V}_{source} are obtained by combining results from (c) and (d).

Highly reduced excursion criteria were defined as a reduction of nasal airflow excursion equal or greater than 65% of the two-minute pre-event baseline as well as a duration greater than four seconds. This airflow reduction threshold was determined with reference to AASM apnea scoring rules. As nasal airflow was calculated by square-root transformation of nasal pressure, the nasal pressure reduction threshold ($\geq 90\%$) used in apnea detection would correspond to a reduction greater than 66.7% in nasal airflow. We used a threshold of 65% very close to this. The duration criterion of at least four seconds was set up to allow for detecting any single obstructive or central apneic breathing cycle. A breathing cycle lasted about 3 seconds. Another 1 second was added in order to account for the time delay between the airflow valley of the last breath before



reduced excursion and the start of the reduced excursion.

Considering highly-reduced excursion periods, the breathing onset cannot be identified on \dot{V}_{source} by definition. Thus, we collected this information from the RIP signal. We determined for each period which RIP signal to refer to, namely thoracic or abdominal. This determination of the reference RIP signal was based on the following requirement: it need be the signal with a higher relative amplitude modulation during the reduced nasal airflow excursion period. Once we had decided upon the reference RIP signal, we used valley time coordinates in the reference RIP signal as the ones of breath onsets for the reduced nasal airflow excursion segments.

Step 4: Detection of apnea events and identification of significant breath attempts

Apnea events were detected according to AASM recommendations for apnea rules updated in 2012 [20]. The main signal used for apnea detection was \dot{V}_{source} . We set a maximal apnea event duration of three minutes to discriminate between reduced breathing and mouth breathing. Furthermore, apnea events detected by \dot{V}_{source} were only considered if there was a simultaneous drop in the thermistance excursion signal or alternatively in the RIP flow excursion signal, which should be greater than 20% compared to the pre- and post-event baselines. For a given period, apneas were directly qualified as central apnea if there were no identified breathing attempts within the RIP signals. Moreover, we checked for the significance of the muscular effort indirectly represented in RIP signals for each breath attempt contained during the period of apnea. Significant breath attempts with collapsed upper airways, namely the obstructive apnea cycles, were then identified; otherwise, they were qualified as central due to a significant reduction of respiratory muscular effort modulation.

For each breath attempt, the significance threshold was set as 10% of the thoracic or



abdominal RIP excursion baseline. The respiratory effort excursion of each breath attempt within an apnea was determined as the excursion value, whose time axis coordinate corresponds to this of the peak position in the RIP signal. The excursion baseline was determined as the within the one minute pre- and post-event excursion average.

Step 5: Detection and characterization of hypopnea events

Our algorithm detected hypopnea events according to the scoring rules of AASM updated in 2012 [20]. Similar to apnea detection, we mainly used \dot{V}_{source} to detect hypopneas. Our algorithm also assessed RIP flow excursion or naso-buccal thermistance excursion. A descending tendency of that signal greater than or equal to 10% in comparison to the one-minute pre- and post-event baseline was required to exclude the possibility of mouth breathing, which could cause an amplitude drop in \dot{V}_{source} as well. Additionally, to assure that this drop in nasal airflow excursion greater or equal to 30% was not due to sensor displacement, we also set a maximal event duration of three minutes.

Moreover, we followed the classification rules recommended by AASM [20] to classify hypopnea events as either obstructive or central hypopneas. Indeed, to consider an obstruction in the upper airway, one of the three following criteria was required: i) snoring, ii) thoracoabdominal paradoxical movements, or iii) flattened inspiratory airflow shape specific to obstruction.

In summary:

- i) We evaluated the audio power difference between the inspiratory phase and expiratory phase to detect snoring.
- ii) To identify the occurrence of thoracoabdominal paradox, the algorithm was based on the temporal closeness between peak and valley positions in RIP thorax and those in RIP abdomen. For example, during a given cycle with a thoracoabdominal



paradox, the RIP thorax peak was supposed to be temporally closer to the valley rather than peak in RIP abdomen.

- iii) We were inspired from the methodology proposed by Zhi *et al.* [23] to detect an inspiratory flow limitation in \dot{V}_{source} . Briefly, we trained a four-layer neural network (7*14*14*1) with seven features extracted from inspiratory airflow as inputs. The features were peak numbers, peak amplitude normalized by precedent 2-minute peak amplitude baseline, scooping index, kurtosis, deviation index, flattening index, skewness.

If none of these three criteria were detected, the candidate hypopnea event was considered as a central event.

Step 6: Calculation of digital inputs for integration into bench hardware

Artificial lung input: simulated respiratory muscular effort pressure ΔP_{mus}

calculation

The relationship between ΔP_{mus} and \dot{V}_{cc} is modeled by equation (1). \dot{V}_{cc} was assigned directly to \dot{V}_{source} for respiratory cycles included in normal breathing or in central respiratory events; \dot{V}_{cc} was then estimated by a sinusoidal form, with an amplitude equal to the 2-minute pre-event baseline for respiratory cycles involved in obstructive events. Inspiratory and expiratory time of \dot{V}_{cc} in obstructive cycles was calculated with respect to the temporality of \dot{V}_{source} (for obstructive hypopneas) and the reference RIP signal (for obstructive apneas).

Due to technical limitations in our bench hardware, inspiratory and expiratory volumes needed to be equal for each cycle. Consequently, we equilibrated inspiratory and expiratory airflow with respect to their inspiratory peak and expiratory valley coordinates.

Starling resistor input: sealed chamber pressure Pch calculation



Here, the aim was to apply the appropriate P_{ch} to transform the amplitude of \dot{V}_{cc} into the desired \dot{V}_{bench} in order to simulate \dot{V}_{source} . Preliminary work allowed us to study the relationship between \dot{V}_{cc} and the resulting flow after application of various P_{ch} , that is to say various levels of obstruction. This relationship was studied respectively for inspiration and expiration. This work allowed us to calculate P_{ch} for each obstructive cycle as a function of \dot{V}_{cc} and \dot{V}_{source} .

Bench simulation performance evaluation

We compared mainly \dot{V}_{bench} with \dot{V}_{source} to evaluate our bench simulation performance with respect to two categories: 1. normal and hypopnea breathing; 2. apneas.

For normal and hypopnea breathing, we assessed the agreement between \dot{V}_{bench} and \dot{V}_{source} cycle-by-cycle in terms of relative peak-to-valley amplitude (A) and T_{tot} by means of linear regression analysis, histogram representation of bias, and Bland and Altman analysis [24]. We measured the similarity in airflow morphology between \dot{V}_{bench} and \dot{V}_{source} cycle-by-cycle by calculating a Pearson correlation coefficient (r) for each corresponding pair of cycles respectively in \dot{V}_{source} and \dot{V}_{bench} . We assumed that the number of airflow samples in each respiratory cycle was ≥ 40 and that the distribution was normal. Then we calculated the mean \pm one standard deviation (SD) of r following two separated groups of respiratory cycles: cycles respectively with obstruction and without obstruction in upper airways.

For apneas, we calculated sensitivity and Positive Predictive Value (PPV) to evaluate the correspondence between apneas detected in \dot{V}_{source} and those in \dot{V}_{bench} . To assess apnea onset time agreement as well as apnea duration agreement between \dot{V}_{source} and \dot{V}_{bench} , we evaluated apnea onset



time differences by calculating its mean and SD, and performed linear regression and Bland and Altman analyses for apnea duration.

Results

Our algorithm allowed us to simulate a breathing profile from polygraph recordings by using a bench. Fig 6 shows two extracts of the bench simulations. The extracts describe respectively an obstructive SDB period and another breathing period without disordered breathing events. There is a graphical correspondence in signal amplitude and breathing events between the bench and the polygraph signals.



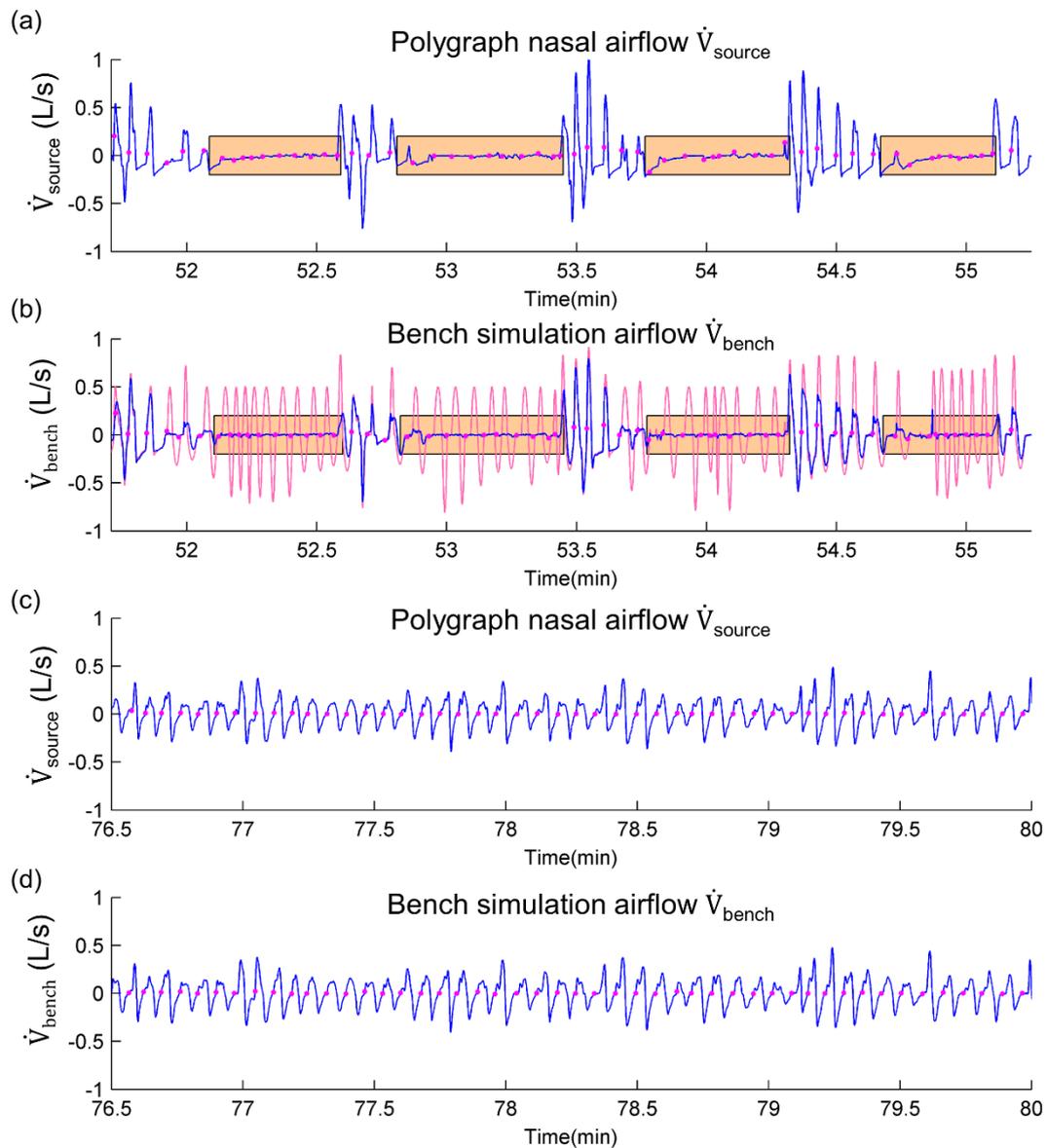


Fig 6. Illustration of bench simulation results: polygraph nasal airflow versus bench airflow.

(a) and (b): example of a breathing profile with obstructive apnea events marked in orange shade.

The polygraph nasal airflow (\dot{V}_{source}) and bench simulation airflow (\dot{V}_{bench}) are respectively showed in (a) and (b) with blue curves. The red curve in (b) represents the estimated non-obstructed nasal airflow (\dot{V}_{cc}), issuing from a central ventilation command. (c) and (d): example of a breathing

profile without disordered breathing events. The \dot{V}_{source} and \dot{V}_{bench} are respectively showed in (c) and (d) with blue curves. The magenta points in all graphs represent the breath onsets.

Concerning bench simulation performance for normal breathing (5,476 cycles) and hypopnea breathing (1,003 cycles), the average bias (M) in A between \dot{V}_{source} and \dot{V}_{bench} was 1.48% with a SD of 6.80% (Fig 7). Taking into account the 95% percent of cycles distributed around M, the SD of their biases decreased to 4.12%, whereas the M remained more or less unchanged (1.88%). The M in T_{tot} for each corresponding pair of respiratory cycles respectively in \dot{V}_{source} and \dot{V}_{bench} was approximately 0, with a SD equal to 0.288 seconds (Fig 8). Considering the 95% percent distributed around the M in T_{tot} , the M \pm one SD was -0.001 ± 0.139 seconds. The similarity assessed by Pearson correlation coefficient between each pair of respiratory cycles respectively in \dot{V}_{source} and \dot{V}_{bench} was 0.98 ± 0.08 considering all the normal and central hypopnea respiration cycles, and 0.87 ± 0.22 among all the obstructive hypopnea respiration cycles.



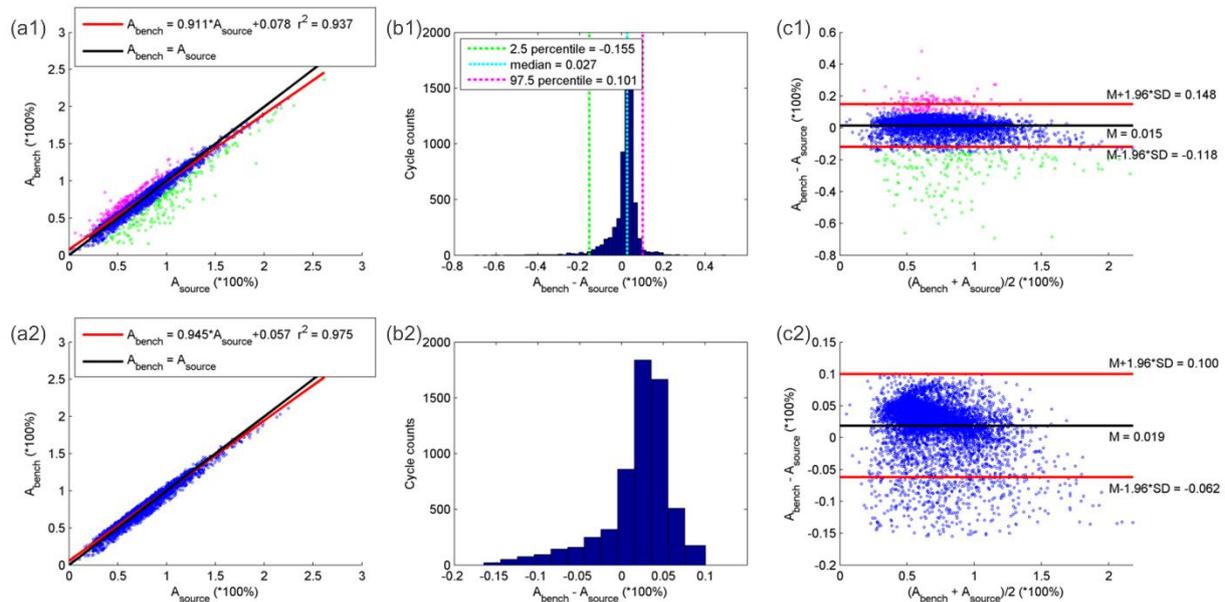


Fig 7. Linear regression, histogram, Bland and Altman plot analyzing similarity in relative amplitude between polygraph nasal airflow and bench airflow for 6,479 normal and hypopnea breathing cycles. (a1): Linear regression between polygraph estimated nasal airflow cycle relative amplitude (A_{source}) and bench airflow cycle relative amplitude (A_{bench}). Red line: the linear regression line. Black line: the identity line. Magenta points: breathing cycles with the difference between A_{bench} and A_{source} ($A_{bench} - A_{source}$) greater than 97.5 percentile. Blue points: breathing cycles with $A_{bench} - A_{source}$ between 2.5 percentile and 97.5 percentile. Green points: breathing cycles with $A_{bench} - A_{source}$ lower than 2.5 percentile. (b1): histogram analysis of difference between A_{bench} and A_{source} . Green cyan and magenta dashed line: their x-axis coordinates represent respectively 2.5 percentile (-15.5%), median (2.7%) and 97.5 percentile (10.1%) of $A_{bench} - A_{source}$. (c1): Bland-Altman plot analyzing the agreement between A_{bench} and A_{source} . Magenta, blue and greens points represent the same breathing cycles as described in graph (a1). Graphs (a2), (b2), (c2): the same

analyses as in graphs (a1), (b1) and (c1) except that the cycles taken into account are those whose $A_{\text{bench}} - A_{\text{source}}$ is between the 2.5 percentile and 97.5 percentile.

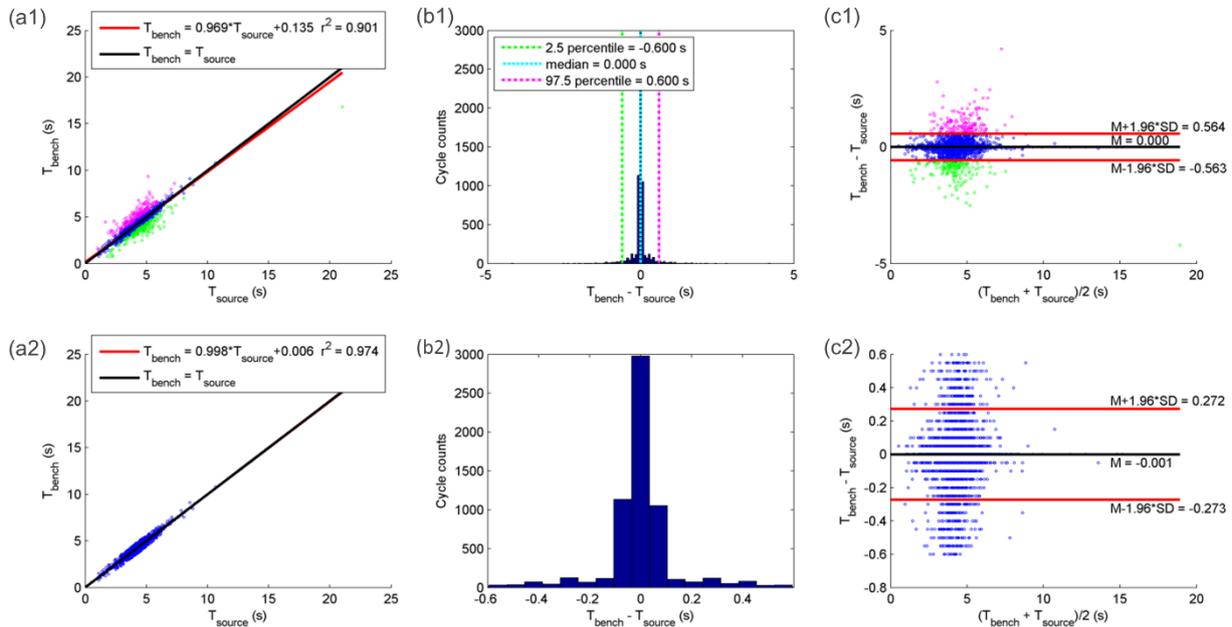


Fig 8. Linear regression, histogram, Bland and Altman plot analyzing similarity in total respiratory cycle time between polygraph nasal airflow and bench airflow for 6,479 normal and hypopnea breathing cycles. (a1): Linear regression between polygraph nasal airflow cycle time (T_{source}) and bench airflow cycle time (T_{bench}). Red line: the linear regression line. Black line: the identity line. Magenta points: breathing cycles with the difference between T_{bench} and T_{source} ($T_{\text{bench}} - T_{\text{source}}$) is greater than 97.5 percentile. Blue points: breathing cycles with $T_{\text{bench}} - T_{\text{source}}$ between the 2.5 percentile and 97.5 percentile. Green points: breathing cycles with $T_{\text{bench}} - T_{\text{source}}$ lower than the 2.5 percentile. (b1): Histogram analysis of the difference between T_{bench} and T_{source} . Green cyan and magenta dashed line: their x-axis coordinates represent respectively 2.5 percentile (-0.600 seconds), median (0 seconds) and 97.5 percentile (0.600 seconds) of $T_{\text{bench}} - T_{\text{source}}$. (c1): Bland-Altman plot analyzing the agreement between T_{bench} and T_{source} . Magenta, blue and greens points represent the same breathing cycles as described in graph (a1). Graphs (a2), (b2),

(c2): the same analyses as in graphs (a1), (b1) and (c1), except that the cycles taken into account are those whose $T_{\text{bench}} - T_{\text{source}}$ is between the 2.5 percentile and 97.5 percentile.

As for apnea events, simulation sensitivity and PPV were respectively equal to 84.7% and 90.3% by taking into account 149 apneas occurring correspondingly both in \dot{V}_{source} and \dot{V}_{bench} . Concerning the precision of apnea onset time, the average difference between apnea onset time in \dot{V}_{source} and \dot{V}_{bench} is equal to 0.19 seconds with a SD of 4.71 seconds (Fig 9). Concerning apnea event duration, the average bias is 0.12 seconds with a SD of 5.11 seconds, comparing the corresponding pair of apneas occurring in \dot{V}_{source} and \dot{V}_{bench} (Fig 10).

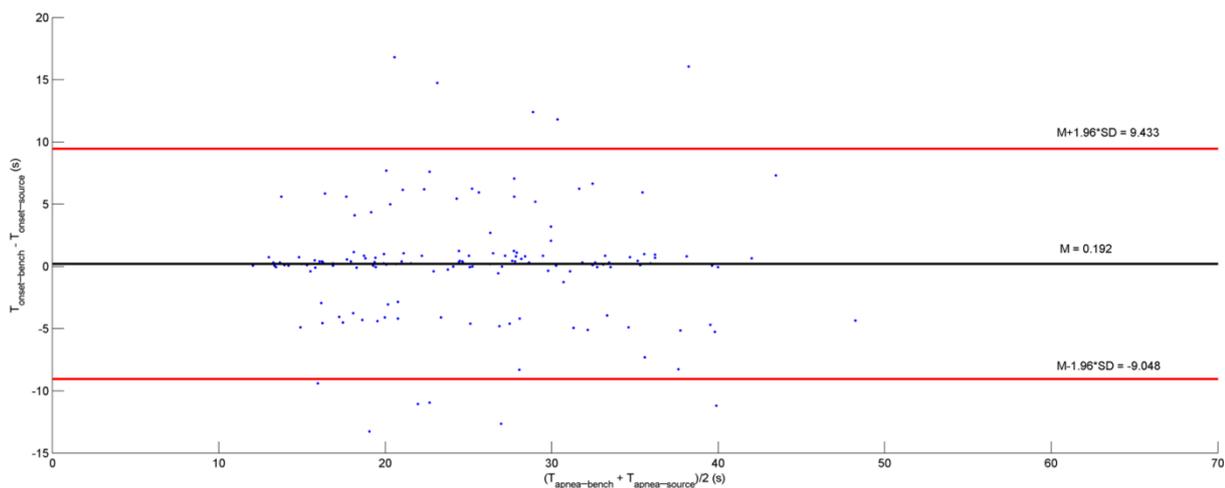


Fig 9. The relationship between apnea-onset time difference and apnea duration for apneas detected correspondingly in both bench airflow and polygraph nasal airflow (149 apneas).

$T_{\text{apnea-bench}}$: duration of apneas detected in **bench airflow** (\dot{V}_{bench}). $T_{\text{apnea-source}}$: duration of apneas detected in polygraph nasal airflow (\dot{V}_{source}). $T_{\text{onset-bench}}$: the apnea onset time of apneas detected in \dot{V}_{bench} . $T_{\text{onset-source}}$: the apnea onset time of apneas detected in \dot{V}_{source} .



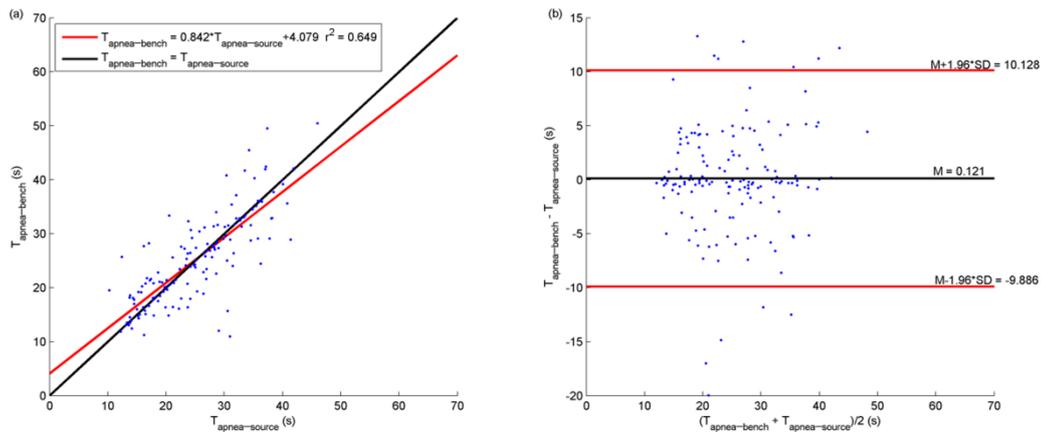


Fig 10. Linear regression, Bland and Altman analyses of apnea duration determined from respectively bench airflow and polygraph nasal airflow (149 apneas). Only the apneas detected both in bench airflow (\dot{V}_{bench}) and in polygraph nasal airflow (\dot{V}_{source}) are taken into account. (a): linear regression analysis between apnea duration determined from \dot{V}_{source} ($T_{\text{apnea-source}}$ in x-axis) and the one from \dot{V}_{bench} ($T_{\text{apnea-bench}}$ in y-axis). Red line: the linear regression line. Black line: the identity line. (b): Bland and Altman analysis of agreement between $T_{\text{apnea-source}}$ and $T_{\text{apnea-bench}}$.

Discussion

Findings statement

Our study proposed a physiological method for developing a bench to test different APAP devices. By processing polygraph data, we derived the digital inputs required to instruct bench hardware, of which the active lung simulator was driven by ΔP_{mus} , and a Starling resistor was regulated by P_{ch} to mimic a polygraph nasal breathing profile on the bench as similarly as possible. The bias existing in the airflow peak-valley amplitude can be partly explained by the limits of pressure regulators in terms of dynamic time response to a decreased P_{ch} , corresponding to breathing cycles represented in green points in Fig 7. Moreover, this is also related to the incertitude in controlling the resistance effect in the Starling resistor.

Our bench seems to have an excellent performance in cycle period simulation and good similarity in terms of signal morphology between \dot{V}_{source} and \dot{V}_{bench} , especially for respiratory cycles without obstruction in the upper airways. However, as for obstructive breathes, similarity was moderate. This can be explained by the fact that when increasing the resistance in the Starling resistor, we can no longer control the \dot{V}_{bench} signal shape. We can only make sure that there are inspiratory flow limitation phenomena occurring among the obstructive breathing cycles and the amplitudes of these obstructive cycles are very similar to those in \dot{V}_{source} .

There was satisfactory sensitivity and a good PPV for apnea-event correspondence between \dot{V}_{source} and \dot{V}_{bench} . There was some mismatch between bench and polygraph recordings for apnea onset and duration. These values are perfectible by optimizing the resistance incertitude in the Starling resistor, thus allowing for the desired reduction in airflow amplitude, as well as by attenuating the artifact in the airflow. Indeed, the airflow artifact was caused by the promptly collapsing rubber tube in the Starling resistor during the transition phase from breathing without obstruction to breathing with obstruction. This artifact was proportional to the level of obstruction. We did not calculate the specificity because we could consider that normal and hypopnea breathing periods account for the majority of polygraph recording time. The correspondence for normal and hypopnea breathing in \dot{V}_{source} and \dot{V}_{bench} should always be near perfect.

Advantages of our new approach

Compared to previous published bench tests, our bench system is able to automatically reproduce an apneic patient nasal breathing profile from its polygraph recordings for both obstructive sleep apnea syndrome and central sleep apnea syndrome. This assures that the bench-simulated airflow contains the breath-to-breath variability showed in real patient airflow. Our bench can simulate an unlimited spectrum of disturbed breathing events issuing from apneic



patients of various phenotypes. Moreover, our bench arranges the occurrence of different disordered breathing events in a physiological order. These depend on many factors related to patient characteristics such as age, gender, body mass index, craniofacial structure, as well as night-to-night variation like sleep stage, body position, alcohol or drug use, etc. Furthermore, the disordered breathing events of the obstructive mechanism simulated on our bench are capable of reacting to small steps of pressure change delivered by APAP devices by gradually increasing airflow amplitudes. This is a so-called closed loop.

Limits of the bench

Only one Starling resistor was used in our study, whose geometrical and mechanical property was unique, such as in the collapsible tube's ellipticity, wall stiffness, and upstream resistance at the onset of inspiratory flow limitation [25]. Thus, it may not represent the physical properties of all apneic patient upper airways. For the critical closing airway pressure, while it can be set to different values by varying P_{ch} in the Starling resistor, we do not have any information about a patient's real critical closing airway pressure from the polygraph examination, nor regarding an effective treatment pressure. Accordingly, the critical closing airway pressure and the effective treatment pressure, which were specific to our test bench, could differ from that of patients. By simulating a patient breathing profile and testing it with different devices on our bench, we cannot determine the exact pressure range needed by a particular patient. However, according to the treatment performance that each device demonstrates and the pressure range used by each device, we can always recommend a suitable device for a particular patient, despite the fact that we cannot know the real treatment pressure range that the patient needs. Furthermore, our bench does not take into account patient physiological responses to previous treated or partially-treated disordered



breathing events, like its ventilatory stability [26], which may influence the occurrence of upcoming disturbed breathing events.

Future improvements

Concerning inspiratory flow limitations in the simulation method, there are two different modes in our bench according to whether the inspiratory flow limited cycle is contained in an obstructive disordered breathing event. If it is, the cycle is simulated with a partially closed rubber tube in the Starling resistor, and the ΔP_{mus} of this cycle is derived from \dot{V}_{cc} . In this case, the bench-generated limited flow shape may present a difference with the one in polygraph recordings. Otherwise, it is simulated by integrating the ΔP_{mus} derived directly from the \dot{V}_{source} , with a completely opened Starling resistor. This results in more similar inspiratory flow limitation morphology, however, without a true obstruction in the Starling resistor.

In the near future, we are considering implementing two other versions of algorithms on our bench, using two different methodologies (version I and version II) to simulate patient inspiratory flow limitation.

Version I: all cycles presenting an inspiratory flow limitation would be simulated as obstructive cycles with the rubber tube in Starling resistor partially collapsed;

Version II: all cycles presenting an inspiratory flow limitation would be simulated in the same manner as cycles of normal breathing or a central breathing event with the rubber tube in the Starling resistor fully open.

These two versions are complementary. With version I, we can learn to what extent the tested ventilation device is able to adapt the treatment pressure to an inspiratory flow limitation, and our bench will react to the pressure change delivered by the device in a closed loop. With version II, our bench would simulate the exact airflow shape of these cycles with an inspiratory flow



limitation. In this way, we can learn whether the test device accurately recognizes such inspiratory flow limitations.

Conclusion

Our new approach for APAP devices test bench overcomes previous existing constraints in simulating all kinds of breathing phenotypes in apneic patients by using a bench. This new physiological bench provides a more detailed characterization of different respiratory devices responses to a specific patient profile. It can serve as an aid tool for personalized therapy to facilitate device selection, option settings, etc. This work reproduces the breathing profile at night during sleep registered in polygraph. The next step would be to further validate this bench by integrating different patient polygraph recordings in order to evaluate inter-individual as well as intra-individual variabilities.

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3.2 Summary

In this study, we developed a new approach of bench test, which enabled automatically reproducing nocturnal breathing patterns of patients with SAS. The hardware consisted mainly of an active lung simulator ASL5000 and a Starling resistor, used for modeling upper airway obstruction. The main work consisted in developing an algorithm, which processed polygraph signals and calculated automatically the digital inputs required by bench hardware to reproduce the breathing profile registered in polygraph. The lung simulator used respiratory muscular effort pressure as inputs. The resistance of Starling resistor was regulated via varying the sealed chamber pressure. By analyzing polygraph signals, the algorithm identified all breathing cycles, and classified them into normal breathing or disordered breathing according to the breathing airflow amplitude and oxygen saturation variations in line with AASM rules of 2012. Then it characterized the mechanisms of the disordered breathings (linked to upper airway obstruction or the damages of central ventilation command) by regarding whether respiratory muscular effort was present during apneas and whether there were snoring, inspiratory flow limitation or thoraco-abdominal paradox accompanying hypopnea events. Considering bench hardware input calculation, during normal breathing or the disordered breathing of central mechanism, the resistance was set at minimum in the Starling resistor. The respiratory muscular effort pressure needed by the active lung simulator was calculated directly from patient's nasal airflow, the pulmonary compliance and clear airway resistance parameters set in the pulmonary model. Nevertheless, simulating obstructive disordered breathing events would more complicated. Their respiratory muscular effort pressure was estimated with reference to this of the precedent normal breathing cycles. The obstructive level set in Starling Resistor was derived in function of the registered patient's reduced nasal airflow amplitude due to the upper airway obstruction and the estimated airflow amplitude issuing from central ventilation command, which should have been if there had not been obstruction in patient's upper



airway. The latter is calculated based on the breathing airflow during pre-event 2-minute normal breathing.

With this new approach, we simulated on our bench a total of 8 hours and 59 minutes of a breathing profile issuing from the demonstration recording of Nox T3 Sleep Monitor. The simulation performance results showed that in airflow amplitude, the simulated bench airflow was biased by $1.48\% \pm 6.80\%$ compared to patient's nasal airflow from polygraph. Considering total respiratory cycle time, the average bias \pm one standard deviation (Std) was 0.000 ± 0.288 seconds. The sensitivity and positive predictive value (PPV) of apnea simulation performance were 84.7% and 90.3%, taking into account 149 apneas detected correspondingly both in polygraph and bench-simulated breathing profile.

In conclusion, this new approach facilitated simulating nocturnal breathing patterns of patients with sleep disordered breathing on bench. The breathing profile reproduced on bench was very similar to that in polygraph. This physiological bench can help evaluate algorithms implemented in PAP devices in a more detailed manner, and aid clinicians in choosing an appropriate PAP algorithm for a specific patient.



Chapter IV. Validation of a new physiological bench test

In the previous chapter, we developed a new physiological bench test approach, which enabled reproducing automatically on bench the breathing profile with sleep disordered breathing registered in polygraph recordings, while taking into account cycle by cycle obstructive or central breathing mechanisms at the same time. However, this novel method of bench simulation had only been tested with the polygraph data issued from the demonstration recording of Nox-T3 sleep monitor.

In this chapter, we would like to validate our new bench simulation approach with a wide spectrum of breathing profiles issued from patients of different phenotypes and characteristics. These breathing profiles vary from one to another, regarding apnea hypopnea indices and the relative distribution between breathing events of central and obstructive mechanisms.



4.1 Article:

Validation of a new physiological bench test reproducing nocturnal breathing profile
of patients with sleep apnea



Validation of a new physiological bench test reproducing nocturnal breathing profile of patients with sleep apnea

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Abstract

Previously, we developed a new approach to reproduce nocturnal breathing profile of patients with sleep apnea syndrome on bench by using their polygraph recordings. The objective of this study was to validate this approach with a wide variety of breathing profiles issued from patients of different characteristics and phenotypes.

We totally extracted 15 polygraph recording samples of 1.3 ± 0.3 hours from 12 subjects diagnosed with moderate-to-severe sleep apnea to reproduce their breathing profiles on bench. According to polygraph scorings, the apnea indices varied from 1.4 to 76.7 events/hour with a mean \pm one standard deviation (std) of 29.6 ± 23.5 events/hour. The apnea mechanisms could be obstructive, mixed or central.

The bench simulation results showed that the airflow simulated on bench had a good similarity to patient nasal airflow. The amplitude bias and total respiratory cycle time bias were respectively $1.14\% \pm 4.65\%$ and 0.014 ± 0.377 second(s). Regarding apnea simulation, the sensitivity and PPV were 92.4% and 90.8%. The apnea-hypopnea index (AHI), apnea index (AI) and hypopnea index (HI) calculated from analyses of patient nasal airflow and bench simulated airflow were highly correlated ($r > 0.95$). The average differences were respectively -2.1 ± 5.5 , 0.6 ± 2.0 and -2.9 ± 5.7 events/hour. Considering the agreement in indices of different types of apneas (noted as OAI for obstructive apnea, CAI for central apneas, MAI for mixed apneas) between patient and bench simulation, they were highly correlated as well ($r \geq 0.90$). The average differences were 1.4 ± 1.9 , 0.1 ± 1.5 and -0.9 ± 1.6 events/hour with respect to the order of OAI, CAI and MAI. We evaluated the event-by-event correspondence between patient and bench simulation as well. The sensitivities and PPV were: 0.90 and 0.84 for obstructive apneas, 0.51 and 0.78 for mixed apneas, 0.83 and 0.82 for central apneas, 0.81 and 0.88 for hypopneas.



In conclusion, this new approach to bench simulation reached a good performance concerning the similarity between bench-simulated airflow and patient nasal airflow, as well as the reproduction of patients' all kinds of disordered breathing events. Thus, it has been proven robust in simulating various kinds of breathing profiles from real patients.



Introduction

Obstructive Sleep Apnea (OSA) is a respiratory disease, occurring during sleep, characterized by repetitive narrowing or collapse of the upper airways.(Patil, Schneider, Schwartz, et al. 2007) Its prevalence in adult population ranges from 6% to 17%.(Senaratna et al. 2017) Patients affected by OSA show symptoms such as heavy snoring, excessive daytime somnolence due to the restless sleep at night, etc. In the long term, this disease could result in cardiovascular complications.(Jean-Louis et al. 2008)

At present, the reference treatment for severe OSA patients is still the nocturnal ventilation via a continuous positive pressure, provided by a non-invasive ventilator.(Calik 2016) The pressure could be set to be either constant, or auto-adjusting, according to the prescriptions effectuated by medical professionals. In the auto-adjusting positive airway pressure (APAP) mode, the ventilator is supposed to be able to detect various sleep disordered breathing (SDB) events like obstructive and central apneas, obstructive and central hypopneas, snoring, inspiratory flow limitation, etc. And it should adapt the treatment pressure based on the previously detected event, in order to prevent the next incoming of the obstructive breathing event. The technologies and algorithms used for detecting and characterizing the SDB events vary among the ventilator manufacturers. They are usually protected by patents. The details of the algorithms are undisclosed to the public. Medical professionals could examine the treatment efficiency retrospectively by viewing their patients treatment data, from which, it is perceived that the pressure responses from ventilators of different manufacturers are not equivalent.

For the purpose of comparing the treatment performances of different ventilators more objectively and under the same conditions, some researchers have developed the bench test to mimic the typical SDB events that OSA patients could meet during sleep.(Farré et al. 2002a; Abdenbi 2004; Rigau et al. 2006; Hirose et al. 2008; Zhu et al. 2013; Isetta et al. 2016)



They reached the same conclusion. However, before 2016, the SDB profile simulated on bench could hardly cover the diversity in OSA patients' characteristics and phenotypes, such as the shape of airflow signal specific to each patient, so it's difficult to transpose the knowledge acquired from bench tests to clinical practice such as selecting an appropriate device for a specific patient, according to its breathing phenotypes. In 2016, Isetta et al. published their study about simulating a female OSA phenotype with taking into consideration the patient's specific respiratory characteristics, the impact of sleep stages and body positions, as well as awake. (Isetta et al. 2016)

We also tried to make our bench test become more physiological, and furthermore in an automatic manner. Concretely, our method was based on taking use of patient's polygraph data, in which our bench enables reproducing the breathing profile registered via a custom-made algorithm. The algorithm analyses automatically patient's polygraph data and calculates automatically the digital inputs needed to be integrated into our bench hardware.

Previously, we only tested our new physiological bench test approach with the polygraph data issued from the demonstration recording of Nox-T3 sleep monitor. To ensure that our bench is capable to reproduce a wide spectrum of breathing phenotypes from patients of different characteristics, the objective of this study is to validate our physiological bench test approach with various polygraph data, taking into account apnea, hypopnea indices and relative distribution of central and obstructive mechanisms.



Materials and Methods

1) Polygraph recording samples

The polygraph recordings obtained from 12 subjects were used in this study (table 1). They were referred to the Sleep Medicine Center of Université Paris-Sud in Clamart by their physicians because of either night clinical signs (snoring, arousals, polyuria) or day dizziness evoking sleep apnea diagnosis. All of them were examined by one of us (GR and MP), and have been recorded by either a NOX T3 or NOX A1 (NoxMedical, Reykjavík, Iceland) polygraphs. They were recruited in order to provide real physiologic signals obtained from patients with sleep apnea diagnosis, and a validation of our physiologic bench model. The use of their personal data has been approved by Comité d’Ethique de l’Université Paris-Saclay (N°2018-032). All subjects provided their informed written consent, and the study was conducted in accordance with the latest release of the Declaration of Helsinki. According to the ethic committee prescription, these data were suppressed after using them in the bench model. There was no interference between this study and the treatment and follow up of all these patients.

We extracted totally 15 polygraph recording samples with obstructive and central sleep apneas from these 12 polygraph recordings to simulate on bench. Each sample lasted 1.3 ± 0.3 hours. The selection was made in order to represent various breathing phenotypes of moderate to severe sleep apnea syndrome in this study.

The characteristics including duration, apnea hypopnea index (AHI) and the related apnea hypopnea indices) of these samples are described in table 1. The related indices about apneas, hypopneas are issued from either polygraph data analysis, performed by the software Noxturnal (V5.1, NoxMedical, Reykjavík, Iceland) and reviewed by 2 physicians, or patient nasal airflow signal analysis performed with our custom-made algorithm.



TABLE 1] Characteristics of 15 polygraph recording samples extracted from 12 patients

Scenario	Patient	Duration (hour)	AHI _{PG}	AHI _{flow_PG}	AHI _{flow_lab}	AI _{PG}	AI _{lab}	[OAI _{PG} - CAI _{PG} - MAI _{PG}]
1	a	1.4	16.6	33.1	27.4	1.5	0	[1.5 - 0 - 0]
2	b	1.1	45.7	58.1	49.9	3.8	4.6	[3.8 - 0 - 0]
3	c	0.9	33.9	65.5	68.6	13.1	10.3	[12 - 1.1 - 0]
4	d	1	38	64	77.5	14	12.7	[10 - 4 - 0]
5	d	0.9	51.5	55.9	62.4	16.5	10.6	[11 - 5.5 - 0]
6	e	1.3	39	58.5	51.9	17.3	14.6	[17.3 - 0 - 0]
7	f	1.8	44.2	55.6	35.4	23.5	25.3	[23.5 - 0 - 0]
8	e	1.5	55.2	65.9	68.4	37.3	31.9	[35.3 - 0.7 - 1.3]
9	g	1.4	90.7	104	99.7	52.4	47.2	[52.4 - 0 - 0]
10	h	1.1	87.1	92.5	77.6	79	81.1	[56.6 - 22.4 - 0]
11	j	1.3	27.6	51.3	48.4	20.5	23.8	[6.3 - 14.2 - 0]
12	k	2	64.7	79.9	72.9	25.8	27.8	[10.1 - 15.7 - 0]
13	l	1.1	50.6	69.7	74.5	32.3	32.2	[9.6 - 18.3 - 4.4]
14	m	0.9	74.4	98.5	88.8	43.8	41.2	[4.4 - 37.2 - 2.2]
15	h	1.1	65.4	82.4	76.7	62.5	66.5	[22.7 - 35.1 - 4.7]

AHI_{PG}: apnea hypopnea index obtained from polygraph software Noxturnal analyzing patient's nasal cannula airflow and arterial oxygen saturation with respect to AASM scoring rules 2012. **AHI_{flow_PG}**: apnea hypopnea index obtained from Noxturnal with use of hypopnea scoring rules that are based only on patient nasal airflow analysis. **AHI_{flow_lab}**: apnea hypopnea index obtained from a custom-made algorithm by analyzing patient nasal airflow based on the same scoring rules in AHI_{flow_PG} calculation. **AI_{PG}**: apnea index in AHI_{PG}. **AI_{lab}**: apnea index calculated by a custom-made algorithm analyzing patient nasal airflow in line with the same apnea scoring rules of AI_{PG}. **OAI_{PG}**: obstructive apnea index obtained from Noxturnal. **CAI_{PG}**: central apnea index obtained from Noxturnal. **MAI_{PG}**: mixed apnea index obtained from Noxturnal.

Indeed, in the configuration of polygraph data analysis of software Noxturnal, we chose an option of polygraph data analysis based on respiratory nasal cannula airflow. Thus, the apneas are defined as a drop in nasal cannula airflow greater than 90% compared to 2 minute pre-event



baseline, which should last between 10 seconds and 2 minutes. As for hypopnea scorings, we used two different scoring rules in Noxturnal software. They are respectively (1) the scoring rules according to AASM: there is a nasal cannula airflow drop $\geq 30\%$, lasting between 10 seconds and 2 minutes, and associated with a decrease in blood oxygen saturation $\geq 3\%$; (Berry, Budhiraja, et al. 2012) (2) the scoring rules with regard only to airflow signal, i.e. only a nasal cannula airflow drop $\geq 30\%$, lasting between 10 seconds and 2 minutes would be sufficient. This choice resulted in two different AHI scorings from Noxturnal: AHI_{PG} , AHI_{flow_PG} . A custom-made algorithm developed by us for analysing patient nasal airflow used the same apnea scoring rules as that in the Noxturnal and the second hypopnea scoring rules defined in Noxturnal, which is only based on air flow reduction, to calculate apnea index (AI) and AHI, noted as AHI_{flow_lab} and AI_{lab} . According to table 1, the apnea index of these polygraph recording samples (AI_{PG}) present a wide range from 1.4 to 76.7 events/hour. The apnea properties could be obstructive, central and mixed.

2) Physiological bench simulation system

The material and algorithm used in this study to simulate patient nocturnal breathing profile is the very same physiological bench simulation described in our previous paper. The hardware of this bench is mainly composed by an active artificial lung and a Starling resistor, which could mimic upper airway collapses. Our algorithm was able to take polygraph signals as inputs and calculate automatically the digital inputs needed to command our bench hardware, i.e., respiratory muscular effort pressure for artificial lung and sealed chamber pressure of Starling resistor, to simulate patient breathing profile, including their various sleep disordered breathing events. All the patient breathing profile samples are reproduced on our bench with connecting to an APAP device set with a constant pressure of 4 cmH₂O.



3) Data analysis

To evaluate our bench performance in simulating all these scenarios, we firstly assessed the similarity between airflow simulated on our bench (L/min) and the patient nasal airflow (cmH₂O). The Nasal and bench airflow were firstly normalized by dividing each value by their respective 85 percentiles of overall airflow amplitudes. Thus we obtained a normalized patient nasal airflow and a normalized bench airflow. In the later part of this article, all mentioned patient nasal airflow and bench airflow refer to the normalized ones. Their agreements in amplitudes and total respiratory cycle time (T_{tot}) were assessed by linear regression, Bland-Altman method (Bland and Altman 1986b) as well as Spearman's rank correlation coefficient. To obtain a more detailed information, we separated them by respiratory cycles without and with obstruction.

Secondly, we evaluated bench-simulation performance specifically concerning apneas, about the agreements in apnea duration and apnea onset time between patient breathing profiles and bench simulation. These were performed with linear regression analysis and Bland-Altman method.

Next, we assessed the agreement in different kinds of SDB indices obtained from analyses of respectively patient nasal cannula airflow and bench airflow. These SDB indices contain AHI, AI, hypopnea index (HI), obstructive apnea index (OAI), central apnea index (CAI) and mixed apnea index (MAI), of which AHI, AI and HI were calculated by using the previously mentioned custom-made algorithm. To calculate OAI, CAI and MAI, we had developed another algorithm to qualify apneas of polygraph recordings and of bench simulation. Concerning apneas of polygraph recordings, we determined an apnea as central if both thoracic and abdominal RIP signals drop by at least 90% compared to their pre-event 2-minute baseline; otherwise, it was supposed that there were significant breathing effort during the corresponding apnea. If muscular effort occurred only in the second half of an apnea period, we would categorize it as a mixed apnea. Otherwise, it was



attributed to an obstructive apnea. The bench-simulated apneas were qualified by criterion of whether the upper airway model was obstructed during simulation. We used respectively the Wilcoxon signed-rank test, Spearman's rank correlation coefficient, linear regression and Bland-Altman analysis to evaluate their agreements.

Finally, to investigate in a further step the SDB event-by-event correspondence between patient breathing profiles and bench-simulated ones, we established a detailed contingency table to check whether our simulation would mistake the SDB event type of patients'.

Results

Comparing airflow from patients and from bench, we found an amplitude bias of 1.14% +/- 4.65% and a Ttot bias of 0.014+/-0.377 seconds(s) (Figure 1 and 2).

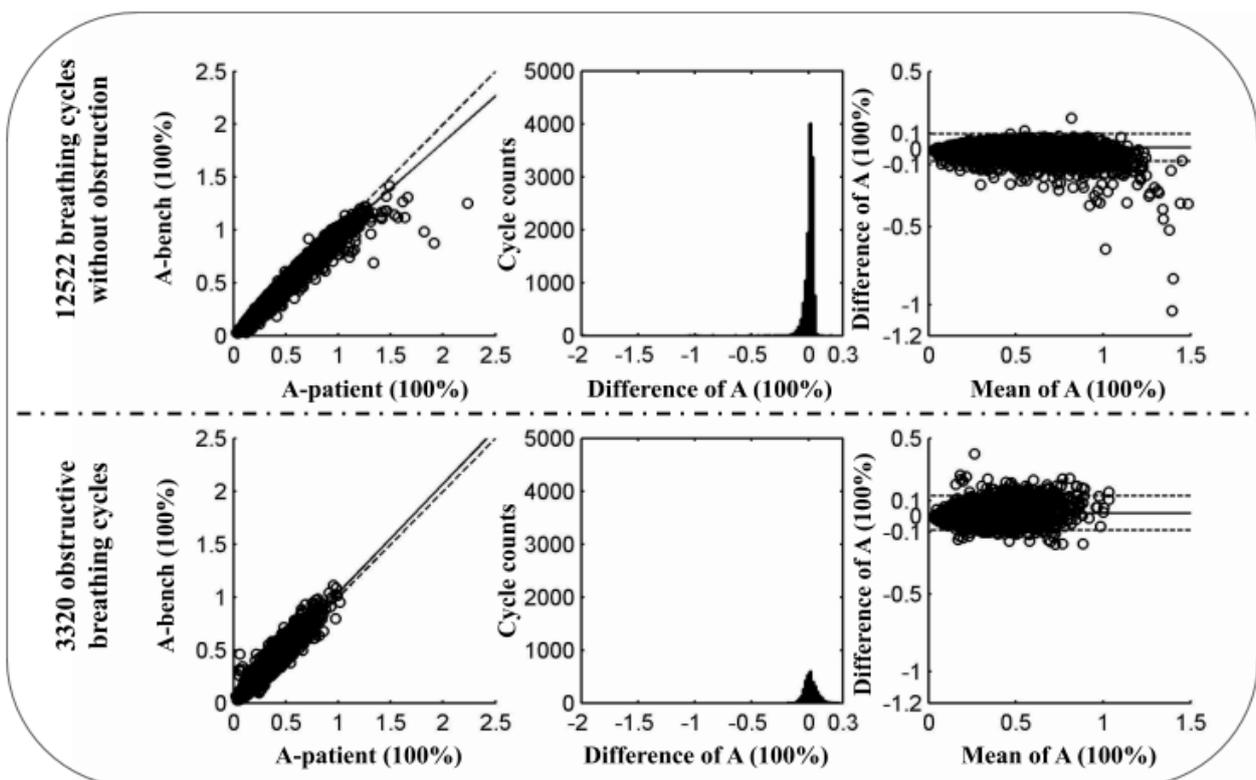


Figure 1 - Bar chart of apnea hypopnea indices obtained from the polygraph analysis of the 25 polygraph samples selected to be simulated on bench. HI = hypopnea index; OAI = obstructive apnea index; MAI = mixed apnea index; CAI = central apnea index.

This result is based on a cycle-by-cycle comparison including normal breathing and hypopneic breathing periods, totally taking 15842 breathing cycles into account, whereas excluding apnea periods.

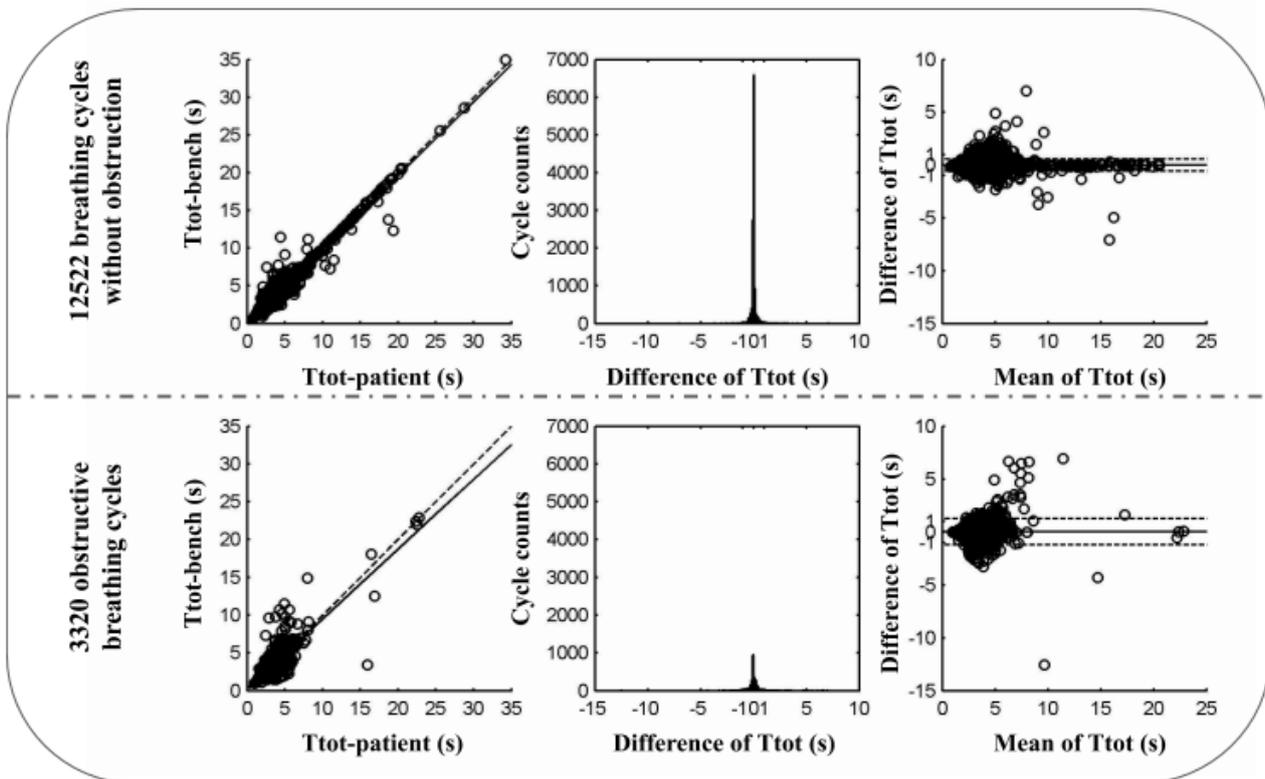


Figure 2 - Linear regression and Bland-Altman plots of apnea hypopnea indices detected by positive airway pressure devices with these determined by polygraph, regarding totally 25 polygraph recording samples. PAP = positive airway pressure devices; PG = polygraph; AHI = apnea hypopnea index.

Considering obstructive hypopnea breathing periods (3320 breathing cycles), the bias in amplitude between patient nasal and bench airflow was $1.9\% \pm 5.5\%$. The linear relationship between those two amplitude variables could be described by a slope of 1.03 and an intercept of 0.01, with a coefficient of determination equal to 0.90 and a Spearman's rank correlation coefficient of 0.95. The bias in Ttot was $0.02 \pm 0.63s$. The linear regression between Ttot from patient nasal

airflow and bench airflow showed a slope of 0.92 and an intercept of 0.31, with a coefficient of determination equal to 0.74 and a Spearman's rank correlation coefficient of 0.85.

Similarly, considering respiratory cycles without obstruction (12522 cycles), i.e. central hypopnea and normal breathing periods, the bias in amplitude between patient nasal and bench airflow was 0.9% +/- 4.4%. The linear relationship between those two amplitude variables could be described by a slope of 0.88 and an intercept of 0.07, with a coefficient of determination equal to 0.96 and a Spearman's rank correlation coefficient of 0.99. The bias in Ttot was 0.01 +/- 0.28s. The linear regression between Ttot from patient nasal airflow and bench airflow showed a slope of 0.98 and an intercept of 0.10, with a coefficient of determination equal to 0.96 and a Spearman's rank correlation coefficient of 0.96.

Regarding apnea simulation performance, there was a total of 501 apneas detected correspondingly at the same time in patient nasal airflow and bench airflow, with a sensitivity and a PPV equal to 92.4% and 90.8%. About the agreements in apnea duration and apnea onset time between patient nasal airflow and bench airflow, the Bland and Altman plot showed an average apnea duration difference of 0.07 seconds with a std of 4.1 seconds (Figure 3). The average difference in apnea onset time was -0.55 seconds with a std of 3.0 seconds (Figure 3).



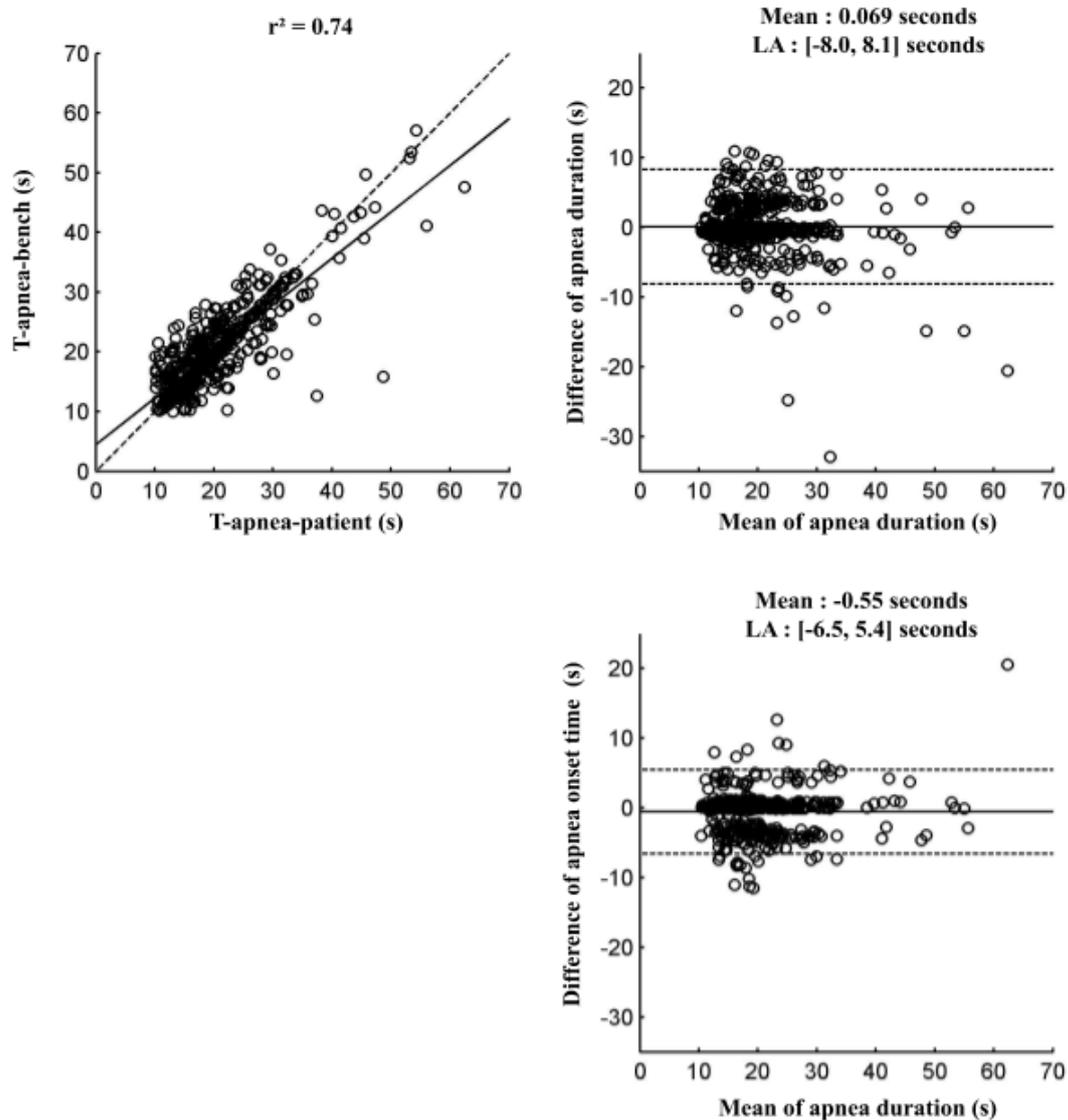


Figure 3: Apnea simulation performance evaluation regarding the agreements in apnea duration and apnea onset time between bench-simulated apneas and the corresponding ones in patients (501 apneas). Only the apneas detected correspondingly both in bench simulated airflow and patient nasal airflow are taken into account. **Graphs in the first row:** linear regression and Bland-Altman plots analyzing the agreement between bench-simulated apneas' duration (T-apnea-bench) and those of the corresponding patients' apneas (T-apnea-patient). In linear regression plot, the solid line is the linear regression line; the dashed represents the identity line; r^2 means the coefficient of determination. In Bland-Altman plot, the y-coordinate of solid horizontal lines represents the mean difference between T-apnea-bench and T-apnea-patient; then the y-coordinate of dashed lines represents 95 percent limits of agreement. **Graph in the second row:** scatter plot of apnea onset time difference versus the mean apnea duration between bench-simulated

apneas and the corresponding patients' ones. Mean: mean difference. LA: 95 percent limits of agreement.

Concerning the agreements of AHI, AI and HI calculated respectively from patient nasal airflow and bench simulated airflow for the 15 polygraph recording samples, the Wilcoxon signed-rank tests demonstrated that the difference in AI was not significant with $p > 0.05$; whereas the differences in AHI and HI were significant ($p < 0.05$). Bland-Altman analysis showed the mean differences in AHI, AI and HI were respectively equal to -2.1, 2.0 and -2.9 events/hour (Figure 4). Their limits of agreement were respectively [-13.1; 8.9], [-3.4; 4.6] and [-14.4; 8.6] events/hour with respect to the order of AHI, AI and HI (Figure 4). Regarding linear correlations, they were highly linearly correlated (Figure 4). Linear regression analyses revealed slopes of 1.02, 0.96 and 0.94, intercepts of -3.61, 1.79, 0.73, with coefficients of determination equal to 0.93, 0.99, 0.91, respecting the order of AHI, AI and HI. Their Spearman's rank correlation coefficients were 0.93, 0.99, 0.97.



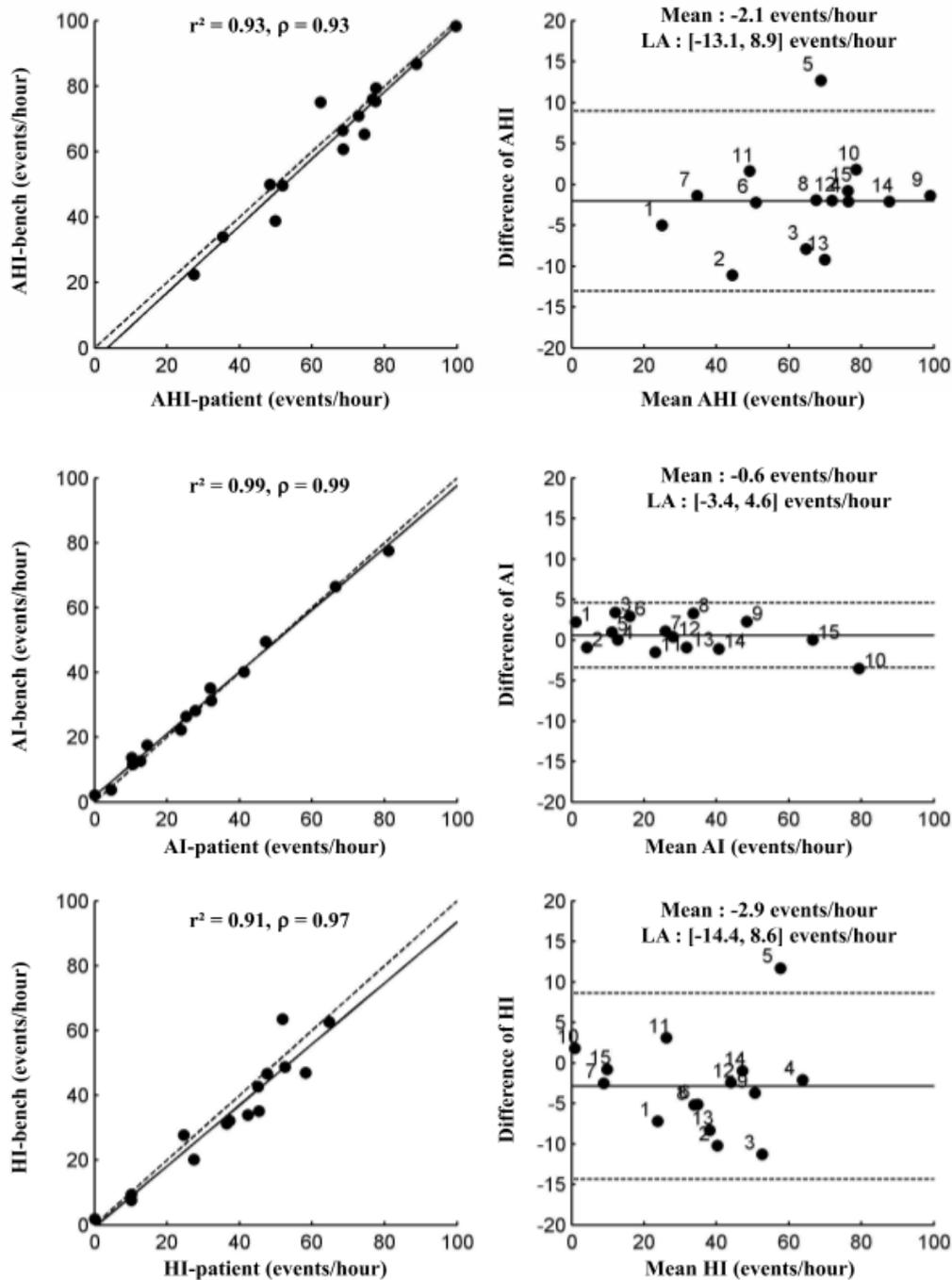


Figure 4: Linear regression and Bland-Altman plots analyzing the agreement of apnea hypopnea indices calculated from bench airflow and patient nasal airflow. AHI: apnea hypopnea index. AI: apnea index. HI: hypopnea index. In linear regression plots, solid lines are linear regression lines; dashed lines are identity lines; r^2 represents coefficients of determination; ρ means the p -values. In Bland-Altman plots, the y -coordinate of solid horizontal lines represents the mean difference between apnea hypopnea indices of bench airflow and those calculated

from patient nasal airflow; then the y-coordinate of dashed lines represents 95 percent limits of agreement. Mean: mean differences. LA: 95 percent limits of agreement.

While investigating in a further step the agreement in apnea indices for different categories of apneas (OAI, CAI and MAI) between patient nasal airflow and bench airflow, the Wilcoxon signed-rank tests showed that the difference in CAI was not significant ($p > 0.05$), whereas the differences in OAI and MAI were significant ($p < 0.05$). According to Bland Altman analyses, the mean differences of OAI, CAI and MAI were respectively 1.4, 0.1 and -0.9 events/hour between patient nasal airflow and bench airflow (Figure 5). Their limits of agreement were respectively [-2.4; 5.2], [-3.0; 3.2] and [-4.2; 2.3] events/hour. Regarding the linear correlation, they were linearly correlated as well. Linear regression analyses revealed slopes of 1.09, 0.85 and 0.63, intercepts of -0.22, 1.13 and 0.08, with coefficients of determination equal to 0.99, 0.99 and 0.81, respecting the order of OAI, CAI and MAI. Their Spearman's rank correlation coefficients were 0.996, 0.96 and 0.81.



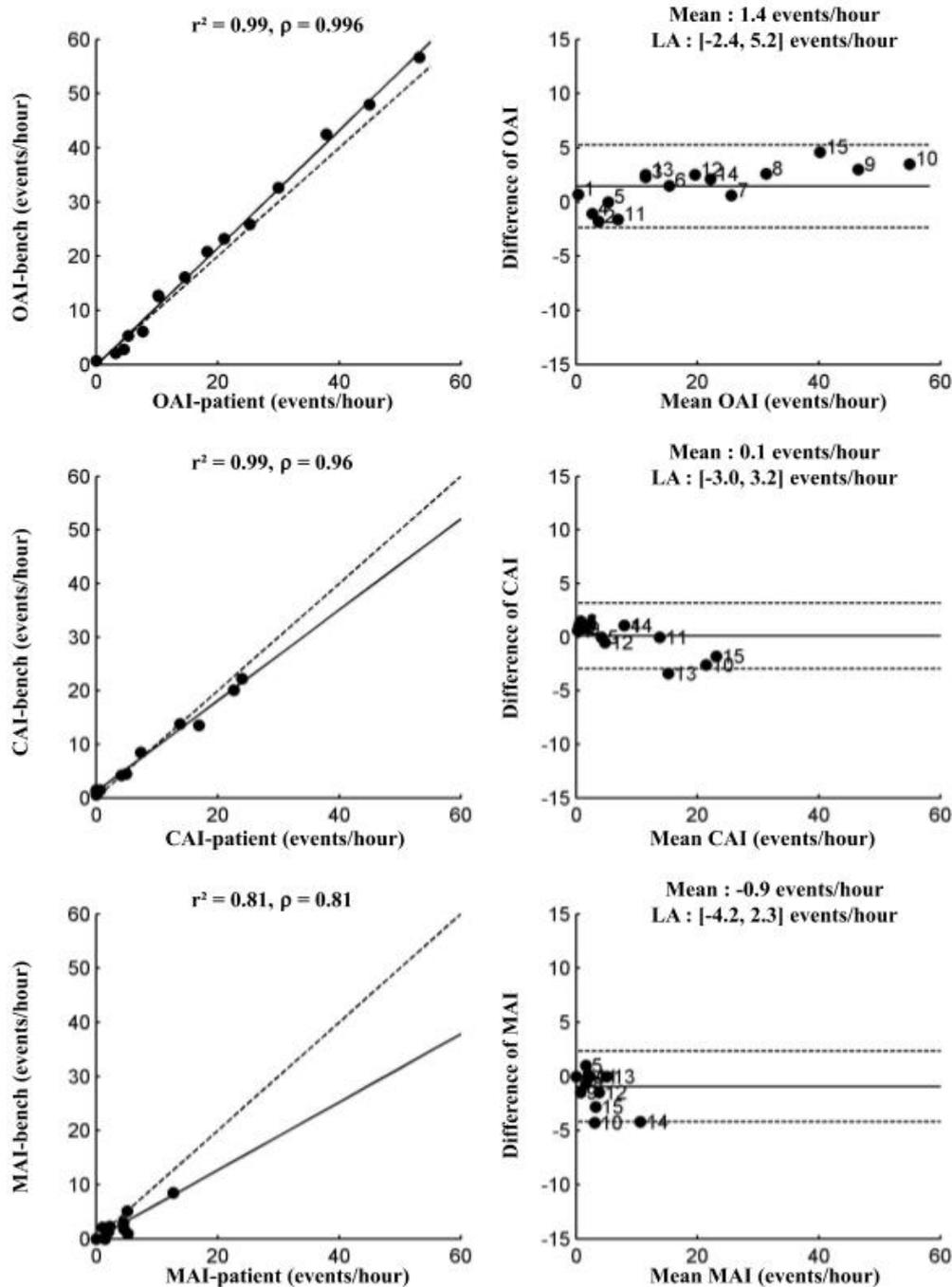


Figure 5: Linear regression and Bland-Altman plots analyzing the agreement in indices of different kinds of apneas calculated from bench airflow and patient nasal airflow. OAI: obstructive apnea index. CAI: central apnea index. MAI: mixed apnea index. HI: hypopnea index. In linear regression plots, solid lines are linear regression lines; dashed lines are identity lines; r^2 represents coefficients of determination; p means the p-values. In Bland-Altman plots, the y-coordinate of solid horizontal lines represents the mean difference between apnea indices of

bench airflow and those calculated from patient nasal airflow; then the y-coordinate of dashed lines represents 95 percent limits of agreement. Mean: mean differences. LA: 95 percent limits of agreement.

Evaluating the qualification correspondence for each pair of SDB events detected in patient nasal airflow and in the bench simulated airflow (Table 2), it was found that the sensitivities for obstructive apnea, central apneas, mixed apneas and hypopneas simulation were respectively 0.90, 0.83, 0.51 and 0.81. And their PPV were respectively 0.84, 0.82, 0.78 and 0.88.

TABLE 2] Sleep disordered breathing events contingency table between patients' and bench-simulated ones

		Patients' SDB			
		OA (n = 374)	CA (n = 119)	MA (n = 49)	H* (n = 705)
Bench-simulated SDB	OA (n = 399)	336	11	18	34
	CA (n = 121)	2	99	5	15
	MA (n = 32)	2	3	25	2
	H* (n = 648)	33	5	1	573
Simulation performance	Sensitivity	90%	83%	51%	81%
	PPV	84%	82%	78%	88%

Integer values represent event numbers for each type of SDB. SDB: sleep disordered breathing; OA: obstructive apnea; CA: central apnea; MA: mixed apnea; H*: hypopneas detected only based on airflow analysis; PPV: positive predictive value.

Discussion

Findings statement

With this new physiological test bench, we are enabled to simulate reliably a wide range of night breathing profiles, issuing from various patient phenotypes. Indeed, the 15 breathings



profiles we have simulated on our bench represent a wide range, taking in account apnea, hypopnea indices and relative distribution of central and obstructive mechanisms. Regarding airflow simulation reliability, our bench reached a satisfying similarity to the patient nasal airflow. This was assessed by analysing biases in cycle by cycle amplitudes, T_{tot} for both obstructive and non-obstructive breathing periods.

About the temporal performance of patient apnea simulation, first of all, we have a satisfactory sensitivity and PPV. Then the average apnea duration difference for each corresponding apnea occurring in patient nasal airflow and bench airflow was nearly 0 seconds, as well as the apnea onset time difference. However, the std of these differences was about 3 to 4 seconds, corresponding more or less to the T_{tot} of a breathing cycle. This is explicable by the simulation bias in breathing airflow amplitudes.

Concerning the agreement for AHI, AI and HI calculated respectively from patient nasal airflow and from bench airflow, the difference in AI was rather distributed symmetrically around 0. However the HI of bench airflow tended to be slightly lower than this of patient nasal airflow, so did the AHI. This could be explained by the inaccuracy of amplitude simulation for obstructive cycles and the bench material limitation for simulating a great inspiratory airflow amplitude or a great tidal volume. The second factor might cause that the moving baselines used for detecting SDB breathing events in bench airflow are sometimes slightly lower than those in patient nasal airflow.

About the consistency of apnea qualifications between patient breathing profile and bench simulation, the sensitivity and PPV for obstructive apneas are the best among all types of apneas. Although, the Wilcoxon signed-rank test showed that the differences in OAI between patient nasal airflow and bench airflow did not distribute symmetrically around 0, the differences were very small compared to the average OAI of patient nasal airflow and bench airflow. Concerning mixed apneas, 46.2% of mixed apneas in patient nasal airflow were then characterized as



obstructive apneas after bench simulation. These mixed apneas in patient nasal airflow were either preceded or followed by an obstructive cycle. If its amplitude simulated on bench was inferior to that in patient nasal airflow and at the same time it satisfied the airflow reduction criterion for scoring apneas, it would be considered as a part of apnea during bench airflow analysis and so as to affect the qualification of the apnea. In analogy, that's also the reason for which some central apneas of patient breathing profile were then characterized as obstructive apneas after bench simulation. We also noticed that within all the central apneas characterized on our bench, about 12% were originally hypopneas in patient breathing profile. By comparing the bench airflow with patient nasal airflow, we found that the patient nasal airflow during these hypopneas were usually contaminated by nasal cannula movement artifact such that the airflow data samples were consistently negative values with sinusoidal shapes. Due to the limit of our bench in simulating a long duration of expiration with a large expiratory volume, finally the bench airflow amplitudes during these periods were attenuated compared to the patient nasal airflow. So they were characterized as central apneas while analyzing bench airflow.

We chose to detect hypopneas by regarding only the patient nasal airflow and bench airflow amplitude changes, without taking into account the arterial oxygen (de)saturation, while assessing the AHI agreement between patient and bench simulation. The first reason is that we do not simulate patient's arterial oxygen saturation on bench. The second reason is that for now, most APAP devices commercialized in market do not take measures of patient's arterial oxygen saturation either. They adapt the treatment pressure based on the breathing airflow characteristics as well as the measured or statistically estimated upper airway resistance. Considering these two reasons, we think it should be more relevant that we detect hypopneas only based on the airflow changes to evaluate our bench simulation performance.

Advantages of the physiological test bench



Compared to previous published APAP algorithm evaluation benches, the main advantage of this bench is the proximity between bench-simulated breathing profile and patient's real breathing profile, as well as the facility to simulate each specific SDB patient breathing profile on our bench, as long as their polygraph recordings are provided.

In this study, we validated the new physiological bench approach by integrating 15 polygraph recording samples. It achieved a rather constant simulation performance, which is conform to our previous paper, regardless of the variations in apnea, hypopnea indices and in ratios between central SDB events and obstructive SDB events. So this bench is able to simulate a wide spectrum of SDB patient breathing profiles, taking into account cycle-by-cycle obstructive and central breathing characteristic. Concretely, patients' obstructive SDB events and inspiratory flow limitations are simulated with an increased resistance in the Starling resistor, which models obstruction in patient upper airways.

Compared to clinical validation of APAP devices, in general, the bench evaluation methods have the advantage of comparing them in an objective and identical condition, however, it could have a main weakness of being a lot artificial and lacking variability compared to a patient breathing profile. Consequently, bench test results could not mimic what really happened while a device treated a patient. According to this study, the new bench simulation method has overcome the conventional challenge. It can reliably simulate a wide range of sleep apnea patient breathing profile by simply using its polygraph recordings. So, right now, bench test results are becoming more convincing than before, by simulating different breathing profiles in a more detailed, automatic and reproducible manner. With the use of this bench, we can verify whether APAP devices are capable of detecting disordered breathing events and correctly characterizing their patterns (central, obstructive or mixed) by setting them at 4cm H₂O to rule out treatment effect.



Furthermore, this bench is also able to react to the pressure increase delivered from APAP devices in a closed-loop manner by reducing the Starling resistor resistance of next upcoming SDB events of obstructive mechanism or inspiratory flow limitations. It can help clinic professionals select appropriate APAP devices and different comfort setting options, specifically adapted to their patients breathing characteristics. With this bench, we can also learn more about APAP algorithms diversity and try to find reasons why sometimes a patient cannot get used to some APAP device.

Bench limits

Of noteworthy, the Starling resistor used in our bench could not represent the physical properties of all apneic patient upper airways, such as patient's critical closing upper airway pressure, the upper airway compliance, the effective treatment pressure, etc., as stated in our previous paper. Therefore, the pressure range needed to overcome the bench-simulated obstructive SDB events could differ from this really required for the patient. However, according to the bench test results, we could always recommend an adapted device for the patient by choosing the device, which could overcome almost all the bench-simulated obstructive SDB events of this patient, at the meantime not increasing the treatment pressure to an unnecessary high level.

Conclusion

In conclusion, our physiological bench enables to simulate reliably and automatically a wide range of breathing profiles issuing from patients of various breathing phenotypes. Our bench could serve as an aid tool of personalized therapy by helping clinical professionals select an appropriate APAP device as well as different setting options likes the comfort modes, adapted to the specific breathing characteristics of their patients.

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4.2 Summary

In this study, we totally extracted 15 polygraph-recording samples of 1.3 ± 0.3 hours from 12 subjects diagnosed with sleep apnea syndrome to simulate on bench, with the objective of validating our novel approach to a physiological bench test. According to polygraph scorings, the apnea index represented a wide range from 1.4 to 76.7 events/hour with a mean \pm Std of 29.6 ± 23.5 events/hour. The mechanisms of apnea could be obstructive, mixed or central.

The bench simulation results showed that the airflow simulated on bench had a good similarity to patient nasal airflow. The amplitude bias and total respiratory cycle time bias were respectively $1.14\% \pm 4.65\%$ and 0.014 ± 0.377 second(s). Regarding apnea simulation, the sensitivity and PPV were 92.4% and 90.8%. The AHI_{flow} , AI, and HI_{flow} scored from patient nasal airflow and bench simulated airflow were highly correlated ($r > 0.95$) as well. The average differences were respectively -2.1 ± 5.5 , 0.6 ± 2.0 and -2.9 ± 5.7 events/hour. Considering the agreement in indices of different types of apneas (OAI for obstructive apneas, MAI for mixed apneas and CAI for central apneas) between patient and bench simulation, they were highly correlated as well ($r \geq 0.90$). The average differences were 1.4 ± 1.9 , -0.9 ± 1.6 and 0.1 ± 1.5 events/hour with respect to the order of OAI, MAI and CAI. We had evaluated the event-by-event correspondence between patient and bench simulation as well. The sensitivities and PPV were respectively: 0.90 and 0.84 for obstructive apneas, 0.51 and 0.78 for mixed apneas, 0.83 and 0.82 for obstructive apneas, 0.81 and 0.88 for hypopneas.

The bench simulation reached a good performance regarding the similarity between bench simulated airflow and patient nasal airflow, as well as the reproduction of patients' all kinds of



disordered breathing events. This novel bench simulation approach has been shown being rather robust to all kinds of breathing profiles from real patients that we tested on bench.



Chapter V. Bench test evaluation of apnea hypopnea indices agreement between PAP algorithms and polygraph in predominant CSA patients

The medical data provided by PAP devices about patient's residual apnea hypopnea indices are of great importance for clinicians to evaluate treatment efficiency, follow up patient health status, and manage their pathways. Since OSA patients are possible to develop emergent CSA during PAP therapy, with a prevalence of 3.5% in week 1 or week 13 after PAP therapy initiation (D. Liu et al. 2017). Hence, the accuracy of PAP device report data plays a crucial role in monitoring patient health status and informing clinicians as early as possible to modify ventilator modalities of patients developing emergent CSA.

In literature, some studies compared the residual apnea hypopnea indices determined by PAP devices with PSG, especially focusing on OSA patients (Baek, Jeon, and Lee 2016; Berry, Kushida, et al. 2012; Li et al. 2015; Stepnowsky et al. 2013; Ueno, Kasai, and Kasagi 2010). They have shown that AHI from PAP devices are linearly correlated with PSG and that the agreements in AI are better than in HI. The latter is explained by different hypopnea scoring rules used by PAP devices and PSG. Some studies involving oximetry (Pittman et al. 2006) or PSG (Baltzan et al. 2006) have also found that a surprisingly large fraction of patients thought to be well treated by PAP, still have a considerable number of residual events. As the apnea hypopnea indices calculated by PAP devices are widely used to monitor treatment efficiency. It should be important that these data are consistent between PAP devices of different manufacturers. At present, there exist few



studies in literature evaluating apnea hypopnea indices agreement between PAP devices because of the intra- and inter-patient variabilities inherent in clinical trials.

Thus, the aim of this study was to evaluate the apnea hypopnea indices agreement between four currently commercialized PAP devices and polygraph, with the use of the new physiological bench developed in this thesis, which simulated reliably the breathing profiles of patients with a co-existence of OSA and CSA, registered in their polygraph recordings.



5.1 Article:

Bench test evaluation of apnea-hypopnea-index agreement between positive air pressure devices and polygraph in predominant central sleep apnea patients



Bench test evaluation of apnea-hypopnea-index agreement between positive air pressure devices and polygraph in predominant central sleep apnea patients

Abstract

Apnea hypopnea index (AHI) determination from positive airway pressure (PAP) devices require a quantitative evaluation. With a physiological bench, composed of an active lung simulator and an upper airway model that is able to simulate breathing profiles from polygraph (PG) recordings, we evaluated AHI, apnea index (AI) and hypopnea index (HI) agreement between four PAP devices and PG.

We extracted a total of twenty-five one-hour samples from four whole-night respiratory polygraph recordings of patients diagnosed with predominant central sleep apnea (CSA). According to polygraph analysis, the AHI of these recordings was 42.3 ± 21.7 events/hour (mean \pm standard deviation), varying from 12 to 77.7. Apneas and hypopneas numbers were balanced (Apneas: 55.3%; Hypopneas: 44.7%). Moreover, central apneas represented $55.8\% \pm 27\%$ among all apneas. Then we simulated on bench each sample four times, while connecting different PAP devices (AirSense 10, DreamStation Auto, S.Box, Prisma 20A) set at 4 cmH₂O to rule out treatment effects.

The results showed that AHI and AI determined by the PAP devices were highly and linearly correlated with PG scorings (AHI: Pearson correlation coefficient (r) = [0.91 (min), 0.94 (max)]; AI: r = [0.92 (min), 0.97 (max)]), whereas relationships in HI were weak (r = [-0.10 (min), 0.59 (max)]). Additionally, the bias value between PAP devices and PG in AI was lower than in HI. The four tested PAP devices showed a tendency to underestimate patient HI. However, the severity of underestimation was not the same between the PAP devices: the average bias between the HI of PAP and PG varied from -14.2 to -2.6 events/hour.



In conclusion, AHI calculated by PAP devices may not be an accurate indicator of real AHI for patients with predominant CSA. We found a non-negligible discrepancy between HI provided by the PAP devices of different manufacturers under the same breathing profile conditions.

Introduction

Positive Airway Pressure (PAP) devices are widely used to treat patients with moderate to severe obstructive sleep apnea (OSA) syndrome¹. The prescribed pressure can be either fixed or auto-adjusting in a preset range. For each treatment session, devices are capable of identifying residual breathing events based on airflow analysis. These data are of great importance for treatment efficiency evaluation, follow up, as well as patient pathway management². During PAP therapy patients may develop central breathing events, with a prevalence of 3.5%³. Risk management of adverse cardiovascular outcomes and comorbidity may be dependent on device data accuracy. This data would play a crucial role in monitoring patient status and informing clinicians as early as possible to adapt treatment strategy.

Some studies have compared PAP residual events with polysomnography (PSG), especially in OSA patients.⁴⁻⁹ The apnea hypopnea index (AHI), apnea index (AI), hypopnea index (HI) from PAP devices have been correlated with indices from PSG. However, AI agreement was better than the one in HI. This could be explained by hypopnea scoring rules used by PAP devices differing from those used in PSG. In addition, some studies involving oximetry¹⁰ or PSG¹¹ found a large fraction of patients thought to be well treated by PAP, with a considerable number of residual events. However, obtaining accurate AHI with PSG in all patients treated by PAP devices is overly time consuming and impractical in most public healthcare systems. Therefore, AHI from PAP devices (AHI_{PAP}) are still widely used to monitor treatment efficiency.

Given the fact that PAP device manufacturers use different technology and



algorithms to detect residual events, we cannot rule out possible AHI_{PAP} discrepancies from different manufacturers. As clinical studies do not allow for an evaluation of different PAP devices simultaneously, the influence of night-to-night breathing profile variability in a patient is difficult to rule out. A method to bypass this methodological shortcoming would be useful and would permit the examination of AHI_{PAP} validity and reliability in identical conditions. An official statement from the American Thoracic Society in 2013 mentioned PAP adherence tracking systems and their related data¹². The statement concluded by encouraging PAP data standardization and further studies to evaluate data outcomes¹². In this context, the aim of our study was to evaluate AHI agreement between a polygraph and four currently commercialized PAP devices with a physiological bench, which can confidently reproduce the breathing profiles of apneic patients. Since an accurate detection of disordered breathing events is an important preliminary step before reaching a more efficient treatment, we aimed to understand SDB event detection in each PAP device as well as differences between the devices.

Materials and Methods

Physiological Bench Test System

The bench test used in this study to simulate a patient nocturnal breathing profile was the same as in our previous paper. This bench was composed of an active lung simulator ASL5000 (IngMar Medical, Pittsburgh, USA) and a Starling resistor, mimicking patient upper airway collapses. We developed an algorithm that is able to process a patient's polygraph signals and automatically calculate related digital inputs to drive the bench simulation process. This allowed the simulation of any patient breathing profile registered by polygraph, taking into account cycle-by-cycle central and obstructive characteristics. Various patient breathing profiles, as inputs, could then be reproduced several times on our bench, with accuracy and reproducibility.



Experimental Data from Polygraph

Four apneic subjects with obstructive and central events were recruited, providing real physiologic signals obtained from their polygraph examination. They were initially referred to the Sleep Medicine Center of Université Paris-Saclay in Clamart by their physicians. All were examined by GR or MP, and were recorded by either NOX T3 or NOX A1 poly(somno)graphs (NoxMedical, Reykjavík, Iceland). Use of their data was approved by the *Comité d’Ethique de l’Université Paris-Saclay* (N° 2018-032). All subjects provided informed written consent, and the study was conducted in accordance with the latest release of the Declaration of Helsinki. According to the ethic committee prescription, the anonymized data was erased from our computer after using them in the bench model. There was no interference between this study and the treatment of these patients.

Twenty-five polygraph samples of one hour were extracted from the four whole-night polygraph recordings without PAP treatment. Those samples were reproduced on our bench with respect to the original breathing profile: amplitude and time parameters as well as their obstructive and central characterization. Periods with movement artifacts greater than two minutes were excluded. The related AHI, AI, HI, Central Apnea Index (CAI), Mixed Apnea Index (MAI) and Obstructive Apnea Index (OAI) of these samples are described in Figure 1. They were scored from the polygraph signals analysis performed by Noxturnal software (V5.1.0.19071, NoxMedical, Reykjavík, Iceland), and reviewed by two physicians (GR and MP). The scoring rules were in line with AASM 2012¹³, using a nasal pressure transducer as a sensor. Apneas were defined as a decrease in nasal cannula airflow $\geq 90\%$ during a period of at least 10 seconds. Hypopneas were scored with respect to a nasal airflow reduction $\geq 30\%$ during a period of at least 10 seconds, with oxygen saturation decreasing by $\geq 3\%$.



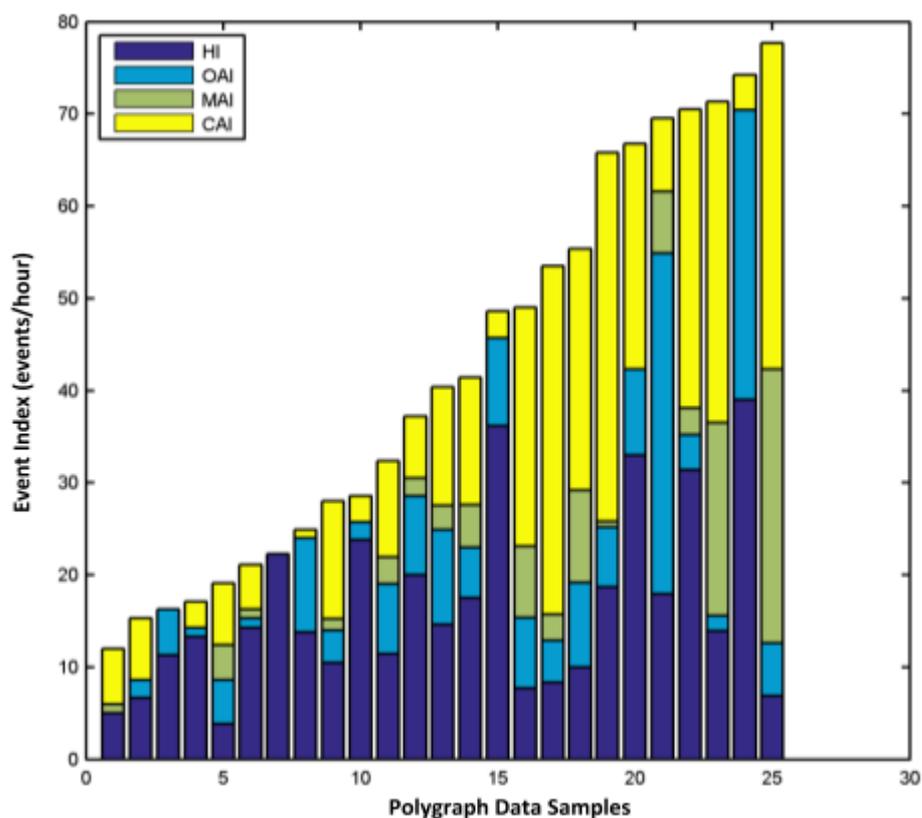


Figure 1 - Bar chart of apnea hypopnea indices obtained from the polygraph analysis of the 25 polygraph samples selected for bench simulation. HI = hypopnea index; OAI = obstructive apnea index; MAI = mixed apnea index; and CAI = central apnea index.

The AHI of simulated samples was 42.3 ± 21.7 events/hour (Fig.1). Apneas were predominant in comparison to hypopnea, representing 55.3% of events. Central apneas represented $55.8 \pm 27\%$ in all apneas.

Experimental Protocol

Four different PAP devices and their related software were included in this study: AirSense 10 Autoset with Rescan by Resmed (San Diego, United States); DreamStation Auto with Encore Pro 2 by Philips Respironics (Murrysville, United States); S.Box with SEFAM Analyze by Sefam (Nancy, France) and Prima 20A with Prisma TS by Löwenstein Medical (Bad Ems, Germany).

AHI_{PAP} and related indices were acquired through the analysis reports generated with the

device-related software. Firstly, we used a custom-made algorithm to process the selected 25 polygraph samples exported in EDF format, to generate the digital inputs: muscular pressure and sealed chamber pressure. Then, we integrated the algorithm outputs in the bench hardware with ASL Software (Version 3.4.0, IngMar Medical, Pittsburgh, USA) to drive the artificial lung and with a custom-made Labview program to pilot the Starling resistor for each breathing cycle.

Each polygraph sample was simulated four times on our bench with the four PAP devices connected to the test bench in a random order. The PAP tubing was 22 mm in diameter, in accordance with the device setting. Devices were set at 4 cmH₂O without any comfort options in order to rule out treatment effect. The airflow produced on bench was sampled at 20 Hz and stored in a PC. Once the simulation of a polygraph-recording sample completed, we exported from a corresponding SD card: AHI_{PAP} ([AHI_{AirSense10}, AHI_{DreamStation}, AHI_{S.Box}, AHI_{Prisma20A}]), AI_{PAP} ([AI_{AirSense10}, AI_{DreamStation}, AI_{S.Box}, AI_{Prisma20A}]) and HI_{PAP} ([HI_{AirSense10}, HI_{DreamStation}, HI_{S.Box}, HI_{Prisma20A}]).

Data Analysis

The similarity between the bench simulation and patient breathing profile was assessed in a cycle-by-cycle manner, using the Bland-Altman method considering airflow amplitudes and total respiratory cycle time (T_{tot}).

Since the data distribution was not Gaussian, agreements between AHI, AI and HI from the polygraph and from PAP devices were assessed by nonparametric Wilcoxon-signed-rank tests. Corresponding biases and limits of agreement in AHI, AI and HI were visualized by Bland-Altman plots. Linear regression, Pearson correlation coefficients (r) and intraclass correlation coefficients (ICC) were also calculated to characterize these relationships. ICC was calculated with a two-way mixed model measuring absolute agreement for single measures. A p-value (p-val) inferior to 0.05 was considered statistically significant.



We developed a custom-made algorithm to score apneas and hypopneas from bench simulated airflow and patient nasal airflow, based only on airflow reduction. These thresholds were applied in line with AASM 2012¹³. In addition, this algorithm excluded bench airflow changes caused by pressure pulses delivered from DreamStation during apneas, by replacing them with patient nasal airflow. Thus, we obtained the related $AHI_{\text{flow_bench}}$ and $AHI_{\text{flow_patient}}$ from bench simulated airflow and patient nasal airflow analyses, respectively. We defined an indicator of bench simulation performance calculated as the absolute difference between $AHI_{\text{flow_bench}}$ and $AHI_{\text{flow_patient}}$. In the same way, we defined an indicator of PAP device performance for event detection by calculating the absolute difference between AHI_{PAP} and AHI from a polygraph (AHI_{PG}). The impact of bench simulation performance on PAP device performance for SDB detection was studied with Spearman's rank correlation coefficient. A multiple linear regression model was also constructed to explain AHI_{PAP} as a function of AI, HI from polygraph (AI_{PG} , HI_{PG}), and the simulation performance indicator.

The accuracy of PAP devices in identifying breathing profiles with $AHI_{\text{PG}} > 30$ was calculated.

A transition matrix for AHI_{PAP} among different manufacturers was established. In this matrix, linear regressions were performed to estimate AHI_{PAP} linear relationships between each pair of devices. Based on these models, one AHI_{PAP} could be estimated from the AHI_{PAP} scored by another manufacturer.

Results

AHI_{PAP} Evaluation

Comparing patient and bench airflow, the simulation process bias was $4.5 \pm 5.4\%$ in



amplitude and 0.007 ± 0.650 s in T_{tot} . These amplitude and T_{tot} biases also remained in the same range when considering the four PAP devices (Table 1).

TABLE 1. Agreement between Patient and Bench Airflow: Amplitude and T_{tot} Biases

	AirSense10	DreamStation	S.Box	Prisma20A	Overall average
Amplitude bias, %	4.6 ± 5.1	4.0 ± 5.5	3.9 ± 5.3	5.4 ± 5.7	4.5 ± 5.4
T_{tot} bias, s	0.007 ± 0.589	0.000 ± 0.910	0.010 ± 0.511	0.009 ± 0.486	0.007 ± 0.650

Values represent means \pm standard deviation. T_{tot} = total respiratory cycle time.

Wilcoxon signed-rank tests showed that AHI underestimation by AirSense10, S.Box and Prisma20A were significant, in comparison with AHI_{PG} (Table 2). Even though AHI_{PG} and AHI_{PAP} were highly correlated (Fig. 2). Noteworthy, AI_{PAP} and AI_{PG} were very greatly correlated (Fig. 3). Agreements between AI_{PG} and AI_{PAP} were better than these of HI. No significant differences were observed from Wilcoxon signed-rank tests between AI_{PAP} of AirSense10, DreamStation, Prisma20A and AI_{PG} . $AI_{\text{S.Box}}$ was a little higher than AI_{PG} . All PAP devices underestimated HI compared to HI_{PG} (Fig. 4). The underestimation magnitude was manufacturer-dependent (Table 2). Linear regression analyses showed poor correlation regarding HI of DreamStation, Prisma20A with HI_{PG} . Whereas, there were no significant correlations between HI_{PAP} of AirSense10, S.Box and HI_{PG} (Fig. 4).



TABLE 2. Agreement Analyses between PAP Devices and Polygraph: AHI, AI and HI

	AHI			AI			HI		
	Bias (p-val)	r (p-val)	ICC (p-val)	Bias (p-val)	r (p-val)	ICC (p-val)	Bias (p-val)	r (p-val)	ICC (p-val)
AirSense10	-14.2 ± 9.0 (<0.001)	0.91 (<0.001)	0.75 (0.04)	0.0 ± 5.5 (0.16)	0.97 (<0.001)	0.97 (<0.001)	-14.2 ± 10.2 (<0.001)	-0.10 (0.62)	-0.02 (0.59)
DreamStation	-2.6 ± 7.3 (0.08)	0.94 (<0.001)	0.94 (<0.001)	3.0 ± 8.7 (0.07)	0.92 (<0.001)	0.91 (<0.001)	-5.6 ± 8.0 (0.002)	0.59 (0.002)	0.47 (0.001)
S.Box	-7.6 ± 8.5 (<0.001)	0.92 (<0.001)	0.87 (0.001)	5.0 ± 8.1 (<0.001)	0.94 (<0.001)	0.90 (<0.001)	-12.6 ± 10.2 (<0.001)	-0.03 (0.87)	-0.01 (0.54)
Prisma20A	-3.9 ± 7.3 (0.02)	0.94 (<0.001)	0.93 (<0.001)	2.8 ± 6.9 (0.08)	0.95 (<0.001)	0.94 (<0.001)	-6.7 ± 8.9 (0.002)	0.56 (0.02)	0.32 (<0.001)

Bias was calculated as the average difference between PAP and polygraph. Wilcoxon-signed-rank tests were conducted to examine whether AHI, AI, HI biases between PAP devices and polygraph were significant. A p value ≤ 0.05 is considered statistically significant. AHI = apnea hypopnea index; AI = apnea index; HI = hypopnea index; PAP = positive airway pressure; p-val = p-value; r = Pearson correlation coefficient; and ICC = intraclass correlation coefficient.



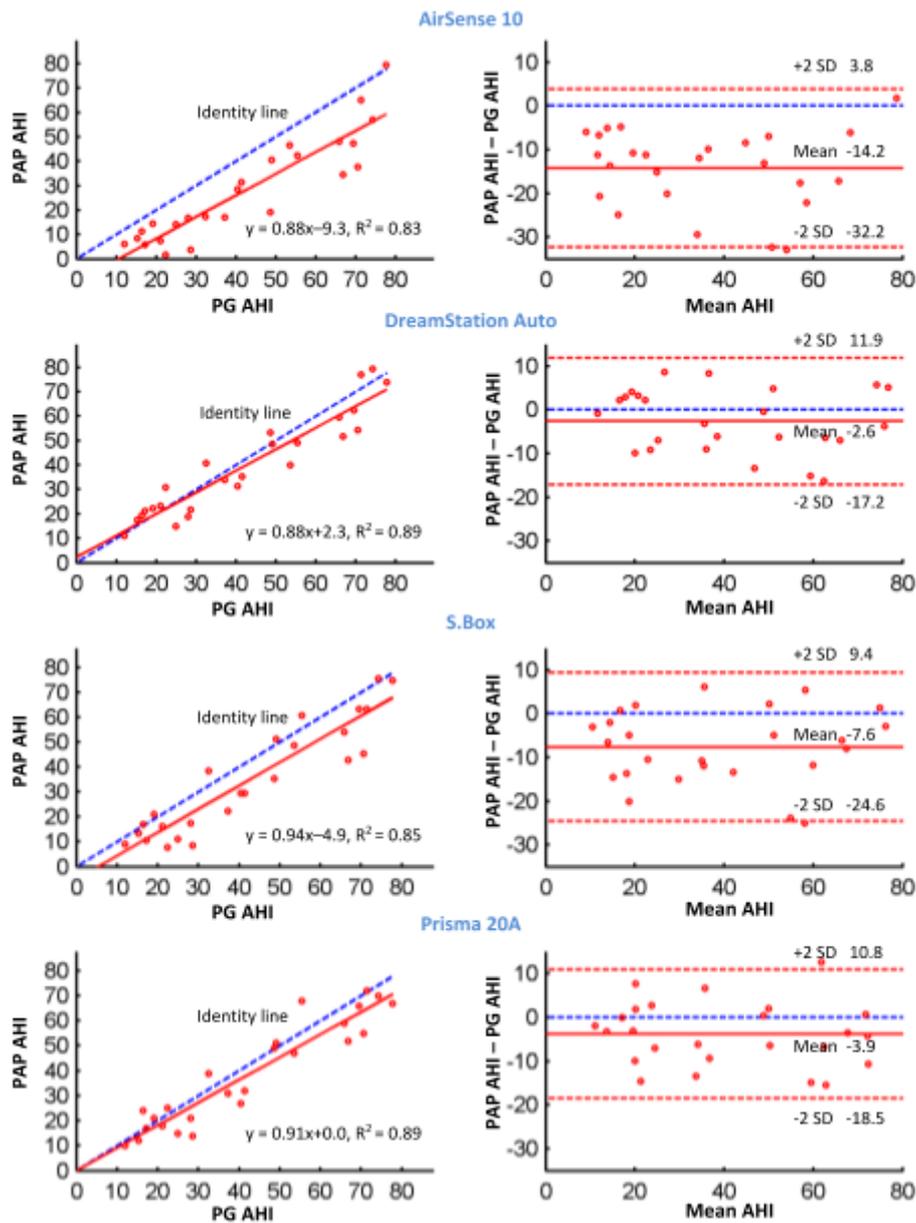


Figure 2 - Linear regression and Bland-Altman plots of apnea hypopnea indices detected by positive airway pressure devices with those determined by polygraph, regarding totally 25 polygraph-recording samples. PAP = positive airway pressure devices; PG = polygraph; and AHI = apnea hypopnea index.

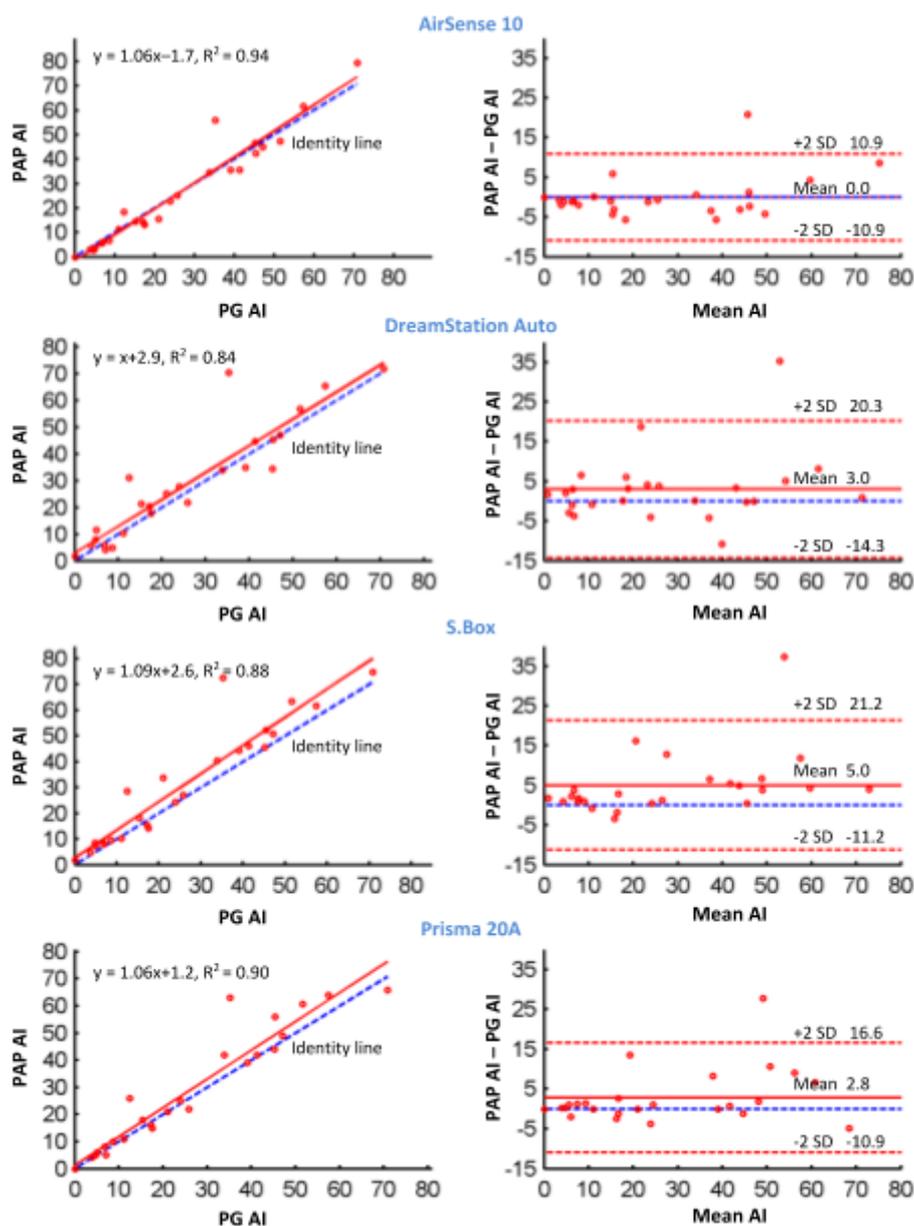


Figure 3 - Linear regression and Bland-Altman plots of apnea indices detected by positive airway pressure devices with those determined by polygraph, regarding totally 25 polygraph-recording samples. AI = apnea index. See Figure 2 legend for an expansion of other abbreviations.

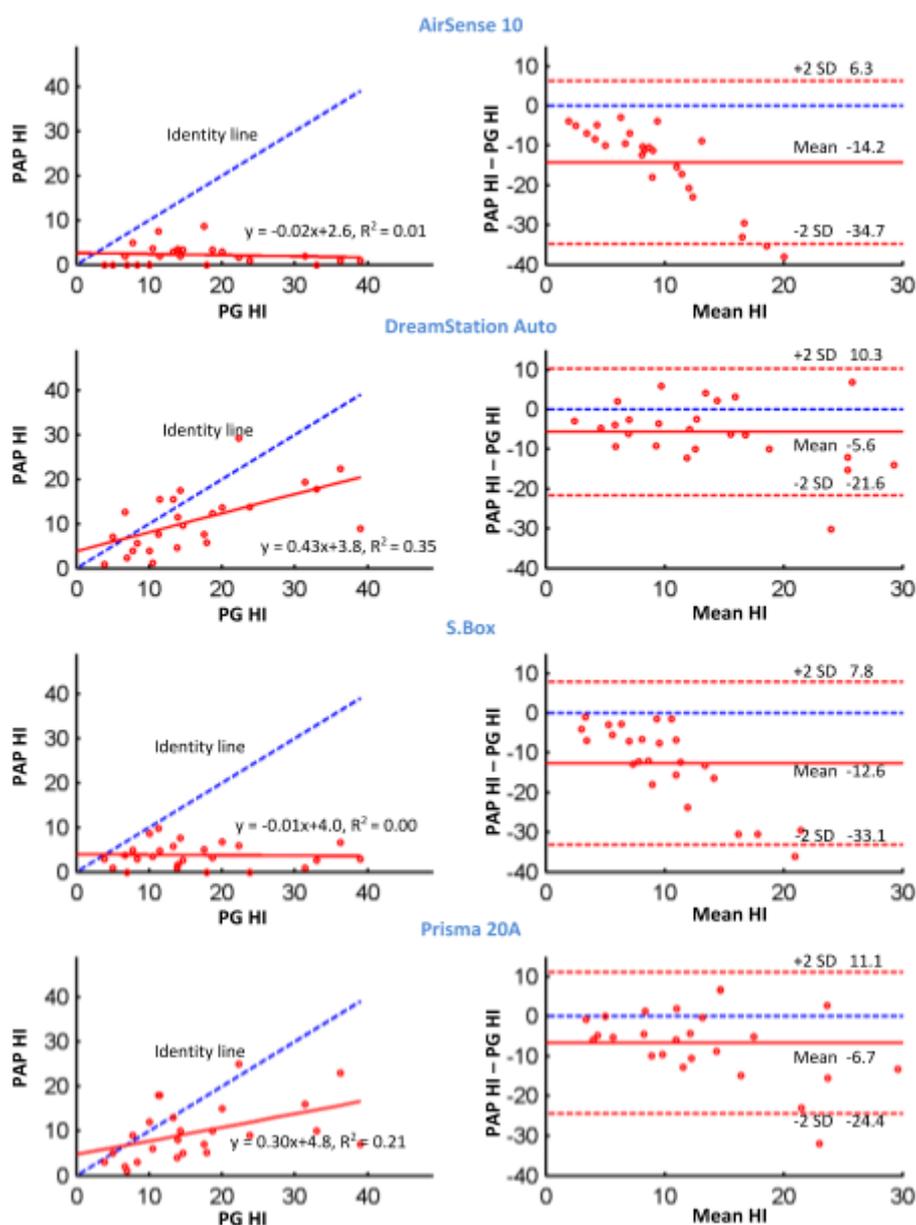


Figure 4 - Linear regression and Bland-Altman plots of hypopnea indices detected by positive airway pressure devices with those determined by polygraph, regarding totally 25 polygraph-recording samples. See Figure 1 and 2 legends for an expansion of abbreviations.

There was no correlation between simulation performance and device performance in detecting SDB. Corresponding Spearman's rank correlation coefficients were 0.12 ($p = 0.55$) for AirSense10, 0.04 ($p = 0.84$) for DreamStation, 0.26 ($p = 0.21$) for Prisma20A, 0.15 ($p = 0.48$) for

S.Box.

Consequently, from the multiple linear regression model, AHI_{PAP} were related to AI_{PG} and HI_{PG} , whereas they were not linked statistically with the bench simulation performance indicator (Table 3).

TABLE 3. Analysis of AHI_{PAP} Determinants by Multiple Linear Regression

	AirSense10 AHI		DreamStation AHI		S.Box AHI		Prisma20A AHI	
	Beta	p-val	Beta	p-val	Beta	p-val	Beta	p-val
Polygraph AI	0.97	<0.001	0.83	<0.001	0.92	<0.001	0.88	<0.001
Polygraph HI	0.11	0.05	0.45	<0.001	0.23	0.003	0.36	<0.001
Bench simulation performance	0.01	0.84	-0.02	0.78	-0.05	0.45	-0.08	0.28
R²	0.947		0.889		0.905		0.901	

Beta represents the weight of each input variable according to the multiple linear regression model. Variables were normalized by its own average and standard deviation before multiple linear regression analyses. p-val are for testing the null hypothesis that the coefficient Beta is equal to zero. A p-val < .05 indicates that we can reject the null hypothesis. AHI = apnea-hypopnea index; AHI_{PAP} = AHI determined by positive airway pressure devices; AI = apnea index; HI = hypopnea index; and p-val = p-value.

The accuracy of PAP devices in identifying breathing profiles with $AHI_{PG} \geq 30$ events/hour were 84% for AirSense10, 96% for DreamStation, 88% for S.Box and 96% for Prisma20A. Chi-square statistics showed that PAP devices' classification was dependent on the polygraph classification.

AHI_{PAP} Relationship between Manufacturers



According to the AHI_{PAP} transition matrix among different manufacturers (Fig. 5), they were correlated from one to another with coefficients of determination (R^2) greater than 0.75. More concretely, $AHI_{AirSense10}$ seemed to correlate more with $AHI_{S.Box}$ than with $AHI_{DreamStation}$ or $AHI_{Prisma20A}$, whereas $AHI_{DreamStation}$ correlated more with $AHI_{Prisma20A}$ than with $AHI_{AirSense10}$ or $AHI_{S.Box}$. $AHI_{S.Box}$ showed a slightly better correlation with $AHI_{Prisma20A}$ and $AHI_{AirSense10}$ than with $AHI_{DreamStation}$. $AHI_{Prisma20A}$ had a stronger correlation with $AHI_{DreamStation}$ and $AHI_{S.Box}$ than with $AHI_{AirSense10}$.

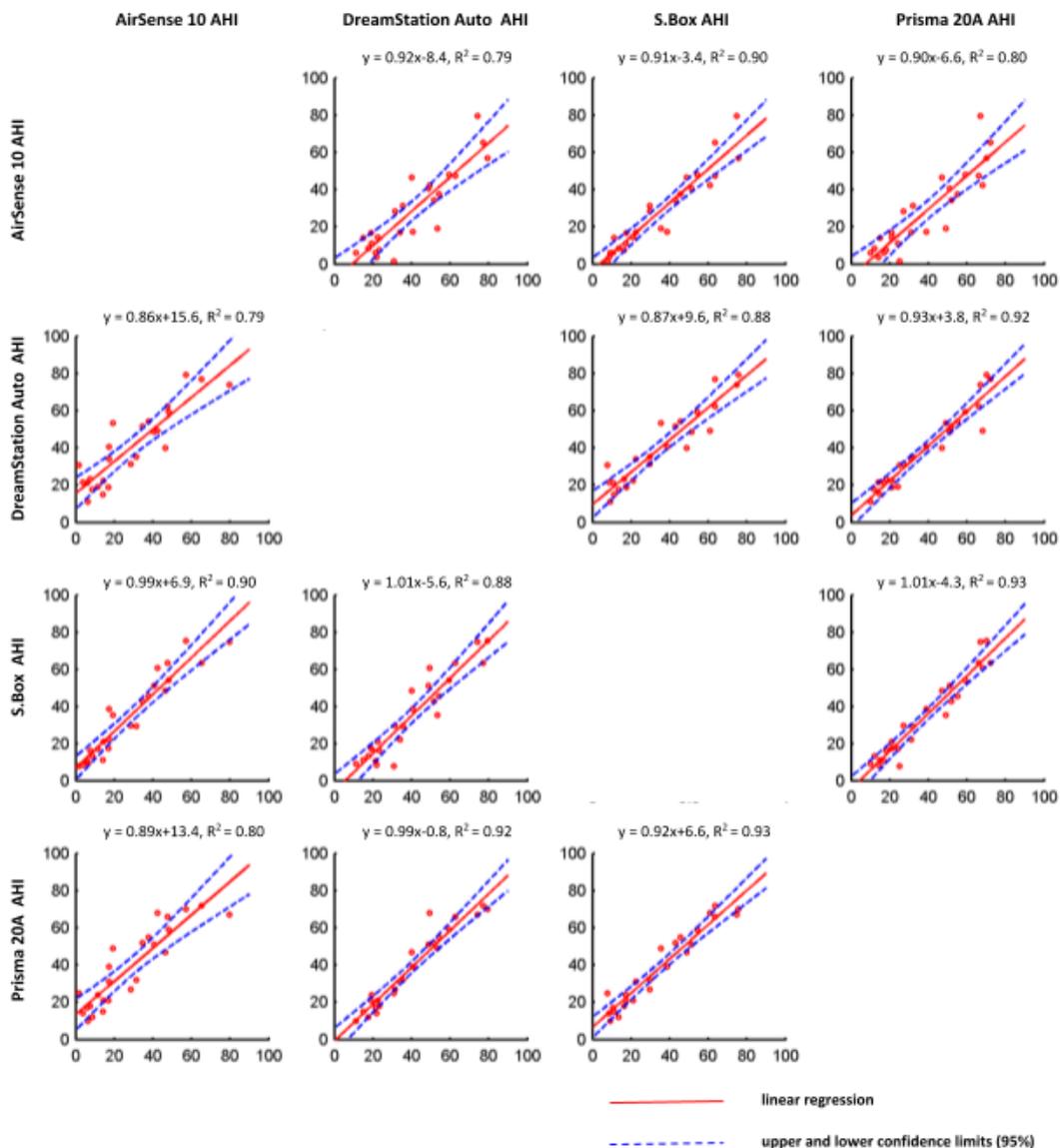


Figure 5 – Apnea hypopnea index transition matrix for switching from one device to another.

Linear regression analysis of apnea hypopnea indices was performed from each possible switch of the four different devices.

Discussion

To the best of our knowledge, this study was the first to evaluate AHI agreement between AASM scoring rules updated in 2012¹³ and algorithms embedded in PAP devices by using reproducible respiratory profiles. This was also the first application of our physiological bench testing which simulated breathing profiles of apneic patients with obstructive and central events by using their polygraph recordings.

AHI_{PAP} were highly and linearly correlated to AASM scoring rules, but still underestimated. This good correlation was largely attributed to a strong linear relationship between AI_{PG} and AI_{PAP}, whereas HI_{PAP} was not satisfactorily correlated with HI_{PG} and was underestimated. These findings were then consolidated by the AHI agreement analysis between polygraph and PAP devices scorings, which showed a better agreement, namely a lower bias, in AI than in HI as well. HI underestimation by PAP devices could be explained by two factors. Firstly, hypopneas scored with polygraph may be considered as normal breathing in PAP devices, rather than detected as flow reduction. Indeed, PAP devices lack physiological measures such as arterial oxygen saturation and EEG to score hypopneas. Thus, PAP device manufacturers may have opted for a higher airflow reduction threshold than AASM rules to avoid hypopneas over-detection. Secondly, the airflow reduction threshold of apneas used in PAP devices may have implied an easier classification of respiratory events as apneas, compared to AASM rules, which resulted in categorizing a



few hypopneas as apneas. Nevertheless, the severity of HI underestimation also varied among PAP devices of different manufacturers. This is to be interpreted with respect to the differences in the scoring rules for each device, particularly the airflow reduction thresholds for hypopneas and other different parameters involved in the baseline calculation, such as window length, feature selection like airflow peak-to-peak amplitude, or minute ventilation as an example. It was noteworthy that when we designed our SDB scoring algorithm based on airflow analysis, we were confronted with various choices in calculating the airflow peak-to-peak excursion baseline. These choices resulted in different hypopnea-scoring results, especially during periods with continuous breathing events. For example, the number of cycles taken in account, the choice between median, mean or a specific percentile to characterize the peak-to-peak excursion baseline feature, significantly influenced the scoring results. Each manufacturer should have made their own choices. Moreover, manufacturers may have added some other features in hypopnea scoring rules. For example, the manufacturer of AirSense10 claimed usage of airflow pattern. Indeed, $HI_{AirSense10}$ takes in account only hypopneas, which are associated with inspiratory flow limitations and thus are considered as obstructive. Apart from algorithm differences, airflow signal quality was also not the same, for example, sampling frequency varied from 5 to 25 Hz depending on manufacturer. This may enhance AHI_{PAP} determination discrepancy.

Of noteworthy interest, the linear relationship and agreement between AHI_{PAP} and AHI_{PG} depended on both AI and HI. The more the AHI_{PG} was linked to AI_{PG} , the better the AHI_{PAP} was correlated to AHI_{PG} . PAP devices displayed better performance in calculating AI rather than HI. This might have an impact on the follow-up of patients characterized by a residual hypopnea predominance. For example, OSA patients with asthma are more like to express this phenotype. Literature shows that their HI account for approximately 75% of the total AHI ¹⁴. Patients with heart failure¹⁵ or those who develop emergent central events after setting up PAP treatment may



also present a non-neglectable amount of hypopneas.

In the literature, some studies have evaluated SDB detection agreements between PAP devices from Philips-Respironics or Resmed, and PSG⁵⁻⁹. Their findings were in accordance with ours. Indeed the AHI, AI, HI determined from PAP devices and poly(somno)graph were linearly correlated and AI agreements were better than HI. Nevertheless, there was a little discrepancy in HI determination for different PAP device generations of Resmed: S8 auto-CPAP tended to overestimate HI compared to PSG,^{7,8} whereas S9 CPAP⁹ had a tendency to underestimate PSG HI. This difference might be due to the algorithm update between S8 and S9, which began to prevent the scoring of hypopneas that were not considered obstructive.

A recent task force of the American Thoracic Society (ATS) recommended that the indices from PAP devices need to be designated with a subscript 'flow', since their scoring rules are different from that AASM recommendation¹². Concerning differences in AHI determination rules used by PAP device manufacturers, care providers were recommended to be familiar with them in order to interpret residual events reported by each PAP device in an optimal manner¹². For a concrete example, when switching the treatment device for a patient from one manufacturer to another, caregivers might need to know how to interpret the difference in AHI determined by the two PAP devices. This could be a difficult task because the modification in AHI could be a combination of different treatment efficacies and different SDB detection algorithms used in the PAP device. Our proposed transition matrix may be a useful reference for clinicians and caregivers to address this issue.

Compared to clinical studies, our methodology used a physiological bench to simulate patient SDB profiles, which provided the means to limit the impact of breathing profile variability on device comparisons. Indeed, in clinical studies comparing different PAP devices, observed behavioral differences might be due to not only to algorithm differences between devices,



but also the various breathing profiles from night-to-night used to test different PAP devices. A typical breathing phenotype could vary in an intra-patient and interpatient manner. Meanwhile, our bench test did not compromise on physiological variability, in comparison with real patients.

Compared to previously published studies, which focused tightly on the agreement of AHI between PAP devices and PSG for OSA patients, our findings should be more relevant for patients who are affected by coexisting OSA and CSA, for example, patients concurrently having comorbidities of obesity hypoventilation syndrome¹⁶, heart failure¹⁷, etc. Moreover, the ranges of AHI (42.3 ± 21.7 events/h), AI (25.9 ± 19.6 events/h) and HI (16.5 ± 9.8 events/h) we simulated on bench were larger than previous studies in the literature. Indeed, past studies evaluated residual breathing event agreement between PAP devices and PSG during CPAP titration process with PSG. Consequently, the majority of obstructive breathing events were treated by PAP. This study could be complementary to those, because we prevent PAP devices to have any treatment action. Our approach presents an opportunity to evaluate how devices differ from one another, without any interference in terms of AHI range magnitude.

In this study, the patient sample size with an overlap between OSA and CSA was relatively small, consisting of four patients. However, the 25 corresponding recordings chosen gave a wide range of AHI (from 10 to 80 events/hour) and CAI was increasing with AHI as well. Thus, as a first attempt to assess PAP devices with this methodology, our samples could be considered as well balanced and representative of miscellaneous challenging situations.

We chose to evaluate the discrepancy in the related apnea hypopnea indices among different PAP devices tested at 4 cmH₂O. It is likely that this discrepancy would not be the same if all devices were set at an efficient pressure that allowed treatment of all obstructive respiratory events. However, this does not jeopardize our comparisons demonstrating that differences do exist among devices from different manufacturers.



Conclusion

In conclusion, AHI determined by PAP devices may not be an absolute indicator of real AHI in OSA patients with residual or emergent central sleep events. The difference in residual AHI among manufacturers is important, especially concerning hypopneas. Accordingly, switching from one device to another, treatment efficiency may be biased by the SDB detection algorithm in cases of AHI interpretation from different manufacturers. Thus, our study reinforces the need for a poly(somno)graph examination during PAP treatment initiation and follow up, which represents an essential step for ensuring treatment efficiency, while waiting for a standardization of AHI_{flow} among manufacturers as suggested by ATS.¹²

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5.2 Summary

In this study, we evaluated the apnea hypopnea index agreement between four positive airway pressure devices and polygraph through a physiological bench, which permitted simulating automatically the breathing profiles registered in polygraph recordings with use of mainly an active lung simulator and a Starling resistor for modeling upper airway obstruction, while connected to a 4 cmH₂O source pressure.

We used twenty-five 1-hour polygraph samples issuing from the whole-night respiratory polygraph recordings of four patients diagnosed with predominant central sleep apnea syndrome. According to polygraph analyses, the AHI (events/hour) of these recording samples varied from 12 to 77.7 with mean (Std) of 42.3 (21.7). Apneas were predominant to hypopneas (55.3% versus 44.7%) and central apneas represented 55.8% \pm 27% among all types of apneas. Then we simulated each polygraph sample four times on bench, with a connection to a different PAP device each time. They were all set to 4 cmH₂O in order to rule out treatment effects. The bench-simulated airflow presented a good similarity to this of patients' (amplitude bias: 4.5 \pm 5.4%; total respiratory cycle time bias: 0.007 \pm 0.650 s).

The bench simulation results showed that AHI_{PAP}, AI_{PAP} determined by PAP devices were linearly correlated to the polygraph scorings AHI_{PG} ($r^2 = [0.83; 0.89]$), AI_{PG} ($r^2 = [0.84; 0.94]$), especially great for AI. The linear relationship between HI_{PAP} and HI_{PG} was much weakened ($r^2 = [0.00; 0.35]$), compared to this of AI. The agreement in AI between PAP devices and polygraph was better than this of HI as well. More concretely, all the four tested PAP devices had a tendency to underestimate HI_{PG} (mean HI_{PG} \pm Std: 16.5 \pm 9.8 evts/hour). Nevertheless, the severity of HI_{PG}



underestimation varied among PAP device manufacturers, which meant that HI determined by PAP devices were not equivalent.

In conclusion, the AHI given by PAP devices may not be an absolute indicator of the realistic AHI for patients with predominant CSA. Therefore, regular poly(somno)graphy examinations after initiation of PAP therapy are important for monitoring patient health status. While switching from a PAP device to another of a different manufacturer, AHI interpretation needs take into account discrepancies of algorithms used by different manufacturers.



Chapter VI. Discussion

The physiological bench developed in this project should be the first one capable of reproducing automatically the breathing profiles of patients affected with sleep apnea syndrome, which are registered in polygraph recordings, according to literatures. The bench reached a great simulation performance, while regarding the similarity between patient breathing airflow and the bench-simulated airflow in terms of airflow intensity, morphology and temporal parameters. In the meantime, it reproduced patients' various SDB events of obstructive and central mechanisms with a satisfying sensitivity and PPV as well. Furthermore, it has also been proved robust in simulating the breathing profiles of diverse phenotypes.

A physiological bench like this allows saving expensive and time-consuming clinical trials, in order to find an optimal PAP device for a specific patient. It also permits comparing PAP devices of different manufacturers under the same physiological conditions, which is indeed not allowed throughout clinical studies. Although this physiological bench has many advantages, it has some limitations like that it cannot react in the same manner as a patient concerning its physiological responses to an increased pulmonary volume and a decreased PaCO_2 , following the pressure increases delivered by PAP devices.

In this chapter, we would like to discuss firstly the technical difficulties that we have encountered during the development of this polygraph-based physiological bench, the solutions that we have brought to try to guarantee that the bench-simulated breathing profile represented a patient's own SDB phenotypes. Only in this approach can the PAP device test results



acquired on bench be better applied to a specific patient for helping choosing an optimal APAP algorithm. Then we will discuss the possible reasons that we think could be relevant to explain the discrepancies between HI determined by different PAP devices. In the next step, we would like to talk about what we have observed on bench about PAP device characteristics, which are specific to each manufacturer for qualifying patient's mixed apneas. Finally, we will approach various perspectives of this new physiological bench.



6.1 Validity of a novel bench-simulation approach from polygraph recordings to reproduce automatically the breathing profiles registered

As APAP algorithms are becoming more and more intelligent and probably adapt treatment strategy to each patient breathing characteristics in the next few years with the benefit of big data, this underlines the need to render the bench test more physiological as well. This is why in this thesis a novel approach to a physiological bench was developed, aimed at reproducing automatically on bench apneic patient breathing profiles registered in polygraph recordings during the diagnostic examination. Our methodology was based on creating an algorithm, which used patient polygraph recordings as inputs and calculated automatically the digital inputs necessary for commanding bench hardware composed by an active lung simulator and an upper airway obstruction model. This permitted simulating automatically the breathing profile of any patient affected by sleep apnea syndrome (SAS) on bench, while taking into account their individual breathing phenotypes at the same time.

According to the literature up to now, the hardware used to simulate breathing profiles of patients affected by SAS consists generally of an active lung simulator and an upper airway obstruction model (for example, a Starling resistor). Ideally, the active lung simulator needs to be driven by patient respiratory muscular effort pressure. The resistance set in the upper airway model needs to approach that of patient as well. However, it is difficult to measure these parameters directly from the patient in a non-invasive manner. With polygraph recordings, we could know about patient's sleep position, breathing airflow, presence of respiratory muscular effort pressure, arterial oxygen saturation, snoring as well. We could not have access to the respiratory muscular effort pressure or the upper airway resistance directly, which thus set up an obstacle for simulating on bench the breathing profiles contained in polygraph recordings. Therefore, the algorithm



developed by us enabled estimating and deriving this implicit information from polygraph data for bench simulation. More concretely, by analyzing polygraph signals, the algorithm firstly detected different disordered breathing events and characterized their mechanisms as well. Then it estimated patient non-obstructive breathing airflow issuing from central command and the obstruction level in upper airways, based on patient's nasal airflow and previously identified SDB events. During central breathing events and normal breathing, the breathing airflow issuing from central command was assumed identical to patient nasal airflow, and the resistance in patient upper airways was assumed at minimum. On the contrary, during obstructive breathing events, the central command airflow was estimated by referring to the nasal airflow during the pre-event 2 minutes, and the obstructive level in upper airways was then assessed by comparing patient actual nasal airflow to its estimated central command airflow. The respiratory muscular effort pressure used for commanding the artificial lung could then be derived from patient central command airflow, and pulmonary parameters (compliance, opening airway resistance) set in artificial lung. The demanded Starling resistor's resistance for each obstructive breathing cycle was calculated according to the relationship between the central command breathing airflow generated by the artificial lung (under the condition of a minimal resistance set in Starling resistor) and the resulted bench airflow amplitude from applying various resistance levels in Starling resistor.



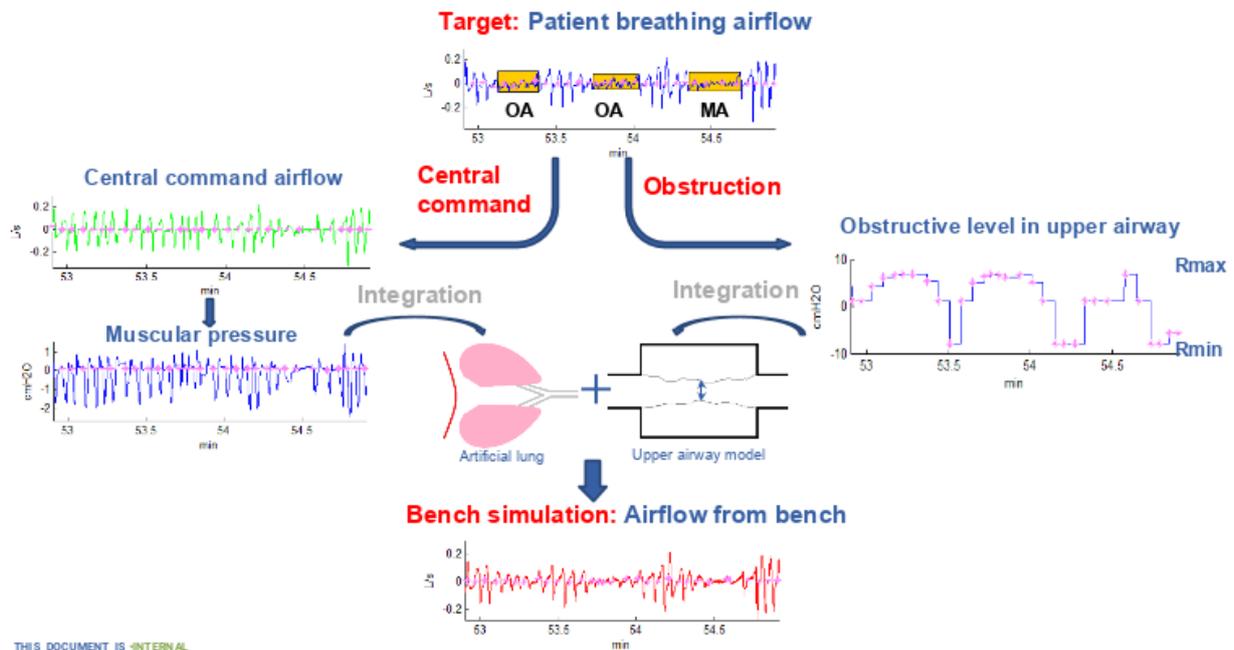


Figure 3-1: A novel bench-simulation approach from polygraph recordings to its breathing profile reproduced automatically on bench. OA: obstructive apnea; CA: central apnea.

6.2 Justification of methodology choices in polygraph signals processing

As described in chapter 3, the algorithm used for analyzing polygraph signals was mainly composed of 6 signal processing steps while totally taking 7 polygraph signals (acceleration, nasal pressure, thermistance or alternatively RIP flow, RIP thorax & abdomen, SpO₂ and audio volume) as inputs:

- Step 1: signal pre-processing: resampling and filtering
- Step 2: automatic segmentation of stable periods by using acceleration signal
- Step 3: identification of breathing cycles
- Step 4: detection of apnea events and identification of significant breath attempts
- Step 5: detection and characterization of hypopnea events
- Step 6: calculation of digital inputs for integration into bench hardware

Some justifications of certain choices made in steps 3-6 are described as follows.

6.2.1 Justification of methodology choices related to polygraph signals processing step 3

6.2.1.1 Why does identification of breathing cycles consist in an important step before bench simulation?

As described previously, we mainly used an artificial lung and an upper airway model Starling resistor to replicate the nocturnal breathing profile of patients affected by sleep apnea syndrome. The artificial lung was set in an active lung mode, modeled by a compliance (pulmonary compliance) and a resistance (airway resistance) connected in series and driven by respiratory muscular effort pressure, in order to mimic patient lung movement in a physiological manner. Starling resistor served for mimicking upper airway obstruction. In fact, there was a



technical constraint about the synchronization between Starling resistor's resistance and pulmonary movement simulated in the artificial lung: the Starling resistor's resistance could only be varied once per breathing cycle and this was triggered by the transistor-to-transistor logic (TTL) signal sent from the artificial lung at the beginning of a breath. Thus, it was considered as important that patient's upper airway resistance could be determined for each breathing cycle in order to better mimic patient's SDB breathing profile on bench with taking into account cycle by cycle obstructive and central characteristics. To achieve this objective, each breathing cycle needs firstly be identified.

6.2.1.2 Why is breathing cycle identification mainly based on nasal airflow?

We chose to mainly use patient's nasal airflow (V_n' , 20Hz) to detect breathing attempts, as our objective was to reproduce patient nasal airflow on bench, in the meantime taking into account their cycle-by-cycle obstructive and central characteristics. The nasal airflow was estimated as the square-root of patient nasal air pressure, which was measured with nasal cannula during polygraph examination. We decided simulating patient nasal breathing profile on bench instead of its oronasal breathing profile by considering that the signal measured by the oronasal thermal airflow sensor was not proportional to flow. According to patient's nasal airflow excursion, 2 different breathing cycle identification methods were applied. During periods with high excursion values in V_n' , breathing onset positions were directly determined as the inflection point in V_n' between expiratory minimal and inspiratory maximal values respecting the order of two consecutive cycles. However, during low excursion periods (a reduction greater than 65% compared to two-minute pre-event baseline), breathing onset positions were inferred from RIP signals.

6.2.1.3 Why is the automatic multiscale-based peak detection algorithm selected to detect peaks (valleys) in nasal airflow?



We firstly detected peaks and valleys in V_n' using an algorithm developed by Scholkmann et al. for automatic multiscale-based peak detection (AMPD) in noisy periodic or quasi-periodic signals. We preferred this algorithm because it could automatically identify the appropriate local maximum in case of several local maximums occurring in a same breathing cycle, without requirements of setting a parameter before, compared to the findpeaks function in Matlab. However, the computational complexity of this algorithm was not very optimal. It was in the order of n^2 where n represents the number of data samples in a signal. Considering this, we applied this algorithm in each 3-minute window with two peaks (valleys) overlap to save computation time. Observing the detection results, sometimes, we found some non-detected peaks and valleys. These could be due to the airflow artifact or breathing instability in certain periods, which broke the quasi-periodic pattern of the signal. So we added a step to check whether there were any missed cycle detection by detecting oscillation around zeros values. The newly added peak (valley) needed also satisfy both amplitude and temporal threshold compatible with a respiratory cycle. The amplitude threshold was defined as at least 10% of a closest previously detected peak (valley) amplitude. Then the time interval between the newly added peak (valley) and two adjacent valleys (peaks) should be both greater than 1.5 seconds. The upper envelope and lower envelope of V_n' were obtained by interpolating peaks and valleys. And the excursion was calculated as the difference between the upper envelope and the lower envelope.

6.2.1.4 How are breathing onset points in nasal airflow during periods without highly reduced excursions determined?

The inflection point in the nasal airflow valley-to-peak segment during periods without highly reduced excursions was determined by regarding the absolute ratio between slopes calculated respectively by fitting the following 7 points and the precedent 7 points with linear



regression. This meant that we did a linear regression in a window of 7 consecutive points. And the window moved forward 1 point each time. Then the inflection point was assigned to the point where this ratio was the biggest, and in the meantime, its absolute amplitude should be inferior to 10% of the difference between peak and valley amplitudes.

6.2.1.5 How is the reference RIP signal chosen for each reduced nasal airflow excursion period to aid in breath onsets' positions determination?

Since we had 2 RIP signals (RIP thorax & RIP abdomen), the reference RIP signal used for inferring breathing onsets during a period with highly reduced V_n ' excursion was chosen according to the following detailed criteria:

- a. Firstly, we calculated the amplitude average of 5 valleys prior to the highly reduced V_n ' excursion period ($A_{\text{valley_prec}}$), the amplitude average of all valleys inside the highly reduced V_n ' excursion period ($A_{\text{valley_in}}$), as well as the amplitude average of all peaks inside the highly reduced V_n ' excursion period ($A_{\text{peak_in}}$) for RIP thorax and RIP abdomen.
- b. If $|A_{\text{valley_in}} - A_{\text{valley_prec}}|$ was bigger than $|A_{\text{peak_in}} - A_{\text{valley_prec}}|$ for one RIP signal whereas it was the opposite for the other RIP signal, the second one was assumed more likely to be in the same phase as patient respiratory muscular effort. So we used this RIP signal as the reference.
- c. Otherwise, the reference signal was attributed to the signal with a higher relative amplitude modulation compared to pre-segment 2-minute amplitude modulation baseline during the reduced excursion periods.



The time indices of valleys in the reference RIP signal were assumed to be patient breathing onset time during highly reduced V_n' excursion periods. Thus the corresponding breathing onset time(positions) in V_n' during highly reduced excursion periods were determined.

6.2.1.6 How are the breath attempts during highly reduced nasal airflow excursion periods identified with use of RIP thorax&abdomen signals?

The peaks and valleys in RIP signals were detected in a similar manner as in V_n' . Firstly, we used the AMPD algorithm to detect peaks and valleys in each 3-minute window with two peaks (valleys) overlap. During obstructive or central breathing events, the amplitudes in RIP signals could be highly reduced. Thus the signal to noise ratio were also decreased. Peak and valley detections in those periods were often influenced by signal noise. To avoid detecting excessive peaks and valleys due to the signal noise, we added a step of filtering peaks and valleys. We calculated the RIP signal excursion. The selected peak should satisfy that its excursion value was greater than 10% of 60 percentile among the corresponding excursion values of all peaks identified within precedent 1-minute. The reason that we used the 60 percentile representing excursion baseline is for the consideration of ruling out the effect of greater amplitude during initial ventilation recovery phase as well as the reduced amplitudes during SDB events. There could be only one valley between 2 adjacent peaks. So we conserved only the valley whose excursion value was the lowest in case of more than one valleys between two adjacent peaks.

6.2.2 Justification of methodology choices related to polygraph signals processing step 4

Why are apneas detected based on nasal airflow instead of nasal pressure or the oronasal thermistance?



We detected apnea events based on V_n ' signal, although American Academy of Sleep Medicine (AASM) rules recommend using oronasal thermal airflow to score apneas. We chose to use V_n ' instead of oronasal thermal airflow because firstly in several patients polygraph recordings, the oronasal thermal airflow was not available. Secondly, as we simulated SAS patient breathing profile on bench for the purpose of testing the algorithm performance in PAP devices. Based on the fact that SAS patients usually wear a nasal mask to receive PAP therapy, therefore it should make more sense that we used V_n ' to detect apneas and simulated patient nasal breathing profile on bench.

6.2.3 Justification of methodology choices related to polygraph signals processing step 5

6.2.3.1 Why are the hypopneas detected on the basis of nasal airflow instead of nasal pressure?

Hypopnea events were detected in our algorithm according to the scoring rules of AASM updated in 2012. It required a reduction in nasal airflow excursion greater than 30% as well as an oxygen desaturation greater than 3% compared to the pre-event 2-minute baseline. We used nasal airflow excursion instead of nasal pressure excursion to detect hypopneas in consideration that we aimed to simulate patient nasal airflow on bench.

6.2.3.2 How are the hypopneas' properties characterized?

We followed the AASM rules updated in 2012 to classify hypopneas as well. The methods used for phase shift detection and snoring detection are detailed below. And we used the methodology invented by Zhi et al for inspiratory flow limitation detection.

Phase Shift Detection



To identify the thoraco-abdominal phase shift in hypopneas, the algorithm was based on the temporal correspondence between RIP thorax peaks and RIP abdomen peaks. For example, $\{B_1, B_2, \dots, B_k\}$ were k breathing cycles contained in the hypopnea. The corresponding time coordinates of peaks occurring in RIP thorax signal and RIP abdomen signal were respectively $\{t_{th_1}, t_{th_2}, \dots, t_{th_k}\}$, $\{t_{ab_1}, t_{ab_2}, \dots, t_{ab_k}\}$, assuming one peak per cycle. Then for every RIP thorax peak occurring time t_{th_i} , there were 4 time coordinates in RIP abdomen corresponding to t_{th_i} : the last RIP abdomen peak occurring time prior to t_{th_i} , named t_1 , the last RIP abdomen valley occurring time prior to t_{th_i} , named as t_2 , the first RIP abdomen peak occurring time posterior to t_{th_i} , named as t_3 , the first RIP abdomen valley occurring time posterior to t_{th_i} , named as t_4 . the algorithm calculated the minimal value from $\{|t_1 - t_{th_i}|, |t_2 - t_{th_i}|, |t_3 - t_{th_i}|, |t_4 - t_{th_i}|\}$. If the minima corresponded to the time interval between an abdominal valley and that thoracic peak, the algorithm noted “0” for the i th cycle in a vector named *thorax_peaks_correspondence*, otherwise, it noted “1”. In the same way, the algorithm calculated a vector *abdomen_peaks_correspondence*. If 2 consecutive “0” occurred in either *thorax_peaks_correspondence* or *abdomen_peaks_correspondence* vector, or there were “0” for the same breathing cycle in both *thorax_peaks_correspondence* and *abdomen_peaks_correspondence* vectors, the algorithm considered that the thoraco-abdominal phase shift took place in the hypopnea.

Snoring Detection

Audio volume signal of 20 Hz was used for snoring detection. The snoring detection algorithm was based on finding an adaptive threshold in frame of 5 seconds with 99% overlap to decide if the data in the middle of the frame is significantly bigger than the two sides. The detailed procedures for analyzing a data frame composed of $\{d_0, d_1, d_2, d_3, \dots, d_{98}, d_{99}, d_{100}\}$ were as follows:



- a. Compute the median of the data frame noted as d_{median} .
- b. Separate the data frame into 2 sub data frames df_1 and df_2 : $df_1 = \{d_0, d_1 \dots d_{48}, d_{49}\}$, $df_2 = \{d_{51}, d_{52} \dots d_{100}\}$. In each sub data frame, calculate the standard deviation (SD) of every 30 data with moving one data forward every time. Therefore, there are 21 standard deviation values in each sub data frame. We note the minimal standard deviation value in each data frame as $SD_{\text{min}0-49}$ and $SD_{\text{min}51-100}$. Calculate an average value between $SD_{\text{min}0-49}$ and $SD_{\text{min}51-100}$, named as SD_{min} .
- c. If $d_{50} - d_{\text{median}} > 13 * SD_{\text{min}}$, then the time of sampling d_{50} is considered as a time point when patient snoring (figure 5(B)).

To regroup all snoring time points detected into cycles, a maximal time interval between two consecutive snoring time points was set as 1 second. So if the time interval between two consecutive snoring time points was bigger than 1 second, the two snoring time points were assigned to 2 different breathing cycles (figure 6-2).



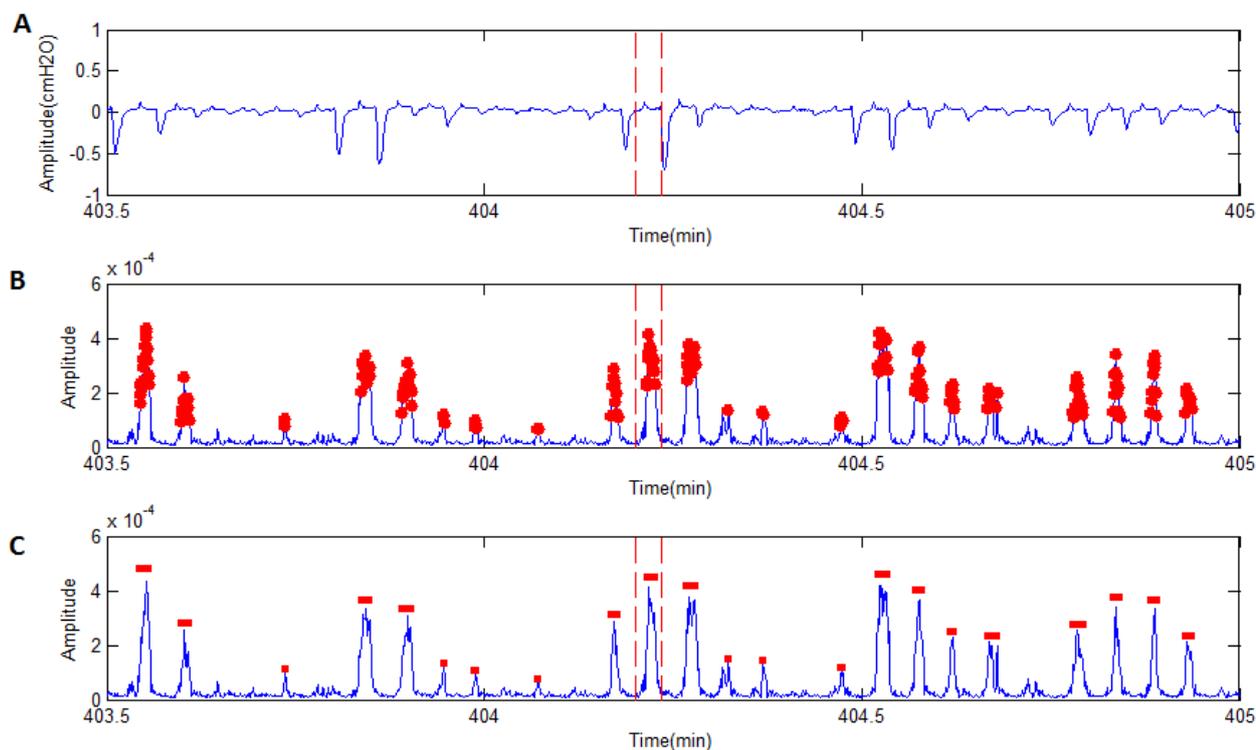


Figure 6-2: An example of snoring detection from audio volume signal.

A) nasal pressure. B) audio volume, wherein data surpassing adaptive threshold marked in red points. C) audio volume, wherein data surpassing adaptive threshold regrouped by respiratory cycles, marked by red bars. Red dashed vertical lines highlight the snoring detected during the inspiratory phase of one respiratory cycle.

6.2.4 Justification of methodology choices related to polygraph signals processing step 6

The digital inputs used for driving bench hardware were calculated in two different approaches, depending on breathing cycles' characterization (obstructive / non-obstructive).

Considering non-obstructive cycles (i.e. normal breathing or central breathing events), their respiratory muscular effort pressure data was directly derived from the patient's nasal airflow, which corresponded to the airflow aimed to be reproduced on bench as well. The resistance in Starling resistor was then set at minimum for these cycles.

During obstructive cycles, as patient's breathing airflow issuing from central command could not be known from its polygraph recordings, we assumed that it was in the same amplitude scale as the pre-event 2-minute nasal airflow amplitude baseline. Then the respiratory muscular effort pressure of obstructive cycles was derived from this estimated non-obstructive nasal airflow (also named as airflow of central command in this thesis). Although in reality, patient's muscular effort pressure during obstructive events perhaps decreases to a more negative value than the ones of precedent normal breathing, our assumption and simulation should not impact the PAP device responses to patient's obstructive events as long as its increased upper airway resistance and limited inspiratory airflow pattern were reproduced on bench. The sealed chamber pressure (P_{ch}) regulated in Starling resistor for obstructive cycles was a function of patient's estimated non-obstructive airflow and its nasal airflow (i.e. the desired bench airflow resulting from a proper resistance applied in Starling resistor). The relationship between different levels of non-obstructed airflow produced by the corresponding muscular effort pressure entered in the active lung simulator, and the resulting bench airflow after application of various P_{ch} was studied via an experimental matrix, in which the upstream pressure of Starling resistor was set at 4 cmH₂O.

Of noteworthy, the P_{ch} could only be constant within a cycle and changed once at the beginning of each breathing cycle due to the material constraints. Therefore, patient's upper airways resistance variation within a breathing cycle was not taken into account on this bench.



6.3 Bench limitations in simulating a specific patient breathing profile from polygraph recordings

The capability to simulate any apneic patient breathing profile on bench from its polygraph recordings permits evaluating different APAP algorithms under the same physiological conditions, and finding more easily an optimal treatment device for a specific patient, in comparison with expensive and time-consuming clinical trials. Nevertheless, we need also keep in minds that so far, the breathing profile simulated on bench could not be completely the same as each patient's physiological behaviors. This is mostly due to that some physical information are difficult to be measured invasively through poly(somno)graph recordings, for example, patient's lung compliance, respiratory muscular effort pressure, airway resistance, pharyngeal critical closing pressure etc. Moreover, we could not know patient's variations of PaO_2 , PaCO_2 , and ventilatory drive stability, in front of an increased pulmonary volume induced by an elevated upper airway pressure. Therefore, the arrangement of SDB simulated on bench does not take into account patient's pathophysiological reactions to physical parameters' changes caused by PAP device's pressure. It remains the same to this registered in the diagnostic examination through a polygraph, in terms of the respiratory muscular effort pressure and the sealed chamber pressure (i.e. the simulated upper airway closing force) set respectively in the active lung simulator and in the Starling resistor. However, this should not jeopardize the accuracy of bench's recommendation about the PAP device, which should be suitable to treat a specific patient, because bench test results can provide us detailed information about whether a PAP device is capable to detect various phenotypes of SDB in a specific patient, and to deliver an efficient and optimal pressure. Despite the efficient pressure of bench is probably different to the one of the patient, a PAP device, which is able to provide an efficient and optimal



pressure for overcoming bench-simulated obstructive SDB, will also be able to achieve the almost same performance while treating the patient.

Another limitation is that the upper airway status simulated on bench during central or mixed SDB events could have a discrepancy from the ones in patients. Because patient's upper airway status is not monitored during poly(somno)graph recordings, we cannot know whether its upper airway is open throughout the SDB of central mechanism. Badr et al. used a fiber-optic nasopharyngoscopy to view pharyngeal patency of central apneas and observed that the upper airway was completely occluded during a majority of central apneas without requirement of sub atmospheric intraluminal pressure in patients with sleep apnea syndrome (Badr, Toiber, Skatrud, & Dempsey, 1995). For now, we set the resistance of the upper airway model to minimum while simulating patients' central SDB events or the central part of mixed SDB events. In the next step, we could also change the resistance to maximum while simulating central apneas or the central portion of mixed apneas to verify whether PAP devices will be able to detect the occlusion and open the upper airway model.

Moreover, hypopneas were detected in our custom-made algorithm through polygraph data analyses, with regard to patient's breathing airflow, arterial oxygen saturation. We did not have access to patient's arousals through polygraph data. Therefore, the hypopneas scored from polygraph data might lack some hypopneas, appearing with micro-arousals. This could lead to that the number of obstructive hypopneas simulated on bench with a partially collapsed upper airway model was less than the real obstructive hypopneas' number of a patient as well. Furthermore, we have noticed a phenomenon that patient's inspiratory airflow limitation can persist during some periods of sleep without inciting a decrease in oxygen saturation greater than 3% while regarding patient's polygraph data. We simulated these breathing periods with a completely open



pharyngeal model, despite flattened inspiratory airflow shapes are a strong sign of an increased upper airway resistance compared to a sinusoidal shape. And we did not simulate patient's snoring on bench neither. Therefore, we think of implementing two other versions of the algorithm, which will simulate patient's inspiratory airflow limitations which are outside of obstructive hypopneas in different manners, respectively with a partially occluded upper airway model (version A), or with a completely open upper airway model (version B). In fact, in version A, the bench-simulated inspiratory airflow limitations will be responsive to the pressure increase from PAP devices, by increasing the airflow amplitude and in the meantime decreasing the degree of flattened shape until it disappears. However, this simulation methodology shows also an inconvenience that the flattened airflow shape produced on bench is not the same as the one in the patient, because we will lose control of airflow shape while increasing resistance in the upper airway model (Starling resistor on our bench), which is related to the Starling resistor's mechanical properties. We could only guarantee that the flattened airflow's amplitudes were almost identical to those of patient while the pressure delivered from PAP devices remains 4cmH₂O (the minimal pressure setting in PAP devices). Consequently, the version B should be complementary to the version A. It permits simulating almost exactly patient's flattened inspiratory airflow shape so that we are able to check whether PAP devices manage to recognize flattened airflow shapes, which are personalized and specific to each patient. Considering snoring simulation, we consider adding a microphone-in-box at the upstream of the Starling resistor. The microphone will play patient's snoring sound, which is synchronized to inspiratory phases, in order to generate high-frequency breathing airflow oscillations.



6.4 Hypopnea scoring rules diversity among PAP devices from different manufacturers

In chapter 5, we studied the apnea hypopnea indices agreement between positive airway pressure devices (PAP) and polygraph via a bench test evaluation method. The PAP devices concerned were AirSense 10 Autoset by Resmed, DreamStation Auto by Philips Respironics, S.Box by Sefam and Prisma 20A by Löwenstein Medical GmbH & Co. Kg. We found that the AHI derived by PAP devices were linearly correlated this scored from polygraph analysis. the agreement in AI between polygraph and PAP devices was much better than HI. PAP devices showed a tendency to underestimate HI when compared to polygraph scorings. Furthermore, there existed a non-negligible discrepancy among HI provided by PAP devices from different manufacturers as well. The HI inconsistencies among PAP devices could be due to the differences of airflow reduction threshold and/or some other airflow features chosen by PAP manufacturers to score hypopneas. For example, the manufacturer of AirSense 10 claimed the usage of inspiratory airflow limitation pattern in their hypopnea scoring rules. All these factors certainly involved in the differentiation of HI obtained from PAP devices of different manufacturers. However, there should exist another factor usually ignored, which we thought of when we designed our own SDB scoring algorithm. It is how to calculate airflow peak excursion baseline, especially in periods with continuous breathing events. According to AASM “Chicago consensus paper” statement in 1999 (“Sleep-Related Breathing Disorders in Adults: Recommendations for Syndrome Definition and Measurement Techniques in Clinical Research. The Report of an American Academy of Sleep Medicine Task Force” 1999), baseline is defined as the mean amplitude of stable breathing in the 2 minutes preceding the onset of the event (in individuals who have a stable breathing pattern during sleep) or the mean amplitude of the 3 largest breaths in the 2 minutes preceding onset of the



event (in individuals without a stable breathing pattern). Nevertheless, when we used the mean amplitude of the 3 largest breaths as the airflow peak excursion baseline, we found that it could result in scoring excessive periods with airflow reduction, especially during periods when the airflow signal measured by the nasal pressure transducer of a nasal cannula was not stable and was possibly contaminated by artifact. In polygraph, a great part of them could avoid being scored as hypopneas thanks to the measure of arterial oxygen saturation and/or EEG signals. As PAP devices do not have these physiological measures, they might apply a different method to define the baseline in order to avoid excessive scorings, such as changing the baseline window length, the number of cycles taken into account to calculate peak excursion baseline, selecting a specific percentile instead of the average, or using the minute ventilation rather than airflow signal to calculate peak excursion baseline, etc. All of these technical choices should also be relevant to the discrepancy of HI determined by different PAP devices.

Indeed, the apnea hypopnea index given by PAP devices serves as an important medical data. Clinicians or caregivers use it to evaluate treatment efficiency under PAP therapy, follow up patients' health status evolutions as well as manage their pathways. Since OSA patients are possible to develop emergent central sleep apnea during PAP therapy, with a prevalence of 3.5% in week 1 or week 13 after PAP therapy initiation, the accuracy of AHI plays a crucial role in informing clinicians as early as possible to adapter treatment strategy for these patients with overlap between OSA and CSA. Since CSA can promote or indicate cardiac arrhythmia, reduced cardiac function and it has a strong correlation with mortality in patients with heart failure. Thus it was recommended by American Thoracic Society in 2013 that the AHI detected by PAP devices was reported as AHI_{Flow} to avoid the confusion with AHI of poly(somno)graph. As for the discrepancies of apnea hypopnea detection rules among PAP manufacturers, at least the clinicians and



caregivers needed to know the apnea hypopnea definitions of the corresponding PAP device in order to interpret the residual SDB indices in an optimal manner.

6.5 Apnea qualification discrepancies between PAP devices

A demand to investigate the apnea qualification agreements between PAP devices has been expressed in literature. During the third study evaluating apnea hypopnea indices agreement between PAP algorithms and polygraph in predominant CSA patients, an apnea qualification difference between PAP algorithms, especially concerning complex apnea type, has been observed, while reproducing on bench breathing profiles from 25 polygraph samples. Figure 6-3 describes different types of apnea indices (OAI, MAI and CAI) for these 25 polygraph samples determined respectively by polygraph analyses in line with AASM rules of 2012, a custom-made algorithm used for analyzing bench-simulated breathing profile, and four PAP devices from difference manufacturers (AirSense 10, DreamStation Auto, S.Box and Prisma 20A).



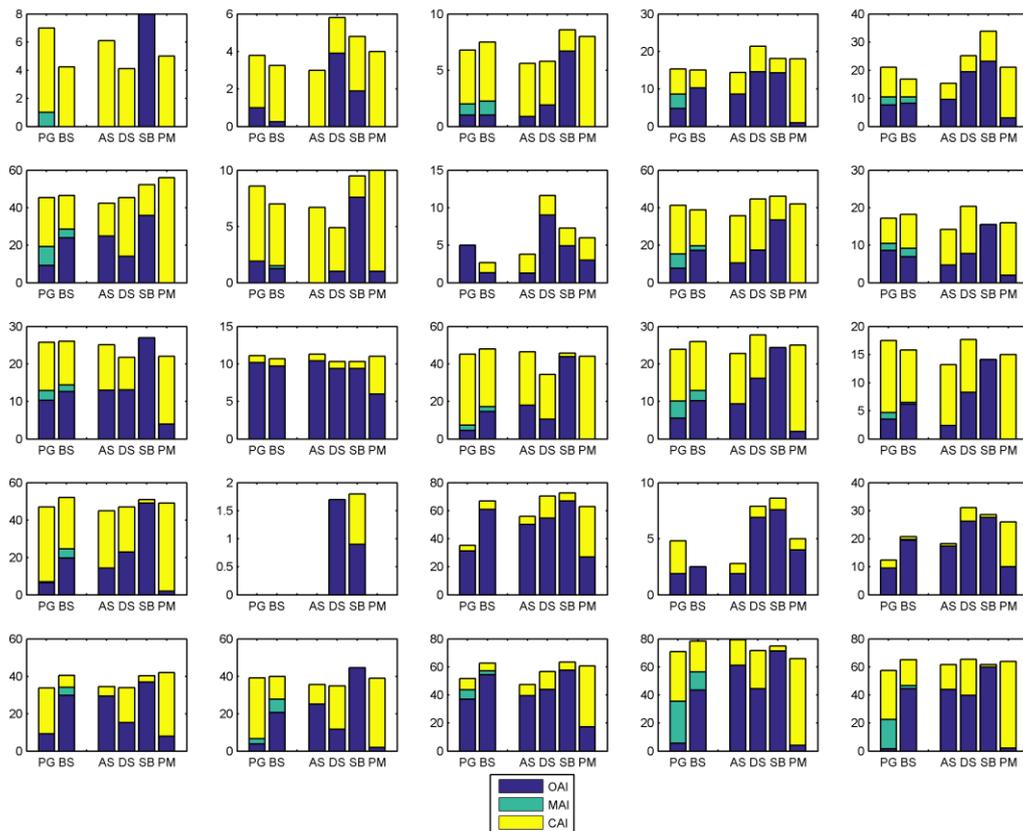


Figure 6-3: Description of different types of apnea indices obtained from polygraph, bench-simulated breathing profile analyses and four PAP devices tested, concerning the breathing scenarios issuing from 25 polygraph samples. OAI: obstructive apnea index. MAI: mixed apnea index. CAI: central apnea index. PG: polygraph. BS: bench-simulated breathing profile analyses. AS: PAP device AirSense 10. DS: PAP device DreamStation Auto. SB: PAP device S.Box. PM: PAP device Prisma 20A. Each barplot represents a polygraph sample.

The custom-made algorithm characterized mechanisms of bench-simulated apneas by regarding the resistance level set in Starling resistor, i.e. the difference between pressure at the upstream segment (P_{us}) and the sealed chamber pressure (P_{ch}) of Starling resistor, namely the transmural pressure (P_{tm}). Indeed, the P_{us} corresponded to the pressure sent by the tested PAP device as well (Figure 2 in the article of Chapter 3). In general, the rubber tube of the Starling resistor used on our bench is completely open at the condition of $P_{tm} \geq 3$ cmH₂O. On the



contrary, when P_{tm} drops below $-4 \text{ cmH}_2\text{O}$, it becomes fully occluded, thus the respiratory muscular effort simulated in the active lung simulator can no longer generate any airflow. This is co-called simulation of an apneic breath of obstructive mechanism. Then an apneic breath of central mechanism is generated on our bench very simply by introducing a very small respiratory muscular effort amplitude (about $0.1 \text{ cmH}_2\text{O}$) in the lung simulator, which increments TTL by 1 so that the P_{ch} can be updated in comparison with the previous breath cycle to make sure the Starling resistor in an opening state. In the meantime, the airflow produced by the lung simulator is almost invisible (valley-to-peak amplitude of about 0.1 L/s). We chose this manner to simulate the breath cessation of central mechanism, due to the technical constraints in our bench hardware. Therefore, if a bench-simulated apnea consisted of only breathes of obstructive mechanisms, it would be classified as an obstructive apnea. On the contrary, if it consisted only of breathes of central mechanisms, it was then categorized as a central apnea. However, if an apnea in a patient has simultaneously obstructive breathes as well as breath cessation of central mechanism, it would then be more difficult to characterize its property, because patient's upper airway status in the central part cannot be derived from poly(somno)graph. Therefore, we defined their characterizations in the custom-made algorithm as follows:

- a. If the apnea were started by an obstructive apneic breath, it would be qualified as an obstructive apnea. Otherwise,
- b. If the time of breath cessation of central mechanism before the first obstructive breath was greater than half of the apnea duration, it would be qualified as a mixed apnea. Otherwise, it would be still attributed to an obstructive apnea.

According to figure 6-3, the bench simulation showed a good performance in reproducing the quantity of patient's apneas. In few polygraph samples, there was a little discrepancy



between AI from polygraph and AI calculated from bench-simulated breathing profile analyses. This was linked to the algorithm differences in detecting apneas between polygraph and the custom-made algorithm, for example, the strategy of determining pre-event airflow baseline, especially during unstable breathing periods. In terms of the proportion of different types of apneas, the agreement between polygraph and bench simulation was great for a majority of polygraph samples. In some polygraph samples, the bench seemed to over-simulate patient's obstructive apneas and under-simulate patient's central apneas. This does not mean that our simulation did not reproduce patient's breathing profile. In fact, polygraph samples used by us were issuing from patients with co-existing OSA and CSA, it was sometimes difficult to characterize the property of their apneas. For example, within a polygraph-scored central apnea, there could exist one or two breath attempts at the end of the apnea (Figure 6-4). Furthermore, before the central apnea, the patient could snore, and the airflow decreased with the sign of inspiratory airflow limitation as well (Figure 6-4). Therefore, our custom-made algorithm would characterize this kind of apnea as mixed apnea or obstructive apnea (in case that the last breath before respiratory muscular effort cessation was included into the apnea event). This could explain the reason why there could have been some difference in indices of different types of apneas between polygraph and bench simulation.



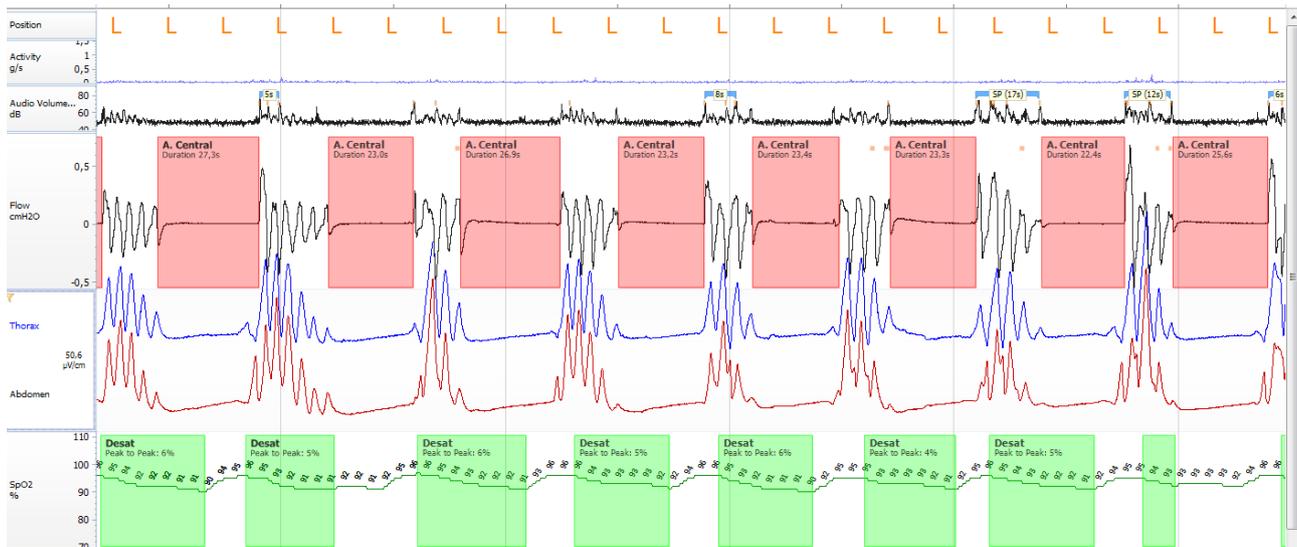


Figure 6-4: Illustration of some polygraph-scored central apneas with one or two breath attempts at the end. Before the central apnea, the patient snored and its airflow decreased, accompanied by inspiratory airflow limitation.

Furthermore, in some obstructive apneas (figure 6-5), there could be a long breath cessation of central mechanism between obstructive breathes. If this lasted longer than 4 seconds, we then simulated it on bench with an open Starling resistor for the central part (figure 6-6).

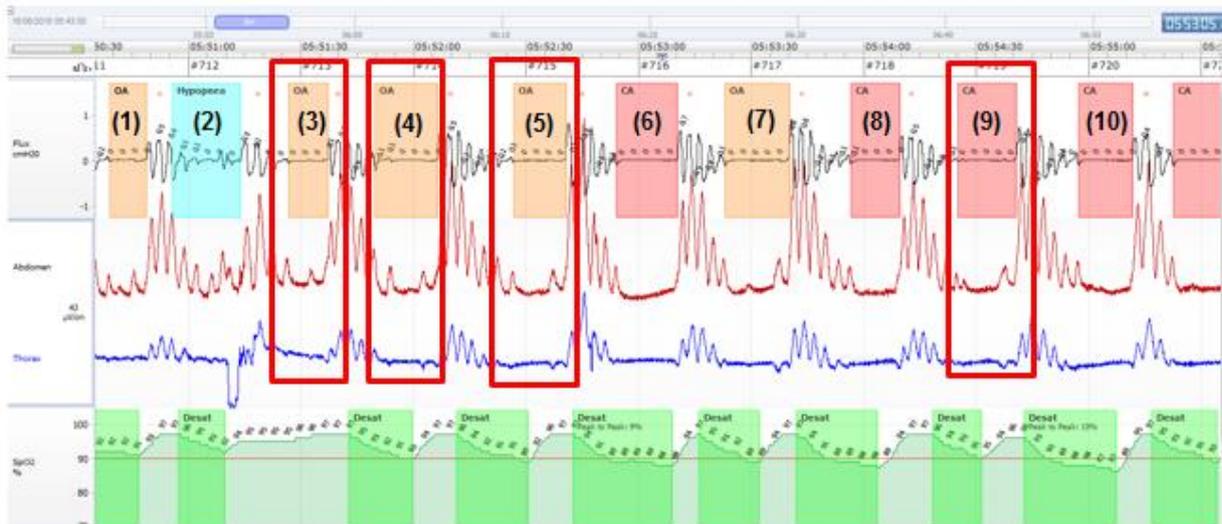


Figure 6-5: An example of polygraph samples showing apneas of both obstructive and central mechanisms. Red frames: There was a respiratory muscular effort cessation between two obstructive breathes in an apnea.

C

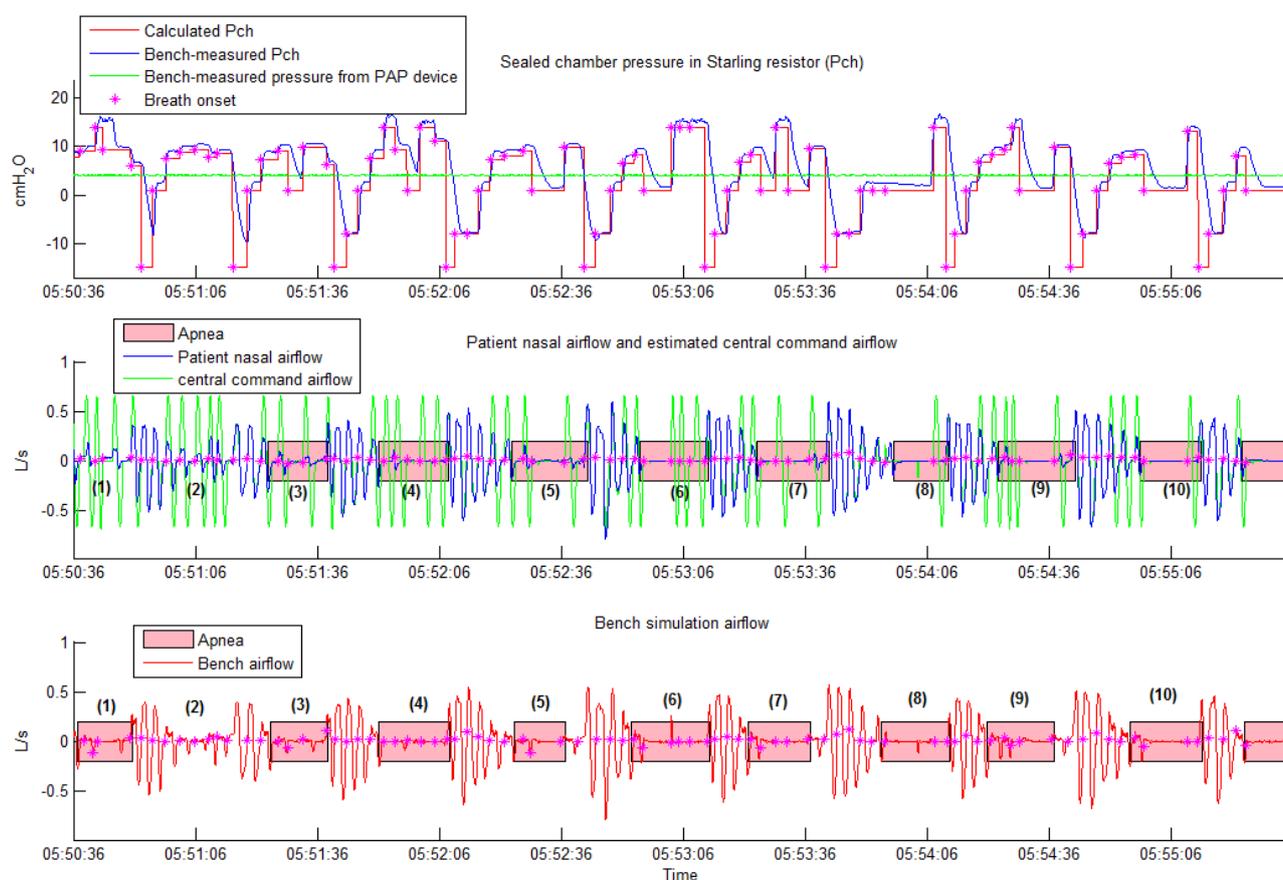
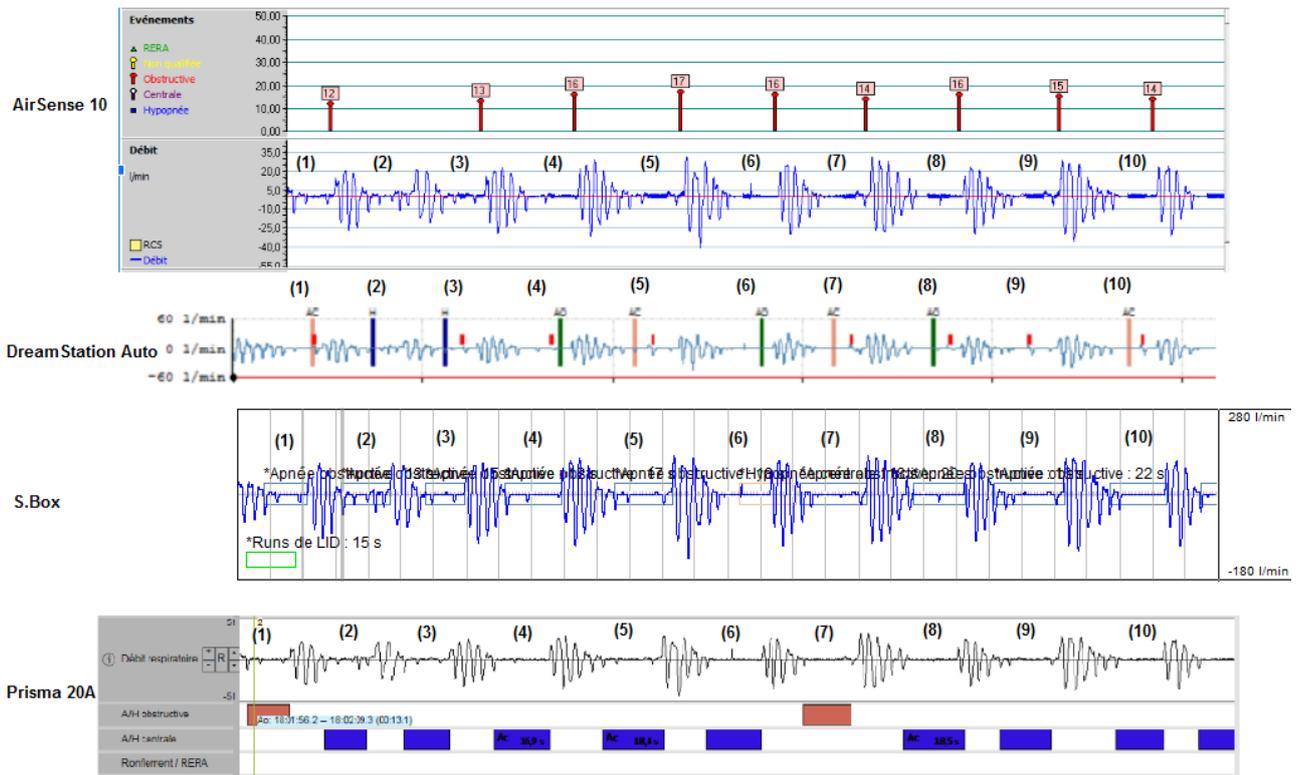


Figure 6-6: Bench simulation of the polygraph example cited in figure 6-5. During periods with breathing muscular effort cessation, patient central command airflow were set to closely 0. So the respiration muscular effort integrated in the active lung simulator were nearly 0 cmH₂O as well. In addition, the Starling resistor was open (bench-measured pressure from PAP device > bench-measured P_{ch}+3). However, during obstructive breathes, patient central command airflow were comparable to this of normal breathing. The Starling resistor was in state of obstruction (bench-measured pressure from PAP device < bench-measured P_{ch}-4).

While subjecting PAP devices of different manufacturers to the same bench-simulated breathing scenarios, a difference between them about apnea mechanism characterization has been observed, particularly concerning apneas with both obstructive and central mechanisms. It was illustrated in figure 6-7, which reflected the SDB events detected by PAP devices while subjecting them to the bench-simulated breathing scenario showed in figure 6-6. AirSense 10 has

shown a good sensitivity in detecting obstructive part of complex apneas, and thus qualified them as obstructive apneas, whereas Prisma 2A was more sensitive to the central part (with open Starling), thus qualified them more often as central apneas. In addition, both AirSense 10 and DreamStation Auto use forced oscillation technics to determine patient's upper airway status. Then, the apnea qualification from DreamStation Auto depended greatly on the status (open or closed) of Starling resistor when the device sent pressure pulses (corresponding to the small red bars marked on the device-measured airflow of DreamStation Auto in figure 6-7). Therefore, it can qualify complex apneas as obstructive or central apneas. Our bench showed a limitation in testing apnea qualification characteristics of S.Box, because S.Box detects central apneas by mainly regarding patient's cardiac oscillations. As we did not simulate them during central apneas, the criteria of S.Box for qualifying a central apnea could become more restrained, based on analyses of breathing airflow shape during the breathing recovery, whose amplitudes should be gradually increasing in the following three consecutive breathes, in the meantime, satisfying a certain threshold. Sometimes, a patient may not necessarily present a crescendo breathing airflow during the breathing recovery after central apneas. This could explain why S.Box scored more obstructive apneas than other devices (Figure 6-3).





SDB event	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
Polygraph scoring	OA	H	OA	OA	OA	CA	OA	CA	CA	CA
Bench simulation	OA	H	OA*	OA*	OA*	MA	OA*	MA	OA*	MA
AirSense 10	OA	ND	OA							
DreamStation Auto	CA	H	H	OA	CA	OA	CA	OA	ND	CA
S.Box	OA	OA	OA	OA	OA	H	OA	OA	OA	OA
Prisma 20A	OA	CA	CA	CA	CA	CA	OA	CA	CA	CA

(A summary table of SDB events correspondence between polygraph, bench simulation and PAP devices.)

Figure 6-7: Apnea characterization differences between PAP devices for the breathing profile described in figures 6-5 and 6-6. H: hypopnea. CA: central apnea. MA: mixed apnea. ND: sleep-disordered-breathing event not detected. OA: obstructive apnea. OA*: obstructive apnea, in which there was respiratory muscular effort cessation of central mechanism. These periods were simulated on bench with an open Starling resistor, except the obstructive breathes. The small red bars marked above the airflow measured by DreamStation Auto represent the moments when the device sends a pressure pulse.

To illustrate more clearly discrepant features of PAP devices in qualifying apneas



with both obstructive and central mechanisms, of patients suffering from an overlap of CSA and OSA, we calculated the ratio of obstructive apneas to all apneas scored by PAP devices, as well as this obtained from analyses of bench-simulated breathing profile by using the previously described custom-made algorithm. As PAP devices do not distinguish mixed apneas from obstructive apneas, we categorized bench-simulated mixed apneas as obstructive apneas to calculate the ratio as well, in order to keep consistent with PAP devices. Then we analyzed the agreement between the ratio of obstructive apnea simulated on bench and this of PAP devices (Figure 6-8). It enhanced our finding that Prisma 20A showed a tendency to characterize mixed apneas as central apneas; S.Box characterized more frequently apneas as obstructive events if a patient did not show the sign of cardiac oscillation during the central part.



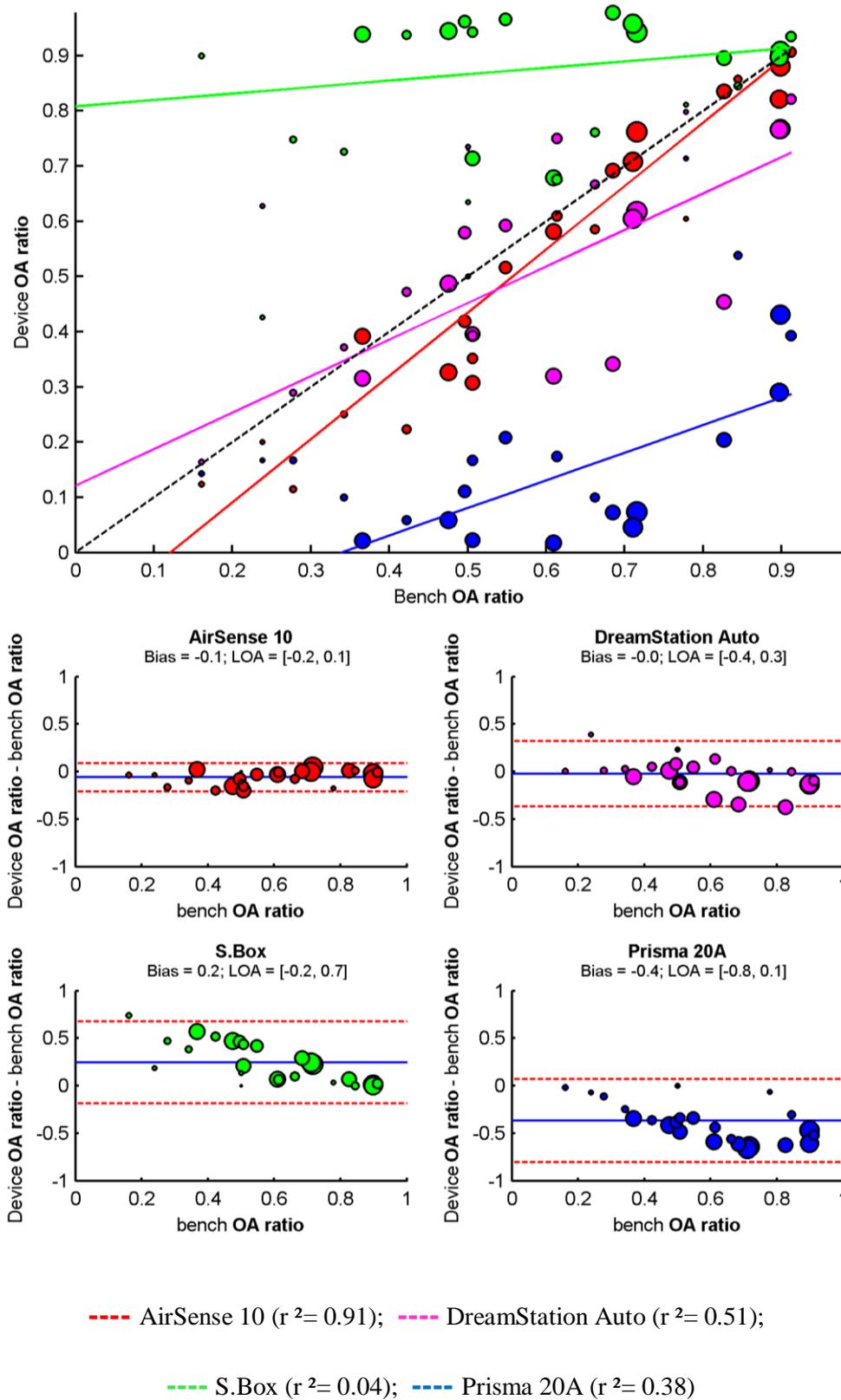


Figure 6-8: Scatter plot and Bland-Altman plot of the obstructive apnea's ratio to all



apneas determined by PAP devices versus this calculated by analyzing bench-simulated breathing profiles. Each circle represents bench simulation of a polygraph sample, with connection to a PAP device. The size of circle is proportional to the apnea index (AI) calculated from analysis of bench-simulated breathing profile. OA: obstructive apnea. The linear regression is weighted in function of AI obtained by analyzing bench-simulated breathing scenario of each polygraph sample.

Therefore, each PAP device had its own and particular behavior in characterizing mixed apneas with both central (an open upper airway) and obstructive (an occluded upper airway) mechanisms on bench tests, depending on the technology and algorithm implemented by each manufacturer. Clinical professionals may need to take into account this subtle distinction between manufacturers while prescribing a PAP device to a patient with mixed syndromes of CSA and OSA.



6.6 Perspectives

This new physiological bench can serve as an APAP algorithm validation tool, checking whether currently commercialized PAP devices arrive at providing an efficient and optimal treatment to the bench-simulated physiological breathing profiles, which are issued from sleep apnea patients of different pathological breathing phenotypes. It can also help check the data accuracy in the reports provided by ventilator devices after each usage session (Lofaso et al. 2006; Ognà et al. 2016), as what we have done to evaluate the agreements between apnea hypopnea indices determined by PAP devices and these scored in line with AASM scoring rules 2012, considering breathing profiles with an overlap of OSA and CSA. In this study, we have set all PAP devices at 4 cmH₂O in order to rule out treatment effects and assure that the bench-generated breathing profiles were the same as the ones registered in polygraph recordings. However, since patients are more often treated with a higher pressure than 4 cmH₂O, it seems worthy that this study is further continued by setting device pressures respectively at 6, 8, 10, 12 cmH₂O to see whether the great discrepancy between HI determined by PAP devices from different manufacturers will persist or in which manner it will evolve. Then the same study can be applied to the breathing profiles of patients suffering OSA, which represent a majority of population receiving PAP therapy.

Moreover, we can try to carry out clinical studies and bench studies at the same time to validate this bench in a further step by confirming that the PAP devices' responses to bench-simulated SDB events are identical to these observed in real patients. This bench can then serve as a personalized therapy tool, which helps clinicians find an appropriate APAP algorithm adapted to a patient specific characteristics. After having accumulated enough knowledge about the optimal matches between patients' breathing phenotypes and different APAP algorithm characteristics, a



digital application could be developed, to recommend a suitable PAP device for a patient based on its polygraph recordings performed during the diagnostic.



Conclusion

A physiological bench has been developed within this thesis, enabling reproducing automatically apneic patient's SDB profiles through its polygraph recordings, performed during the diagnostic examination. It is achieved via an algorithm, which analyzes patient's polygraph signals and then calculates the corresponding digital inputs required by the active lung simulator (i.e. respiratory muscular effort pressure) and the Starling resistor (i.e. upper airway resistance) in order to reproduce the specific breathing profile on bench.

Then this new approach to bench simulation has been validated by simulating 15 various breathing scenarios, each of which lasted about 1-hour, issuing from 12 patients affected by moderate-to-severe sleep syndrome. These scenarios were different from one to another, regarding the apnea hypopnea indices as well as the portion represented by each mechanism (obstructive or central) of SDB event. The bench simulation results showed that its performance remained robust regardless a variety of patients' breathing phenotypes.

With this bench, the accuracy of residual apnea hypopnea indices provided by different PAP devices (AirSense 10, DreamStation Auto, S.Box, Prisma 20A) has been investigated in comparison with polygraph scoring results which are in line with AASM apnea hypopnea scoring rules of 2012, especially concerning the breathing profiles of patients with a predominant central sleep apnea syndrome. All PAP devices showed a better agreement in AI than in HI with AASM scoring rules because all PAP devices tended to underestimate HI, with a severity depending on manufacturers. It is noteworthy that the HI determined by PAP devices is not equivalent, which can have impacts on treatment efficiency comparison between devices subjected to a same patient.



Compared to precedent benches, this bench permits easily reproducing the pathological breathing characteristics specific to each patient, according to polygraph recordings. It permits comparing APAP algorithms under the same conditions, with polygraph scoring from sleep physicians. This work is the first step to a personalized treatment by allowing recommendation of the most appropriated device to a specific patient breathing phenotype.



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Annexes

A.1 Submission proof for article described in chapter III

PLOS ONE

New physiological bench test reproducing nocturnal breathing pattern of patients with sleep disordered breathing --Manuscript Draft--

Manuscript Number:	
Article Type:	Research Article
Full Title:	New physiological bench test reproducing nocturnal breathing pattern of patients with sleep disordered breathing
Short Title:	Physiological bench test simulating sleep breathing profiles
Corresponding Author:	Michel Petitjean Universite Paris-Sud FRANCE
Keywords:	bench test; sleep; sleep disordered breathing; polygraph; respiratory simulation
Abstract:	<p>Previous studies have shown that Automatic Positive Airway Pressure devices display different behaviors when connected to a bench using theoretical respiratory cycle scripts. However, these scripts are limited and do not simulate physiological behavior during the night. Our aim was to develop a physiological bench that is able to simulate patient breathing airflow by integrating polygraph data. We developed an algorithm analyzing polygraph data and transformed this information into digital inputs required by the bench hardware to reproduce a patient breathing profile on bench. The inputs are respectively the simulated respiratory muscular effort pressure input for an artificial lung and the sealed chamber pressure to regulate the Starling resistor. We did simulations on our bench for a total of 8 hours and 59 minutes for a breathing profile from the demonstration recording of a Nox T3 Sleep Monitor. The simulation performance results showed that in terms of relative peak-valley amplitude of each breathing cycle, simulated bench airflow was biased by only 1.48% \pm 6.80% compared to estimated polygraph nasal airflow for a total of 6,479 breathing cycles. For total respiratory cycle time, the average bias \pm one standard deviation was 0.000 \pm 0.288 seconds. For patient apnea events, our bench simulation had a sensitivity of 84.7% and a positive predictive value equal to 90.3%, considering 149 apneas detected both in polygraph nasal simulated bench airflows. Our new physiological bench would allow personalizing APAP device selection to each patient by taking into account individual characteristics of a sleep breathing profile.</p>
Order of Authors:	Shuo Liu Yann Rétory Amélie Sagniez Sébastien Hardy François Cottin Gabriel Roisman Michel Petitjean



A.2 Award Demeny-Vaucanson 2018 for this PhD research

AHI agreement evaluation (PAP Vs. polygraph): Conclusion



La remise des **prix Demeny-Vaucanson 2018** a eu lieu lors de la Journée FéDeV 2018. Après une phase de pré-sélection, 5 communications orales ont concouru lors la phase de sélection. Après délibération, les membres du jury ont décerné trois prix à (de gauche à droite sur la photo ci-dessous) : Simon Bastide, Shuo Liu, et Mohamed Younes. Félicitations à tous !



Synthèse en Français

Le syndrome d'apnées obstructives du sommeil représente un problème de santé publique, en affectant environ 6% à 17% de la population adulte. Ce syndrome entraîne de nombreuses conséquences cardio-vasculaires d'où l'importance de son traitement qui consiste à maintenir ouvertes les voies aériennes supérieures (VAS) du patient à l'aide d'une machine de pression positive continue (PPC). L'efficacité du traitement par PPC autopiloté dépend des algorithmes et technologies implémentés qui détectent les événements respiratoires et qualifient leur mécanisme : soit l'obstruction des VAS, soit une altération de la commande centrale de respiration. Ces procédés sont protégés par les fabricants par des brevets et perçus comme une boîte noire par le public. En pratique, le comportement de ces machines est observé par enregistrement de la ventilation de patients sous traitement. Il paraît cependant difficile de comparer les différentes machines à cause des variabilités respiratoires inter- et intra-patient. Ainsi, des bancs d'essai ont été développés pour compenser ce manque en simulant des débits respiratoires et des périodes d'obstruction de VAS, représentant des patients apnéiques, à l'aide d'un simulateur pulmonaire et d'un modèle de résistance de VAS. Les scénarios respiratoires simulés sont composés par une répétition d'événements respiratoires extraits de patients ou conçus artificiellement. Avec les bancs d'essai précédents, la simulation d'un profil respiratoire entier enregistré par poly(somno)graphie peut sembler laborieuse parce que elle n'est pas automatisée.

L'objectif de cette thèse a donc consisté à développer un banc d'essai physiologique, capable de reproduire automatiquement le profil respiratoire nocturne de patients enregistré par polygraphie, en tenant compte des caractéristiques obstructives et centrales des événements respiratoires.



Comme le profil respiratoire des patients apnéiques est issu d'une combinaison de la contraction diaphragmatique et des obstructions potentielles dans les VAS, un algorithme a ainsi été développé pendant cette thèse pour analyser les signaux polygraphiques et calculer les données digitales demandées par le matériel du banc: la pression de l'effort musculaire inspiratoire et la résistance des VAS pour piloter sur banc respectivement le simulateur pulmonaire et la résistance de Starling qui est utilisé pour modéliser des obstructions de VAS (Figure 10-1). Concrètement, en analysant les signaux polygraphiques, des événements respiratoires sont identifiés, par exemple, des apnées, hypopnées de mécanisme obstructif, central ou mixte. Le débit respiratoire issu de la commande centrale ou également de la contraction diaphragmatique pourrait être estimé à partir du débit respiratoire réel du patient et des événements respiratoires détectés. Lors de la respiration normale ou des événements de type central, le débit de la commande centrale est supposé égal au débit respiratoire réel. Par contre, lors des respirations obstructives, il est estimé à partir du débit respiratoire réel de base pendant les 2 minutes précédant l'évènement. Ainsi la pression musculaire de respiration à intégrer dans le simulateur pulmonaire est calculée en fonction du débit de la commande centrale et de la compliance et la résistance pulmonaire saisie dans le simulateur pulmonaire. Le niveau de la résistance dans les VAS du patient est évalué par le ratio entre le débit réel et le débit issu de la commande centrale. Plus ce ratio est petit, plus la résistance dans les VAS est importante. La pression à régler dans la chambre hermétique de la résistance de Starling est adaptée à ce ratio. En utilisant ce nouveau banc physiologique, le profil respiratoire simulé a révélé une similitude satisfaisante avec celui des patients concernant des paramètres temporels, d'amplitude du débit respiratoire et la capacité à reproduire des événements respiratoires de différentes natures.



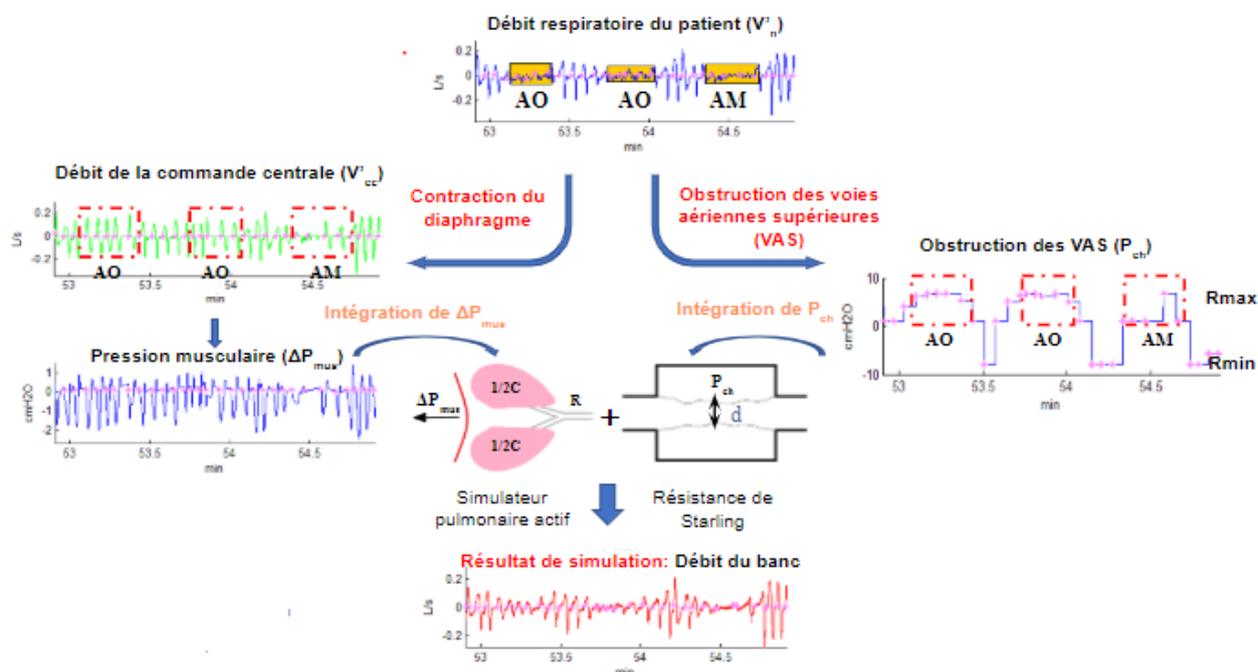


Figure 10-1: Principe d'un nouveau banc d'essai physiologique, reproduisant automatiquement le profil respiratoire enregistré par polygraphie ventilatoire. AO : apnée obstructive ; AC : apnée centrale ; AM : apnée mixte ; ΔP_{mus} : pression musculaire de respiration ; R : résistance pulmonaire ; C : compliance pulmonaire ; P_{ch} : pression dans la chambre hermétique de la résistance de Starling ; R_{max} : résistance maximale de la résistance de Starling ; R_{min} : résistance minimale de la résistance de Starling. * : positions de début de respiration.

Ensuite, cette approche innovante a été validée avec simulation de 15 scénarios respiratoires d'une heure, issus de 12 patients apnéiques (modérés ou sévères), exprimant tous types d'événements (i.e. obstructif, central et mixte). La performance de simulation du banc d'essai a été jugée robuste face aux profils respiratoires testés.

La capacité de simulation a finalement permis de déterminer la précision de l'index d'apnée-hypopnées (IAH) résiduel estimé par des machines de PPC, en comparant les IAH déterminés par 4 dispositifs (AirSense 10, DreamStation Auto, S.Box et Prisma 20A) avec ceux obtenus en polygraphies diagnostiques des patients présentant des événements centraux et obstructifs.

Les résultats ont montré que toutes les PPC testées ont eu un accord meilleur en index d'apnées qu'en index d'hypopnées avec la polygraphie. En plus, elles ont montré une tendance à la sous-estimation de l'IAH par rapport à la polygraphie avec un degré variant en fonction du dispositif considéré.

Ce nouveau banc d'essai physiologique permet de simuler facilement le profil respiratoire d'un patient spécifique à partir des données polygraphiques. Il pourrait être un outil utile pour la compréhension et la comparaison des appareils ventilatoires ainsi qu'un pas vers la personnalisation du traitement en aidant au choix de la machine la plus adaptée à son profil.



Titre : Développement et application d'un banc d'essai physiologique, capable de simuler automatiquement les profils respiratoires enregistrés par polygraphie ventilatoire

Mots clés : banc d'essai, simulation respiratoire, syndrome d'apnée du sommeil, polygraphie, pression positive continue, index d'apnée-hypopnée

Résumé : Le syndrome d'apnée obstructive du sommeil affecte 6% à 17% de la population adulte. Le traitement de référence est la ventilation nocturne par une pression positive continue (PPC) fixe ou autopilotée afin de maintenir les voies aériennes ouvertes. L'efficacité de traitement des PPC autopilotées dépend des algorithmes et technologies pour détecter et qualifier les événements respiratoires. Des bancs d'essai ont été créés pour évaluer les PPC autopilotées en conditions comparables, en simulant des scénarios respiratoires composés de chaînes répétitives d'événements respiratoires. Les profils respiratoires simulés par les bancs d'essai précédents sont standardisés et simplifiés par rapport au profil respiratoire du patient.

Pour tendre vers des essais plus réalistes, un nouveau banc d'essai physiologique permettant de reproduire automatiquement les profils respiratoires à partir des données polygraphiques a été créé pendant cette thèse. Il a été validé en évaluant la simulation de scénarios respiratoires de différents phénotypes issus de 12 patients.

Via ce banc d'essai, la précision de l'index d'apnée-hypopnée (IAH) résiduel fourni par PPC a été évalué en comparant les IAH déterminés par 4 dispositifs de PPC (AirSense 10, DreamStation Auto, S.Box et Prisma 20A) avec ceux de polygraphie. Les résultats ont permis de quantifier les différences d'IAH afin d'aider les médecins à en tenir compte.

Title : Development and application of a physiological ventilation device test bench, capable of reproducing automatically respiratory profiles registered with ventilation polygraph

Keywords : bench test, respiration simulation, sleep apnea syndrome, polygraph, positive airway pressure, apnea-hypopnea index

Abstract: Obstructive sleep apnea syndrome affects 6% to 17% of adult population. The reference treatment is nocturnal ventilation via an either fixed or auto-titrating positive airway pressure (APAP) to maintain upper airway (UA) open. Treatment efficiency of APAP depends greatly on algorithms and technologies used for detecting and characterizing disordered breathing events (linked to UA obstruction or central command). Bench tests have been developed to evaluate APAP devices under the same conditions, by simulating respiratory scenarios composed of a repetitive string of several disordered breathing events registered from apneic patients or artificially designed. Therefore, breathing profiles simulated on

benches are standardized and simplified, in comparison with patients'. To improve this disadvantage, a new physiological bench, which enables reproducing automatically a specific patient breathing profile from its polygraph recordings, has been created. It has been validated by simulating various breathing profiles issuing from 12 patients of different pathological phenotypes.

Through this new bench, the accuracy of residual apnea hypopnea indices (AHI) determined by 4 APAP devices (AirSense 10, DreamStation Auto, S.Box and Prisma 20A) has also been investigated in comparison with polygraph scorings. The results would help physicians in clinical practice thanks to the quantification of AHI discrepancies between manufacturers.