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Evaluation des techniques pour la prise en charge diagnostique et thérapeutique de l'insuffisance respiratoire chronique

Maxime Patout

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Normandie Université

THESE

Pour obtenir le diplôme de doctorat

Spécialité SCIENCES DE LA VIE ET DE LA SANTE

Préparée au sein de l'Université de Rouen

Evaluation des techniques pour la prise en charge diagnostique et thérapeutique de l'insuffisance respiratoire chronique

Présentée et soutenue par
Maxime PATOUT

Thèse soutenue publiquement le 20 décembre 2019
devant le jury composé de

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Evaluation of new techniques for the diagnosis and the management of
chronic respiratory failure

Évaluation des techniques pour la prise en charge diagnostique et
thérapeutique de l'insuffisance respiratoire chronique

Soutenue et présentée par

MAXIME PATOUT

né le 13/04/1984 à Suresnes (France)

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What will you say

Résumé

L'insuffisance respiratoire chronique est un syndrome défini par une défaillance mono-viscérale respiratoire. Sa principale origine est aujourd'hui le syndrome obésité-hypoventilation qui concerne 4 à 5% des patients obèses. L'IRC est aussi le stade évolutif terminal de la bronchopneumopathie chronique obstructive qui touche 6 à 8% de la population adulte. L'incidence de ces pathologies et donc de l'insuffisance respiratoire est en augmentation constante. Dans cette thèse, nous avons évalué les nouvelles modalités diagnostiques et thérapeutiques qui pourraient améliorer la prise en charge des patients atteints d'insuffisance respiratoire chronique.

Concernant la prise en charge diagnostique, nous avons montré que les données fournies par l'électromyographie de surface des muscles intercostaux, outil qui évalue le travail respiratoire, constituent un marqueur pronostique indépendant chez les patients atteints de bronchopneumopathie chronique obstructive. Nous avons également montré leur pertinence pour prédire l'efficacité clinique et l'observance à la ventilation non-invasive à domicile.

Concernant la prise en charge thérapeutique, nous avons montré que l'utilisation d'un mode semi-automatisé de ventilation non-invasive a la même efficacité que celle de modes classiques en permettant une mise en place plus rapide du traitement. Nous avons également rapporté l'intérêt de l'oxygénothérapie à haut débit au domicile alors que ce traitement était utilisé jusque-là dans le seul cadre des soins intensifs. Enfin, nous avons rapporté les bénéfices de la pression positive continue au cours de l'effort chez les patients ayant une trachéobronchomalacie.

Concernant le suivi des patients, nous avons montré que les données des logiciels de ventilation non invasive permettent de prédire la survenue d'une exacerbation sévère de BPCO mais que l'utilisation de la télémédecine chez les patients insuffisants respiratoires chroniques ne peut être encore pleinement intégrée dans la pratique clinique.

Au cours de cette thèse, nous avons identifié de nouveaux outils physiologiques, de nouvelles modalités d'administration des traitements et de nouveaux outils de suivi à domicile, à même d'améliorer la prise en charge des patients insuffisants respiratoires chroniques.

Summary

Single-organ respiratory failure defines chronic respiratory failure. Obesity hypoventilation syndrome is the main cause of chronic respiratory failure and occurs in 4 to 5% of obese patients. Chronic respiratory failure is also the end-stage evolution of chronic obstructive pulmonary disease that has a prevalence of 6 to 8% in the adult population. The incidence of these diseases increases so does the incidence of chronic respiratory failure. In this thesis, we will evaluate novel diagnostic and therapeutic modalities that could improve the care of patients with chronic respiratory failure.

Regarding diagnostic modalities, we have seen that evaluating the work of breathing with surface parasternal electromyography was an independent prognostic marker in patients with chronic obstructive pulmonary disease. We have also seen that it was a relevant tool to predict the clinical efficacy and compliance to home non-invasive ventilation.

Regarding therapeutic modalities, we have shown that the use of a semi-automatic mode of non-invasive ventilation had the same efficacy of a standard mode with a shorter length of stay for its setup. We have shown the relevance and feasibility of the use of high-flow oxygen therapy in the home setting whilst it was only used in intensive care units. Finally, we have shown the benefits of continuous positive airway pressure during exertion in patients with tracheobronchomalacia.

Regarding patients' follow-up, we have shown that the use of data from built-in software could predict the onset of a severe exacerbation of chronic obstructive pulmonary disease. However, we also show that the implementation of tele-medicine in patients with chronic respiratory failure cannot be included in daily clinical practice yet.

In this thesis, we have identified novel physiological tools, novel ways to administer treatments and novel follow-up tools that can improve the management of patients with chronic respiratory failure.

Mots-clés

Insuffisance respiratoire chronique / Électromyographie parasternale / Ventilation non-invasive /
Oxygénothérapie haut débit / Télémédecine / Exacerbation / Trachéobronchomalacie

Keywords

Chronic respiratory failure / Parasternal electromyography / Non-invasive ventilation / High-Flow
oxygen therapy / Tele-medicine / Exacerbation / Tracheobronchomalacia

Abbreviation

ABG: Arterial blood gas

AECOPD: Acute Exacerbation of chronic obstructive pulmonary disease

ALS: Amyotrophic lateral sclerosis

APAP: Automated Positive Airway Pressure

CO₂: Carbon dioxide

COPD: Chronic obstructive pulmonary disease

CPAP: Continuous positive airway pressure

CRF: Chronic respiratory failure

CWD: Chest wall disease

DMD: Duchenne's muscular dystrophy

EDAC: Excessive dynamic airway collapse

EMG: Electromyography

F_IO₂: inspired fraction of oxygen

HFO: High flow oxygen therapy

ILD: Interstitial lung disease

MEP: Maximal expiratory pressure

MIP: Maxime inspiratory pressure

NIV: Non-invasive ventilation

NMD: Neuro-muscular disease

NRD: Neural respiratory drive

NRDI: Neural respiratory drive index

OHS: Obesity hypoventilation syndrome

OSA: Obstructive sleep apnoea

O₂: Dioxygen

P_aO₂: dioxygen partial pressure

P_aCO₂: carbon dioxide partial pressure

PH: Pulmonary hypertension

SNIP: Sniff nasal inspiratory pressure

TBM: Tracheobronchomalacia

6MWT: 6-minute walking test

Chapter 1: Introduction

I. Generalities about chronic respiratory failure

1. Definitions

Aerobic cellular respiration is the process that uses dioxygen (O_2) to produce energy in the form of adenosine triphosphate. A consequence of the aerobic cellular respiration is the production of carbon dioxide (CO_2).

The role of the respiratory system is to provide sufficient O_2 to cells through the blood stream and to ensure clearance of CO_2 . O_2 supply is made during the inspiratory phase where a volume of room air containing 21% of O_2 is brought to the alveolar compartment and diffuses into the blood stream. CO_2 diffuses from the blood stream to the alveolar compartment and is exhaled during the expiratory phase.

Respiratory failure can be defined by the inability of the respiratory system to provide sufficient oxygenation (hypoxemic respiratory failure or type I) or to provide an insufficient CO_2 clearance (hypercapnic respiratory failure or type II). Respiratory failure can be explained by four mechanisms that can be intricate¹:

- Ventilation-perfusion (V/Q) mismatch. Mismatches between alveolar ventilation and pulmonary perfusion results in hypoxemia. V/Q mismatch is the most common cause of hypoxemia but is less frequently associated to hypercapnia. Indeed, the respiratory system increases alveolar ventilation to increase the oxygen supply. However, hypercapnia can occur when the respiratory system cannot further increase alveolar ventilation.
- Hypoventilation. Decrease in the alveolar ventilation results in a lower alveolar O_2 level and an increase in the alveolar CO_2 level, resulting in hypoxemia and hypercapnia. The decrease in alveolar ventilation can be caused by a relative or absolute muscle weakness, loss of respiratory drive, a decrease in lung volumes or an increase of the dead space.
- Diffusion limitation. It results in an increase in the transit time of oxygen from the alveoli to the blood stream. As the diffusion capacity of O_2 is lower than CO_2 , it results primarily in hypoxemia.
- Shunt. Shunt is a process where venous blood is recirculated in the arterial system without going through the lung. It results in hypoxemia.

Chronic respiratory failure (CRF) is the final evolution of every chronic respiratory disease. However, we can divide the aetiologies causing CRF according to the type of CRF that they cause:

- Type I CRF that should be treated with oxygen supplementation
- Type II CRF that should be treated by non-invasive ventilation (NIV)

To diagnose respiratory failure, an arterial blood gas (ABG) needs to be performed. ABG's are usually performed by a puncture in the radial artery. ABG analysis reflects the O₂ and CO₂ content of the arterial blood and, therefore, how blood was oxygenated and decarboxylated by the lung. Respiratory failure is usually defined by a partial pressure of O₂ (P_aO₂) < 8kPa and / or a partial pressure of CO₂ (P_aCO₂) > 6kPa².

CRF can be defined as a persistent inability of the respiratory system to maintain sufficient oxygenation or CO₂ clearance. To diagnose CRF, ABG needs to be performed in stable state and repeated once within at least a two-week interval. Arterial puncture is therefore a very common practice for the management of patients with CRF. From the patients perspective, ABG's are more painful than venous puncture³ and are a source of anxiety⁴.

A. *Original research: A randomised controlled trial on the effect of needle gauge on the pain and anxiety experience during radial arterial puncture (PlosOne, 2015).*

As ABG are widely used, we conducted a monocentric randomised controlled clinical trial to assess the impact of the needle gauge on the pain.

Firstly, we identified that in our centre none of the staff that were performing the ABG were using a local anaesthetic ^{3,5}. We then interviewed the staff on the type of needle gauge that they were using and noted that they were using 23 and 25-gauge needle according to their own preference.

We then conducted the randomised controlled trial that was published in PlosOne ⁶.

Patout M, Lamia B, Lhuillier E, Molano L-C, Viacroze C, Benhamou D, Muir JF, Cuvelier A. A Randomized Controlled Trial on the Effect of Needle Gauge on the Pain and Anxiety Experienced during Radial Arterial Puncture. PLoS ONE. 2015;10(9):e0139432.

RESEARCH ARTICLE

A Randomized Controlled Trial on the Effect of Needle Gauge on the Pain and Anxiety Experienced during Radial Arterial Puncture

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Abstract

Background

Arterial punctures for assessment of arterial blood-gases can be a painful procedure. Lidocaine can be used to reduce pain prior to needle insertion but it is not a widely accepted practice. The purpose of this study was to determine whether a large size needle induces more pain compared to a smaller size needle for radial arterial puncture and to assess the anxiety associated with radial arterial punctures.

Methods

We conducted a prospective, double-blind, randomized, controlled, monocentric study including all outpatients who had a planned assessment of arterial blood gas analysis. Patients were randomized to have the arterial puncture performed with a 23 or a 25 G needle. The main judgement criteria was pain during arterial puncture. Visual analogue scale for pain (VAS-P) and visual analogue scale for anxiety (VAS-A) were used to assess pain and anxiety during radial arterial puncture.

Results

Two hundred consecutive patients were randomized. The 25 G needle was as painful as the 23 G needle (6.63 mm [0–19 mm] vs. 5.21 mm [0–18.49 mm], respectively, $p = 0.527$). Time for arterial puncture was longer with the 25 G needle than with the 23 G needle (42 s [35–55 s] vs. 33 s [24.5–35 s], respectively, $p = 0.002$). There was a correlation between the level of anxiety prior to the arterial puncture and the pain experienced by the patients ($\rho: 0.369, p < 0.0001$). There was a correlation between the pain experienced by patients and the anxiety experienced in anticipation of another arterial puncture ($\rho: 0.5124, p < 0.0001$).

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Conclusions

The use of 23 G needle allows quicker arterial sampling and is not associated with increased pain and symptoms. Anxiety was correlated with the pain experienced by patients during arterial punctures.

Trial Registration

Clinicaltrials.gov: [NCT02320916](https://clinicaltrials.gov/ct2/show/study/NCT02320916)

Introduction

Arterial blood-gas (ABG) measurements are the gold standard to evaluate pulmonary gas exchange [1]. However, arterial punctures are more painful than venous punctures [2] and, in ICU patients, cause greater anxiety than tracheal aspiration [3]. The only technique that has been shown to effectively reduce pain during arterial punctures is the subcutaneous injection of lidocaine [2,4]. However, this technique is more time consuming and is poorly used, even though it is recommended in Spanish guidelines [5–7] and teaching materials [8].

Capillary sampling of arterialised blood taken from the earlobe is another technique to assess pulmonary gas exchange. This technique is less painful than arterial puncture without subcutaneous anaesthesia [9]. Capillary sampling allows an adequate evaluation of pH and carbon-dioxide levels [10] but does not provide an accurate estimation of the level of oxygen [11,12]. Non-invasive technique such as transcutaneous oxymetry shares with capillary sampling its inaccuracy for the assessment of arterial oxygenation, especially when arterial oxygenation is low. Topical anaesthesia is widely used during arterial punctures despite the lack of proof of efficacy [13,14]. It is believed that the greater pain associated with arterial punctures is due to arterial innervation. It has also been shown that large gauge needles can cause more damage to the arterial wall [15]. As such, smaller gauge needles should cause less pain during arterial punctures. While performing arterial punctures with small gauge needles is feasible [16,17], to the best of our knowledge no studies have assessed the effect of needle gauge on arterial puncture related pain.

The aim of the present study was to compare the pain experienced during arterial punctures performed with a 25 G or 23 G needle. The secondary endpoints were the characterization of the pain and the anxiety associated with the arterial punctures.

Materials and Methods

We conducted a monocentric, prospective, randomized, double-blind study.

Patient Selection and Recruitment

All consecutive outpatients who had planned assessment of arterial blood gas as part of their routine clinical care in our Respiratory Department between April 11 and May 25, 2013, were asked to participate in the trial. Written and oral information was provided to all the patients. They were then asked to provide written informed consent for their participation in the study. Exclusion criteria included patients under the age of 18, inability to provide consent, or the presence of a contraindication to arterial punctures based on the American Association of Respiratory Care Guidelines [1].

Ethics Statement

Our Institutional Review Board at Rouen University Hospital approved this study.

Study Design

After inclusion, the patients were randomized based on instructions in sealed envelopes, which were prepared using a computer-generated randomization list by a third-party not involved in the randomization. A 23 G or a 25 G needle was assigned to each patient.

All arterial punctures were performed by one of the five nurses in the ambulatory unit without subcutaneous injection of lidocaine nor topical anaesthesia. The nurses who performed the arterial punctures were board certified nurses with at least 3 years experience in working in the respiratory ward. They collected anthropometric data from the patients, including the diameter of the punctured wrist. They also assessed the quality of the radial pulse, which was classified as imperceptible, weak, normal, strong, or visible. They assessed anxiety prior to the arterial punctures using a visual analogue scale for anxiety (VAS-A), which consisted of a horizontal 100-mm-long line with “no anxiety” indicated at the far left and “the highest level of anxiety that you can imagine” at the far right. Patients filled the VAS-A scale by themselves. Subjective quantification of this sort has been validated recently in recent studies on painful dental procedures [18]. In order to blind patients to the gauge of the needle, they were installed behind an opaque curtain through which they inserted their arm so that the nurse could perform the arterial puncture [S1 Image](#). The duration of the arterial puncture was measured from needle insertion to full syringe filling.

During the medical consultation after the arterial puncture, the physician in charge of the patient, who was blinded to the needle gauge, assessed the pain felt during the arterial puncture using a visual analogue scale for pain (VAS-P), which was a horizontal 100-mm-long line with at the far left, “no pain” and “the highest level of pain that you can imagine” at the far right. Patients filled the VAS-P scale by themselves. If patients had multiple punctures, they were asked to rate their pain level for all the punctures performed. The patients were then asked about the most painful time of the procedure: needle insertion, during puncture, after puncture, repeat puncture, or no pain at all. They were also asked about their medical history, including tobacco use, risk factors for atheroma, and main respiratory diagnosis and whether they had undergone an arterial puncture in the past. The physician assessed the anxiety that patients may feel with respect to future arterial punctures using the same VAS-A described above.

Patients were followed-up until the end of the consultation with the physician. Eleven physicians were involved in the study.

The primary outcome was pain experienced during arterial puncture using VAS-P. Secondary outcomes were the anxiety experienced before and after arterial puncture using VAS-A, time to perform arterial puncture, the most painful moment of the procedure.

The present study was conducted in accordance with the amended Declaration of Helsinki. Our Institutional Review Board approved the protocol (CPP-SC 2011/01), and written informed consent was obtained from all patients prior the study. The study was registered with ANSM (Agence nationale de sécurité du médicament et des produits de santé/French Drug and Healthcare Product Safety Agency) (number 2010-A01373-36) prior its initiation. The study was registered at ClinicalTrials.gov (identifier [NCT02320916](#)) after completion, as it was already registered in the national registry. All the data were collected in Rouen Respiratory Department.

Statistical Analysis

In order to detect a clinically significant 13-mm change in the pain score [19] with an alpha risk set at 0.05, a beta-risk set at 0.1 resulting in a power of 0.9 and an expected standard

derivation set at 28mm based on the results of prior studies [2,13,14], a total of 196 patients were needed. We planned to include 200 patients in the study to ensure that we would have clinically significant results in the event of patient non-compliance or withdrawal.

Results are expressed as headcounts and percentages, means and standard deviation (SD) or medians, and first and third quartiles (IQR). Comparisons were performed using the Mann-Whitney, Wilcoxon match-paired ranking test, Kruskal-Wallis, ANOVA, and chi-square tests. Correlations were assessed using the Spearman correlation coefficient. A multiple linear regression was performed to look for independent variables related to the pain experienced by the patient. Following univariate analysis, a p value lower than 0.20 for a clinically relevant variable was necessary to enter stepwise multiple regression analysis. Assumptions of linearity and normality and no multicollinearity have been fulfilled before performing multiple regression analysis. Multiple linear regression was used for multivariate analysis. All tests were two-sided, the type I error rate was set at 0.05. The analyses were performed using GraphPad Prism 6[®] for Mac OS X[®] (GraphPad Software, La Jolla, CA, USA).

Results

Two-hundred-twenty-four consecutive patients were screened, and 200 were included in the study (Fig 1) between April 11 and May 25, 2013 after full recruitment was achieved. Of the 24 patients excluded from the study, 18 refused to give consent and 6 were unable to give consent. As shown in Table 1, there was no statistically significant difference between groups at baseline.

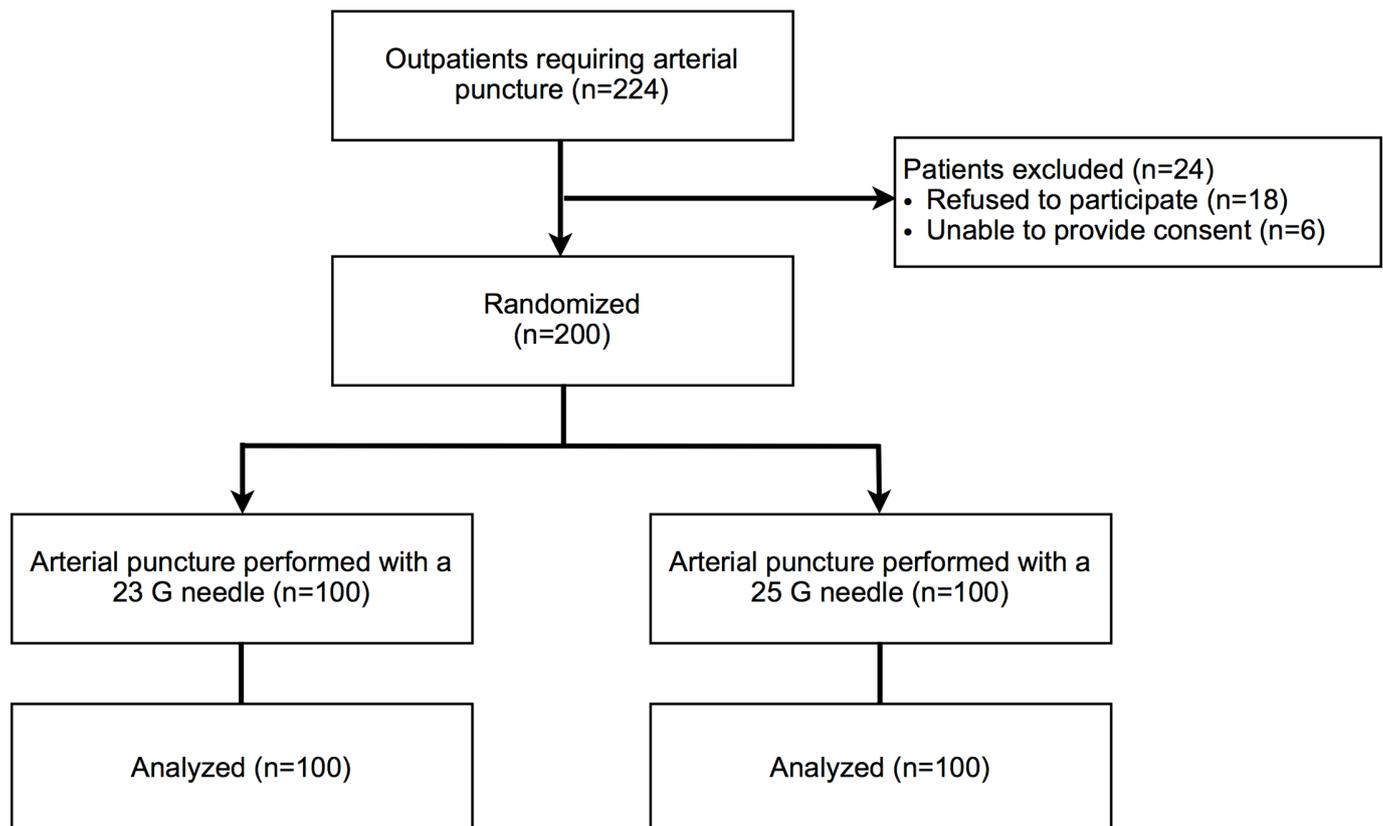


Fig 1. Flowchart.

doi:10.1371/journal.pone.0139432.g001

Table 1. Characteristics of patients.

Variables	23 G needle (n = 100)	25 G needle (n = 100)	p
Age, mean (SD)	66.01 (13.17)	63.39 (15.21)	0.35
Gender, n(%)	53 (53%)	53 (53%)	1
Body Mass Index, mean (SD)	32.03 (8.24)	31.6 (9.42)	0.35
Underlying respiratory disease			
COPD, n(%)	29 (29%)	30 (30%)	
Asthma, n(%)	12 (12%)	6 (6%)	
OHS, n(%)	7 (7%)	6 (6%)	0.78
OSA, n(%)	24 (24%)	23 (23%)	
Other, n(%)	28 (28%)	35 (35%)	
Tobacco use			
Never smoked, n(%)	38 (38%)	38 (38%)	
Former smoker, n(%)	51 (51%)	46 (46%)	0.65
Active smoker, n(%)	11 (11%)	16 (16%)	
No previous arterial puncture, n(%)	21 (21%)	22 (22%)	0.86
Wrist diameter (cm), mean (SD)	17.84 (2.54)	17.68 (2.45)	0.42
Quality of radial pulse			
Pulse not felt, n(%)	2 (2%)	0 (0%)	
Weak pulse, n(%)	25 (25%)	34 (34%)	
Normal pulse, n(%)	56 (56%)	46 (46%)	0.13
Hard beating pulse, n(%)	16 (16%)	15 (15%)	
Visible pulse, n(%)	1 (1%)	5 (5%)	

doi:10.1371/journal.pone.0139432.t001

The most common underlying respiratory disease was COPD (29% in the 23 G needle group, 30% in the 25 G needle group), and most of the patients had a history of tobacco use (62% in both group). At inclusion, most of the patients had undergone a previous arterial puncture (79% in the 23 G needle group, 78% in the 25 G needle group). Five experienced nurses performed a total of 210 arterial punctures. There was no statistical difference in the number of arterial punctures they performed in each group ($p = 0.47$).

There was no statistically significant difference in the pain experienced by patients using a 23 G needle (6.63 mm [0–19 mm]) or a 25 G needle (5.21 mm [0–18.49 mm]) ($p = 0.53$) (Table 2). There was no nurse-related difference in pain experienced by the patients ($p = 0.49$). There was a significant inter-group difference in terms of the most painful time during the arterial punctures ($p = 0.03$). In the 23 G needle group, pain was more frequent at needle insertion than in the 25 G needle group ($p = 0.047$) (Fig 2). Rate of failure to perform arterial

Table 2. Time required for and pain and anxiety related to arterial punctures.

	23 gauge needle (n = 100)	25 gauge needle (n = 100)	p
Pain (mm), median [IQR]	6.63 [0–19]	5.21 [0–18.49]	0.53
Time required for AP (s), median [IQR]	33 [24.5–35]	42 [35–55]	0.002
Anxiety prior to AP (mm), median [IQR]	5.21 [0–27.9]	5.21 [0–24.7]	0.88
Anxiety after AP (mm), median [IQR]	1 [0–8]	1 [0–8]	0.99

doi:10.1371/journal.pone.0139432.t002

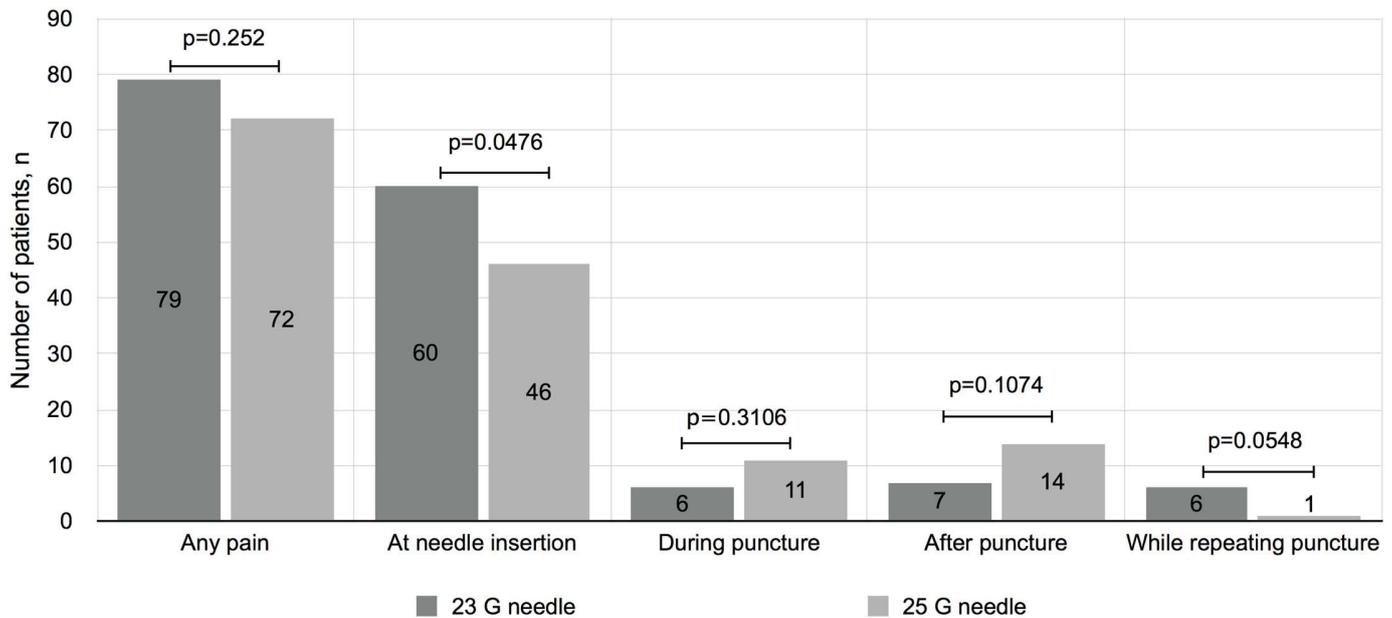


Fig 2. Most painful moment during arterial puncture. Distribution of the most painful time during the arterial punctures for each needle size ($p = 0.0348$).

doi:10.1371/journal.pone.0139432.g002

puncture was similar in both group: 7% in the 23 G needle and 3% in the 25G needle ($p:0.19$). None of the patients had more than two arterial punctures in either arm. Seven of these ten patients reported that the repetition of the arterial punctures was the most painful experience. All second arterial punctures were successfully performed using the same needle.

Arterial punctures took significantly more time when using the 25 G needle (42 s [35–55 s]) compared to the 23 G needle (33 s [24.5–35 s]) ($p = 0.002$) (Table 2). There was no correlation between the time required for the arterial punctures and the pain experienced by the patients ($p = 0.42$) or between the time required for the arterial punctures and wrist diameters ($p = 0.95$). However, the correlation between the time required for the arterial punctures and the quality of the pulse was statistically significant. The arterial punctures took significantly more time for patients with the weakest pulses ($p: -0.244, p < 0.001$).

The anxiety experienced by the patients in each group was similar prior to and after the arterial punctures ($p = 0.88$ and $p = 0.99$, respectively) (Table 2). In the overall study population, the anxiety experienced by the patients prior to the arterial punctures was moderately correlated with the pain experienced by the patients ($p: 0.369, p < 0.001$). In the overall study population, the anxiety experienced by the patients with respect to future arterial punctures was correlated with the pain experienced during the arterial punctures ($p: 0.512, p < 0.001$). In the overall study population, there was a correlation between the anxiety experienced with respect to future arterial punctures and the level of anxiety experienced prior to the arterial punctures ($p: 0.461, p < 0.001$) (Fig 3). In the overall population multivariate analysis indicated that pain was related only to anxiety prior to arterial punctures (multiple $r^2 = 0.32, p < 0.001$) (Table 3). While there was a significant difference among nurses with respect to the level of anxiety experienced by the patients prior to the arterial punctures ($p = 0.004$), there was no difference with respect to the level of anxiety following the arterial punctures ($p = 0.59$). There was a decrease in the level of anxiety before and after the arterial punctures (5.28 mm [0–25 mm] and 1 mm [0–7.3 mm], respectively, $p < 0.001$).

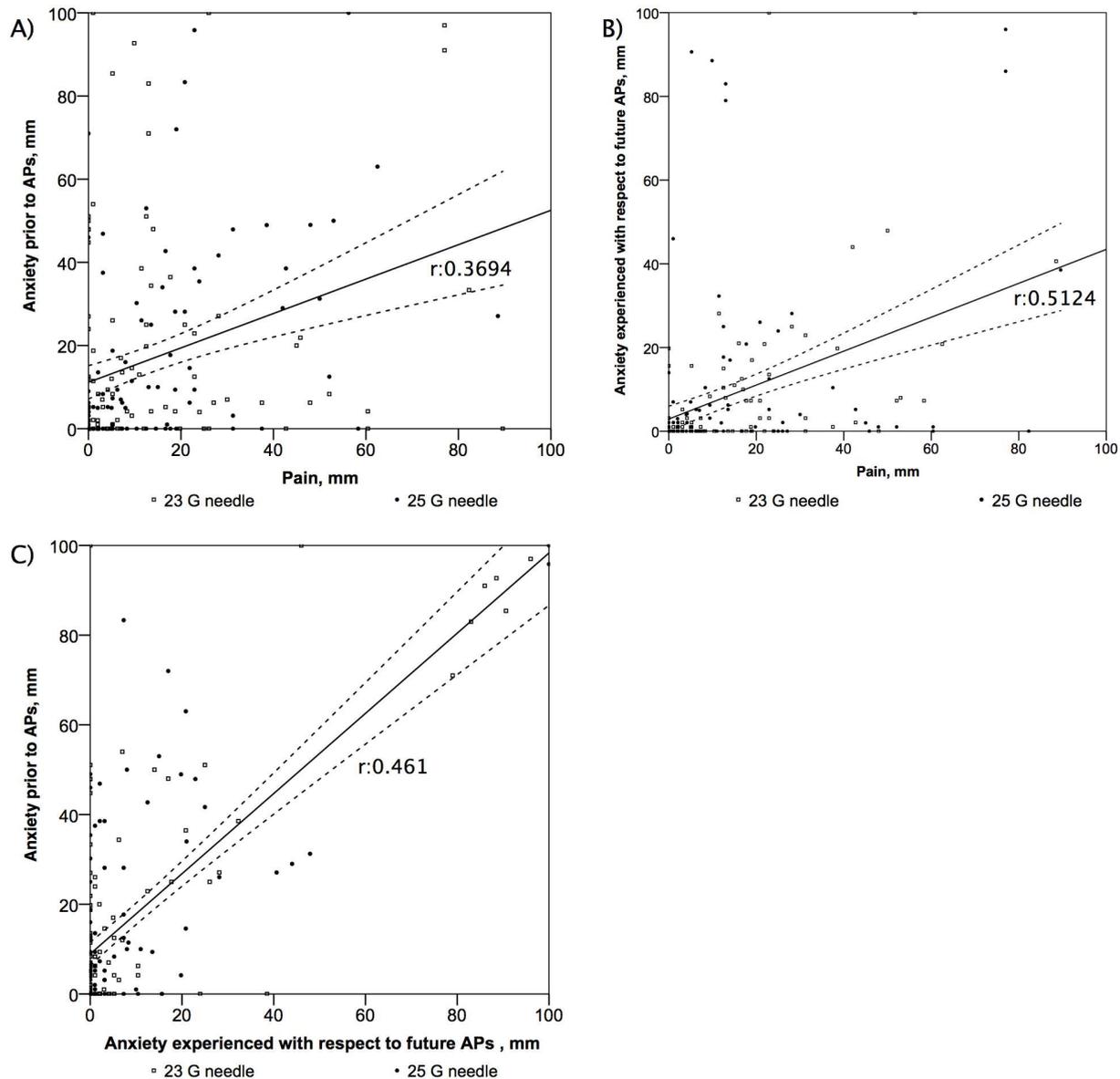


Fig 3. Correlations between anxiety and pain. (A) Correlation between anxiety prior to the arterial punctures and pain ($\rho:0.3694$, $p<0.001$), (B) Correlation between the pain experienced during the arterial punctures and the anxiety experienced with respect to future arterial punctures ($\rho:0.5124$, $p<0.001$), (C) Correlation between the anxiety experienced prior to the arterial punctures and the anxiety experienced with respect to future arterial punctures ($\rho:0.461$, $p<0.001$).

doi:10.1371/journal.pone.0139432.g003

Table 3. Multivariate analysis: independent pain-related variables.

Variable	Correlation coefficient	Multiple correlation coefficient	Coefficient	Standard error	p
Anxiety prior to AP		0.31	0.24	0.05	<0.001
Time required for AP	0.09	-	-	-	NS
Numbers of previous AP	0.04	-	-	-	NS

NS = non significant

doi:10.1371/journal.pone.0139432.t003

Discussion

Our study showed that needle gauge has no significant impact on the pain experienced by patients during arterial punctures and that the use of small gauge needles lengthens the time required for the arterial punctures by about 10 s. Our study also provided more detailed information on the type of pain experienced by patients and its correlation with anxiety.

Arterial blood pressure is correlated with the filling time of syringes with 23 G needles [20]. While we did not record the arterial blood pressure of our patients, the time required to fill the syringes may explain the lack of a significant difference in pain experienced by patients between the needle gauges. Patients in the 25 G group reported experiencing pain during the arterial punctures more frequently than patients in the 23 G group. This might be due to greater nociceptive stimulation caused by the longer time required for needle insertion. On the other hand, the 23 G needle caused more pain at insertion, which may be due to the wider skin breach. Since the time required for arterial punctures was longer for patients in the 25 G group and since the level of pain experienced was similar to the 23 G group, we do not recommend the use of 25 G needles for arterial punctures.

Like previous interventional studies on pain associated to ABG, our study did not find any difference in the level of pain between each group. Interestingly, the level of pain experienced in our study is lower than the level of pain described in the literature. Indeed, the level of pain assessed was 6.63 and 5.21mm in each group. This level of pain is lower than the ones that have been reported in previous works in the placebo groups: 30.1 [2], 20.7 [13] and 23.8 [14]. We hypothesize that this difference may be due to the fact that trained nurses performed the arterial punctures. Recently, the effect of cryoanalgesia prior to arterial puncture was assessed and showed a significant reduction in the level of pain due to arterial puncture [21]. This study on cryoanalgesia was not double-blind but all the arterial punctures were performed by a same experimented pulmonary function technologist. In the intervention arm, the median level of pain was similar to the ones observed in our study.

To the best of our knowledge, our study is the first to assess the impact of anxiety on the pain experienced by patients during arterial punctures. Several studies have reported a correlation between anxiety and pain in other settings [22,23]. Our results showed that there is a correlation between the level of anxiety and the pain experienced by patients. This correlation is mild but was still significantly associated with pain in multiple linear regression. Even if the correlation between pain and anxiety is mild, reassurance of patient prior to puncture appears as a simple, non-pharmacological and inexpensive way to decrease the level of pain felt by the patients. Thus, we think that providing explanations to patients and reassuring them may decrease the level of arterial puncture-related pain. This hypothesis is reinforced by our results showing that the level of anxiety reported by patients was significantly different with respect to the nurse performing the arterial puncture. This may be due to differences in the behaviour of the nurses. While the use of a VAS-A has not been validated to the same extent as VAS-P, previous studies have shown that a VAS-A is a reliable way to evaluate anxiety [18]. To maintain the blindness of our study, we prevented patients from seeing their wrist during the arterial punctures. We could not determine whether this had a positive or negative impact on the level of anxiety.

As pain management is now a cornerstone of the care that has to be provided to patients and as pulmonary gas exchange assessment remains central to manage patients with breathing disorder, we think further research should be led in that field. As they often tend to have repeated ABGs, patients in acute respiratory failure are of special interest. Indeed, rather than a precise isolated value, the kinetic of their gas exchange is a more relevant information as it guides physicians' treatment. In that perspective, non-invasive tool such as transcutaneous capnography or electrical impedance tomography could be of particular interest.

Our study had several limitations. First, it was conducted in a single center with nurses experienced in performing arterial punctures and with patients in a steady state. We cannot thus extrapolate our results to patients with acute respiratory failure and to patients in whom arterial punctures would not be performed by experienced nurses. However, our study reproduced the daily clinical practice of chest physicians. Second, most of the patients had already experienced arterial punctures in the past. This may explain why the level of pain observed in our study was lower than in previous studies.

Conclusion

Our study showed that pain associated with arterial puncture is not correlated with needle gauge and that anxiety is correlated with pain. We recommend the use of 23 gauge needles since they require less time than 25 gauge needles to perform the procedure. We also recommend that patients should be reassured prior to the arterial puncture. Further studies should be conducted to identify novel strategies to reduce the level of pain experienced by patients undergoing arterial punctures.

Supporting Information

S1 File. Research protocol.

(PDF)

S2 File. Dataset.

(PDF)

S3 File. Consort check list.

(PDF)

S1 Image. Setup to ensure that the patient is blind for the needle used by the nurse. Patients were installed on the right of the curtain and inserted their wrist between the curtains. Nurses were installed on the left of the curtain and performed the arterial puncture as well as the record the duration of the sampling using the chronometer.

(TIFF)

Acknowledgments

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Full protocol can be accessed by simple request to the correspondent author.

Author Contributions

Conceived and designed the experiments: MP BL AC JFM. Performed the experiments: MP BL LCM CV DB AC JFM. Analyzed the data: MP BL EL AC. Contributed reagents/materials/analysis tools: MP BL EL LCM CV DB AC JFM. Wrote the paper: MP BL EL AC JFM.

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Figure 1: Setup to ensure that the patient was blinded to the needle used by the nurse in study ⁶.

In this study ⁶, the main findings were:

- Needle Gauge does not have an impact on the level of pain experienced by the patient.
- A faster filling of the syringe is achieved with the larger Gauge.
- The weight of the patient and their wrist diameter does not impact success rate.
- Pain is closely related to the level of anxiety prior to the ABG. Reassurance could therefore be an easy way to decrease the level of pain experienced.
- An ABG performed by a trained nurse is associated to a low level of pain.

2. Aetiologies of type I respiratory failure

a) Interstitial lung diseases

Advanced interstitial lung diseases (ILD) are an heterogeneous group of disease that share in common an altered diffusion of O₂ secondary to alveolar wall thickening and V/Q mismatch. Although antifibrotic treatment are now available ⁷, the mortality of ILD remains high ⁸. In this group of disease, the use of long-term of oxygen therapy (LTOT) is not supported by randomised clinical trial ⁹. However, national and international guidelines recommend the use of long term oxygen therapy ¹⁰⁻¹³ and a growing level of evidence suggests the benefit of exercise ¹⁴ or ambulatory oxygen ¹⁵.

Although patients with end-stage ILD may develop hypoventilation secondary to a severe reduction of their vital capacity, the use of NIV is not supported by any data and its use during acute exacerbation of the disease is associated to a 50% mortality rate ¹⁶. Introduction of NIV in this population should be discussed in expert centres in collaboration with palliative care team.

b) Pulmonary hypertension

Pulmonary hypertension (PH) can complicate chronic hypoxemia ¹⁷. It has been shown, that in that circumstances, the administration of oxygen could reverse PH ¹⁸.

In primary PH, very few studies have assessed the benefit of LTOT. Hemodynamic data show a physiological benefit ¹⁹. A large cohort data suggests a mortality benefit in patients receiving supplemental oxygen ²⁰. Recently, a randomised controlled trial showed a benefit in exercise capacity and quality of life ²¹.

c) Other respiratory diseases

Other diseases may require LTOT like lung cancer. In these situations, LTOT is delivered as part of multidisciplinary management and targets symptoms relief rather than hypoxemia correction ²².

3. Aetiologies of type II respiratory failure

When CRF is only caused by alveolar hypoventilation, the sole administration of oxygen is contra-indicated as it blunts the hypoxic drive and results in a P_aCO_2 worsening. Patients with chronic hypoventilation have a decreased hypercapnic drive response²³. Therefore, in type II CRF, NIV is the first line treatment of CRF. When setup, NIV needs to overcome hypoventilation and to target P_aCO_2 reduction. Similarly to oxygen, the number of patients setup on home NIV is increasing over time²⁴. Despite some variations across Europe²⁵, diseases causing type II respiratory failure can be categorised as follow:

a) Slowly progressive neuro-muscular diseases

Slowly progressive NMD are characterized by a low decrease of vital capacity that result firstly in nocturnal hypoventilation²⁶ and then, type II CRF. The diagnosis of the neuromuscular disease is usually made before the onset of the CRF. Therefore, multidisciplinary follow-ups that include chest physicians are required to identify when NIV needs to be introduced.

The most frequent cause of slowly progressive NMD with respiratory involvement in children is Duchenne muscular dystrophy (DMD)²⁷. In this population, change in the breathing pattern preceded NIV requirements²⁸ and were influenced by the degree of scoliosis and the use of steroids. Systemic steroids have meaningful benefit in that population^{29,30} and delay NIV initiation³¹ but cannot avoid it. The use of NIV is well established in this population^{32,33}.

In adults, the most frequent neuromuscular cause of congenital type II CRF is type I myotonic dystrophy. There is no randomised clinical trial evaluating the benefit of home NIV in this population. However, cohort data suggest a benefit on mortality. O'Donoghue *et al.* shown that NIV withdrawal is associated to a significant increase of P_aCO_2 after one month³⁴. In this population, the use of NIV is particularly challenging as their compliance is poor mainly because of the cognitive impairment associated to the disease³⁵. Yet, successful NIV setup is a factor associated to survival³⁶.

In adults, post-polio syndrome was a frequent cause of type II CRF. Thanks to vaccination, the number of patients is decreasing³⁷. However, numerous patients benefit from the use of NIV that provide them with satisfactory quality of life^{38,39}.

The other NMD that can cause respiratory failure are summarised in table 1 derived from⁴⁰.

Neuropathic disease
<i>Motor neuron disease</i>
Amyotrophic lateral sclerosis
Poliomyelitis, post-polio syndrome
Spinal muscular atrophy
Paralytic rabies
<i>Peripheral neuropathies</i>
Guillain–Barré syndrome, Chronic inflammatory demyelinating polyneuropathy
Critical illness polyneuropathy
Unilateral or bilateral diaphragm paralysis
Charcot–Marie–Tooth disease
Disorders of the neuromuscular junction
Myasthenia gravis, congenital myasthenic syndrome, Lambert–Eaton myasthenic syndrome
Botulism, poisoning with curare and organophosphate
Myopathies
<i>Acquired myopathies</i>
Polymyositis, dermatomyositis
Critical illness myopathy
<i>Inherited myopathies</i>
<i>Progressive muscular dystrophy</i>
Duchenne muscular dystrophy
Becker muscular dystrophy
Facioscapulohumeral muscular dystrophy
Limb-girdle muscular dystrophy
Myotonic dystrophy
<i>Congenital myopathies</i>
Nemaline myopathy, core diseases, myotubular myopathy
<i>Congenital muscular dystrophy</i>
Ullrich congenital muscular dystrophy, Emery–Dreifuss muscular dystrophy, merosin-deficient congenital muscular dystrophy, merosin-positive congenital muscular dystrophy, rigid spine muscular dystrophy
<i>Metabolic myopathies</i>
Mitochondrial myopathy, glycogen storage disease type 2

Table 1: Neuromuscular diseases affecting respiratory function ⁴⁰.

b) Rapidly progressive neuro-muscular diseases

The most frequent rapidly NMD is amyotrophic lateral sclerosis (ALS). Patients with ALS have a wide range of symptoms and a variable but generally poor prognosis ⁴¹. Patients with bulbar symptoms may be at higher risk of developing CRF ⁴² as well as those with rapid decline of their vital capacity ⁴³. In patients with CRF, the use of NIV improves survival and quality of life ⁴⁴. In this population, NIV can be particularly challenging because of bulbar symptoms that can cause upper airway obstruction ⁴⁵.

c) Chest-wall diseases

Chest wall diseases are characterised by a decrease in chest wall compliance that lead to a restrictive CRF ⁴⁶. The most frequent causes of chest-wall diseases are kyphoscoliosis, thoracoplasty, pectus excavatum, ankylosing spondylitis or extensive scleroderma. In this indication, NIV has been shown to be beneficial since the late 80's ⁴⁷⁻⁴⁹.

d) Obesity hypoventilation syndrome

Obesity hypoventilation syndrome (OHS) has become one of the leading causes of NIV initiation ^{25,50}. NIV is an effective treatment to improve quality of life, P_aCO_2 , and sleep disordered breathing in patients with OHS and obstructive sleep apnea (OSA) ⁵¹⁻⁵⁵. With a growing number of obese patients worldwide ⁵⁶, the use of CPAP as an alternative mode of treatment ^{51,52,57} has been endorsed in American Thoracic Society guidelines ⁵⁸.

However, as it will be shown later in this thesis and highlighted by others ⁵⁹, patients with OHS should remain a significant proportion of patients setup on NIV because of (1) the existence of OHS without apnea ⁶⁰ (2) CPAP failure in OHS ⁶¹ and (3) the increased number of respiratory depressant drugs prescribed ^{62,63}. Moreover, as we will show later, a significant proportion of patients are setup following an acute type II respiratory failure. Such timing of NIV setup is associated to a poorer outcome ⁶⁴.

e) Chronic obstructive pulmonary disease

Although chronic obstructive pulmonary disease (COPD) also causes type I CRF, the management of type II CRF has been an ongoing debate over the last decades. The use of NIV in

COPD patients is part of clinical practice for the management of acute type II respiratory failure ^{65,66}. However, despite some physiological and clinical benefit shown in small sample size studies ⁶⁷⁻⁷⁰ or retrospective studies ⁷¹, the first randomised clinical trials were not conclusive ⁷²⁻⁷⁴. Failure to improve survival was probably explained by to the use of low level of pressure ^{72,73} and inadequate patient selection ^{74,75}.

In line with these hypothesis, more recent trials using high intensity NIV ⁷⁶⁻⁷⁸ have shown an improved survival in stable hypercapnic patients ⁷⁹ and a decrease in the readmission rate following an acute exacerbation ⁸⁰. Indication for the use of NIV in CRF secondary to COPD have been recently clarified by the European Respiratory Society ⁸¹.

f) Overlap syndrome between chronic obstructive pulmonary disease and obstructive sleep apnea

Given the prevalence of COPD ⁸² and of OSA, the estimated prevalence of overlap syndrome between COPD and OSA is 1% of the general population ^{83,84}.

COPD-OSA overlap syndrome is associated to a greater incidence of type II CRF ⁸⁵ and worsen hypoxemia ⁸⁶. Untreated, COPD-OSA overlap syndrome is associated with an increased mortality ⁸⁷. In COPD-OSA patients specially with hypercapnia, CPAP is more likely to fail ⁸⁸. Therefore, in patients with hypercapnia, NIV should be initiated. To date, there is no data regarding the benefit of NIV on exacerbation in patients with COPD-OSA.

4. Epidemiology of severe chronic respiratory failure

The prevalence and mortality of chronic respiratory diseases have increased over years across the world with international and national variations ^{89,90}. As CRF is the final evolution of chronic respiratory disease, it is not surprising to see an increase in the number of patients with CRF. The prevalence of LTOT had a 3.7 fold increase from 1987 to 2015 in Sweden ⁹¹ and is expected to increase furthermore specially in women ⁹². In France, the proportion of patients setup on LTOT alone is decreasing in favour of administration of both NIV and LTOT ⁹³.

Despite some differences between countries ²⁵, NIV is now part of common clinical practice for patients with CRF. Though, there is very few data available regarding the long-term outcome of patients established on home NIV.

B. Original research: Long Term Survival Following Initiation of Home Non-invasive Ventilation: a European Study (Submitted to Thorax, 10/2019)

Data available regarding the long-term outcome of patients are focused on specific disease and/or single centres ⁹⁴⁻⁹⁷. The only large-scale cohort data available are ancient and also included patients established on LTOT ⁹⁸. More recent large scale data were only based on administrative data and lack of clinical information ⁹³.

We decided to review the outcome and setup of patients established on long-term non-invasive ventilation in the two centres in which this thesis was made. These two centres have different healthcare organisation and different ways to established home NIV.

The work was presented as an oral communication during the ERS 2015 ⁶⁴ and is currently under review in Thorax.

Patout M, Lhuillier E, Kaltsakas G, Declercq P-L, Benattia A, Dupuis J, Arbane G, Ramsay M, Marino P, Molano L-C, Artaud-Macari E, Viacroze C, Steier J, Douiri A, Muir JF, Cuvelier A, Murphy PB, Hart N. Long Term Survival Following Initiation of Home Non-invasive Ventilation: A European Study

Long Term Survival Following Initiation of Home Non-invasive Ventilation: A European Study

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AD: analysis, interpretation, revising critically

Abstract

Introduction: Although home non-invasive ventilation (NIV) is increasingly used to manage patients with chronic ventilatory failure there are limited data on the long-term outcome of these patients. Our aim was to report the home NIV populations and the long-term outcome from two European centres.

Methods: Cohort analysis, including all patients established on home NIV from two European centres, between 2008 and 2014.

Results: Home NIV was initiated in 1,746 patients to treat chronic ventilatory failure caused by a) obesity hypoventilation syndrome (OHS) +/- obstructive sleep apnea (OSA) (29.5%); b) neuromuscular disease (NMD) (22.7%); and c) obstructive airway diseases (OAD) (19.1%). Overall cohort median survival following NIV initiation was 6.6 years. Median survival varied by underlying aetiology of respiratory failure: rapidly progressive NMD 1.1 years, OAD 2.7 years, OHS+/-OSA > 7 years and slowly progressive NMD > 7 years. Multi-variate analysis demonstrated higher mortality in patients with: rapidly progressive NMD (HR 4.78, 95% confidence interval (CI) 3.38-6.75), COPD (HR 2.25, 95% CI 1.64-3.10), age > 60 years at initiation of home NIV (HR 2.41, 95%CI 1.92-3.02), and NIV initiation following an acute admission (HR 1.38, 95%CI 1.13-1.68). Factors associated with lower mortality were NIV adherence > 4 hours per day (HR 0.64, 95%CI 0.51-0.79); OSA (HR 0.51, 95%CI 0.31-0.84) and female gender (HR 0.79, 95%CI 0.65-0.96).

Conclusion:

Mortality rates following initiation of home NIV is high but varies significantly according to underlying aetiology of respiratory failure. In patients with chronic respiratory failure initiation of NIV following an acute admission and low levels of adherence are poor prognostic features. In patients with chronic respiratory failure initiation of NIV following an acute admission and low levels of adherence are poor prognostic features and may be amenable to intervention.

Key messages

What is the key question?

What is the long term the outcome of patients treated with home non-invasive ventilation?

What is the bottom line?

Median survival following home non-invasive ventilation initiation is 6.6 years. Adherence to treatment (>4hours/night) and elective timing of initiation of home non-invasive ventilation are modifiable factors associated to survival

Why read on?

This study identified factors associated to survival in a large cohort of patients treated with home non-invasive ventilation.

Introduction

Home non-invasive ventilation (NIV) is widely used for the management of chronic hypercapnic respiratory failure in both Europe [1] and the United States [2]. Whilst initially used in patients with chronic respiratory failure secondary to neuromuscular disease [3], there are increasing observational and randomised clinical trial data supporting the provision of home NIV in patients with obesity related respiratory failure [4,5] and chronic obstructive pulmonary disease (COPD) [6-8]. These data along with the increasing prevalence of obesity has led to an expansion in the number of patients established on home NIV [9,10]. However, unlike other chronic respiratory diseases such as idiopathic pulmonary fibrosis [11], lung cancer [12] and pulmonary hypertension [13], the long-term outcome of patients with chronic hypercapnic respiratory failure treated with home NIV remains unclear. Previous data included patients receiving long-term oxygen and invasive ventilation [14] and lack generalizability due to the focus on a specific underlying respiratory disease from single centres [15-19]. Furthermore, since the available cohort data were published NIV devices [20,21] and setup strategies [22,23] have evolved leading to significant changes in clinical practice. The aim of the current study was to report the underlying disease types for patients established on home NIV, the NIV device parameters and the long-term outcome from two European specialist centres.

Methods

We conducted a cohort analysis of patients set up on home NIV in two expert centres; one in France and one in the United Kingdom. The study was approved by the local ethic committee of Rouen University Hospital, France (#E2017-21), and registered as a service evaluation at Guys and St Thomas' NHS Trust, London, United Kingdom (#7511).

Population

Patients were prospectively included in administrative databases used for equipment-related purposes in two adult respiratory centres. Medical data and clinical outcome were retrospectively reviewed by selecting all patients that were newly established on long-term home NIV between 2008 and 2014. We excluded all patients set up on continuous positive airway pressure (CPAP), adaptive servo-ventilation and patients receiving invasive ventilation via a tracheostomy. Decision to initiate home NIV was made by a home ventilation specialist. Patient selection was in line with published guidelines; with NIV prescribed for patients with chronic hypercapnic respiratory failure and sleep disordered breathing or in eucapnic patients with severe OSA with significant residual apnoea-hypopnea index (>30/hour) on maximal (20cmH₂O) CPAP therapy. Home NIV was established at inpatient assessment using respiratory polygraphy and/or overnight transcutaneous oximetry and/or morning arterial blood gas according to local established protocols. Overnight titration was performed to treat sleep disordered breathing and manage daytime chronic ventilatory failure. Based on clinical practice, patients were instructed to use their NIV for at least 4 hours/day but ideally the full duration of their sleep. Patients with progressive neuromuscular disease were provided with devices with an internal battery and advised to extend use into wakefulness with disease progression.

Ventilator databases

For Rouen, the database was retrieved from ADIR Assistance (Asten santé, Orvault, France) a healthcare provider that delivers home NIV for Rouen University Hospital. For London, the database was retrieved from Lane Fox Respiratory Service technical ventilator database e-record system that records home NIV set up for Guy's & St Thomas' NHS Foundation Trust. In both centres, those technical databases included patients' identification, date of birth, date of setup, initial ventilator and settings used,

interface, prescribed duration of ventilation, hours of NIV use (adherence), and date of last contact with patient. Adherence to NIV was measured using the number of device blowing hours divided by the number of days following NIV setup. Change in settings or interface were not systematically recorded and therefore were not included in the analysis. Patients were followed up until death or censored at the point of last verified health status or loss of contact with home ventilation centre. When applicable, date of cessation of follow up from the NIV centre was recorded. Reasons for follow up cessation were classified as follows: a) death; b) non-adherence (< 4 hours per night and clinical decision to withdraw therapy); c) NIV no longer required; d) care transferred to another centre. Satisfactory adherence was defined as a use >4 hours/day however, NIV cessation was led to physician discretion.

Medical electronic record

Medical data were retrieved from hospital electronic medical record by respiratory physicians using a standardised collection sheet (MP, EL, AB) who checked and confirmed their accuracy. Collected data were gender, underlying respiratory disease and timing of NIV setup. Timing of NIV setup was defined as follow: elective admission for stable patients referred for respiratory review that were subsequently established on home NIV and following an acute episode for patients admitted for decompensated respiratory failure and for which, after clinical stabilisation but before hospital discharge, transfer to a specialist centre for home NIV setup was decided to be clinically necessary. Data from technical databases were cross-checked with medical records and corrected accordingly. Based on the underlying pathology, patients were categorized into six different groups: neuromuscular disease (NMD), chest-wall disease (CWD), obesity-hypoventilation syndrome (OHS), obstructive sleep apnoea (OSA), obstructive airway diseases (OAD) or with an overlap between and chronic obstructive pulmonary disease and obstructive sleep apnoea (COPD-OSA Overlap). For survival analysis, the NMD group was subdivided into rapidly progressive NMD (e.g. motor neuron disease) or slowly progressive NMD (e.g. Duchenne muscular dystrophy, myotonic dystrophy) (a full list of underlying neuromuscular disorders can be found in Table E1 of the On-Line Supplement).

Statistical analysis

Continuous data are presented as mean and standard deviation if normally distributed or median and interquartile range if non-normally distributed. Categorical data are presented as frequency counts and percentages. Comparisons are performed using Kruskal-Wallis test, chi-square Test, ANOVA and Mann-Whitney Test, as appropriate. Survival data were analysed using Kaplan-Meier method and log-rank tests. Patients for whom home NIV was withdrawn and were censored at point of cessation of follow up. Prognosis factors were analysed in univariate analysis and with a multivariate Cox model. For all tests, significance level was set at 0.05. Analyses were performed using SPSS v23.0 (IBM Corp., Chicago, IL, USA) and Prism v6.0(h) for MacOs X (GraphPad Software, La Jolly, Ca, USA).

Results

Diagnostic groups

From 2008 and 2014, 1,746 patients were established on home NIV: 1,118 (64%) in London and 628 (36%) in Rouen (*Figure 1*) with median follow up of 1.97 [0.78 – 3.78] years.

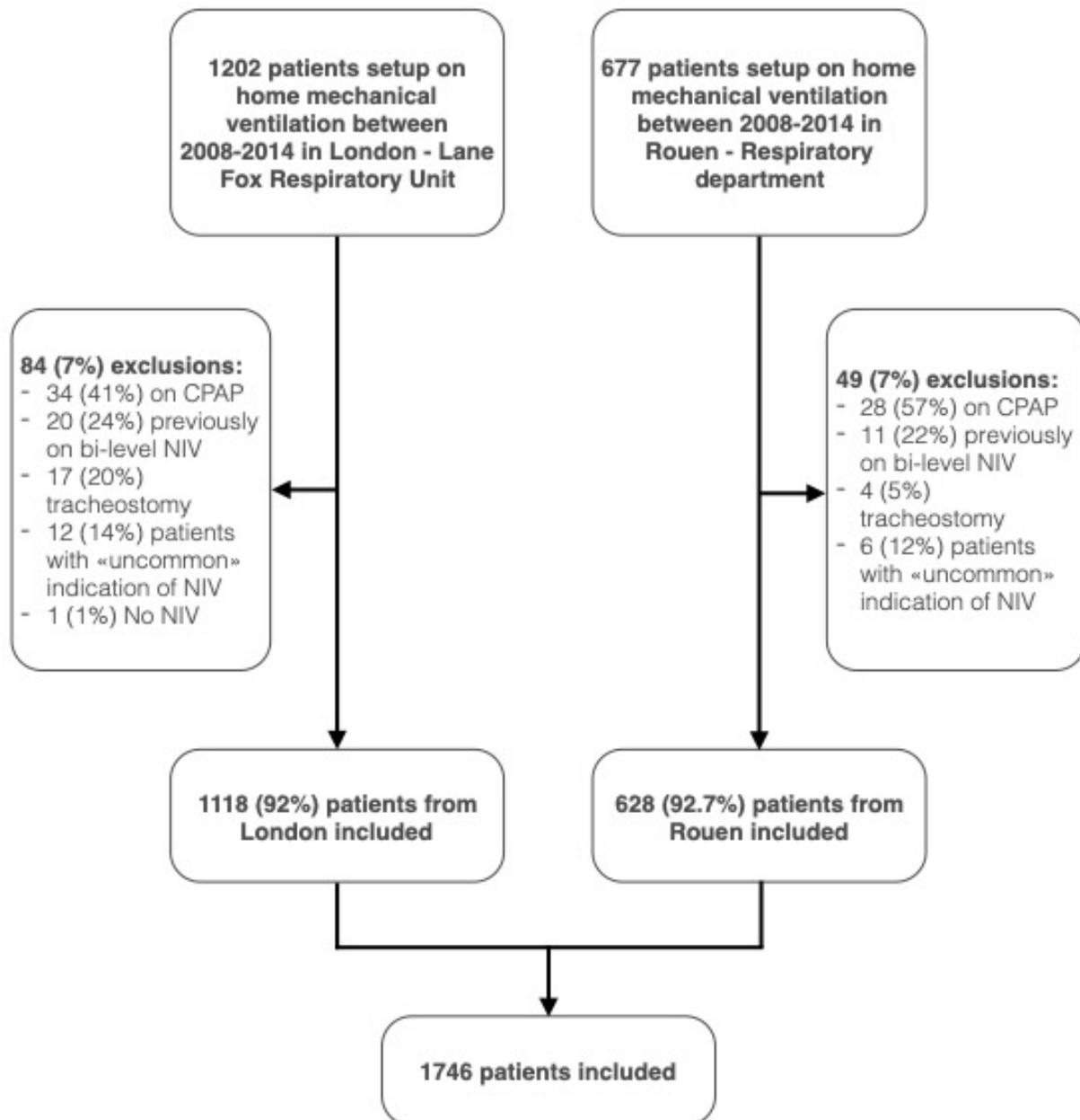


Figure 1: Study population flow-chart. (CPAP: continuous positive airway pressure, NIV: non-invasive ventilation)

Over the study period, the number of patients' set up on home NIV increased by 5% per year with 203 patients being setup in 2008 and 298 in 2014 (*eFigure 1*). Baseline characteristics of the population are

described in *Table 1*. Patients set up in London were younger than patients set up in Rouen ($p:0.001$). Most frequent diagnostic category was obesity hypoventilation syndrome ($n=515$, 29.5%), followed by neuromuscular disease ($n=397$, 22.7%), obstructive airway disease ($n=334$, 19.1%) and COPD overlap with obstructive sleep apnea ($n=221$, 12.7%). Obstructive sleep apnea and chest wall diseases were less frequent ($n=184$, 10.5%, and $n=95$, 5.4%, respectively). The distribution of diagnostic categories was different between the two centres ($p:0.007$). There was a higher proportion of NMD and lower proportion of obstructive airways patients in the London centre compared to the Rouen centre ($p=0.001$).

	Total population (n=1,746)	London population (n=1,118)	Rouen population (n=628)	P
Age (years)	60.5 (±15.9)	58.8 (±15.7)	63.6 (±15.8)	<0.001
Gender (male)	949 (54%)	613 (55%)	336 (54%)	0.617
PaCO₂ at admission for NIV setup (kPa)*	7.1 [6.2 – 8.1]	7 [6.1 – 8.0]	7.5 [6.6 – 8.8]	<0.001
Spirometry at NIV setup **				
FEV1 (L)	1.1 [0.7 – 1.6]	1.1 [0.7 – 1.7]	1.0 [0.7 – 1.4]	0.078
FVC (L)	1.7 [1.2 – 2.4]	1.7 [1.1 – 2.4]	1.9 [1.4 – 2.4]	<0.001
Underlying respiratory disease				0.007
Neuromuscular diseases	397 (22.7%)	290 (25.9%)	107 (17%)	<0.001
Motor neuron disease	144 (36.3%)	84 (29%)	60 (56.1%)	
Duchenne muscular dystrophy	49 (12.3%)	37 (12.8%)	12 (11.2%)	
Post-polio syndrome	40 (10.1%)	39 (13.4%)	1 (0.9%)	
Myotonic dystrophy	27 (6.8%)	19 (6.6%)	8 (7.5%)	<0.001
Spinal cord injury	24 (6%)	14 (4.8%)	10 (9.3%)	
Diaphragm palsy	21 (5.3%)	13 (4.5%)	8 (7.5%)	
Other neuromuscular conditions [£]	92 (23.2%)	84 (29%)	8 (7.5%)	
Obstructive airway diseases	334 (19.1%)	199 (17.8%)	135 (21.5%)	0.001
Chronic Obstructive Pulmonary Disease	305 (91.3%)	182 (91.5%)	123 (91.1%)	
Bronchiectasis	14 (4.2%)	8 (4%)	6 (4.4%)	
Asthma	10 (3.0%)	5 (2.5%)	5 (3.7%)	0.733
Other obstructive conditions [£]	5 (1.5%)	4 (2%)	1 (0.7%)	
Chest wall diseases	95 (5.4%)	59 (5.3%)	36 (5.7%)	0.714
Kyphoscoliosis	58 (61.1%)	32 (53.3%)	26 (72.2%)	
Scoliosis	15 (15.8%)	15 (25.0%)	0 (0%)	
Post-tuberculosis	10 (10.5%)	3 (5.0%)	7 (19.4%)	0.003
Pneumonectomy	5 (5.3%)	3 (5.0%)	2 (5.6%)	
Other restrictive conditions [£]	7 (8.3%)	7 (11.6%)	1 (2.8%)	
Obesity hypoventilation syndrome with or without obstructive sleep apnea	515 (29.5%)	319 (28.5%)	196 (31.2%)	0.251
Obstructive sleep apnea	184 (10.5%)	122 (10.9%)	62 (9.9%)	0.517
Overlap between obstructive airway disease and sleep apnea	221 (12.7%)	129 (11.5%)	92 (14.6%)	0.072
Chronic Obstructive Pulmonary Disease	206 (93.2%)	122 (94.6%)	84 (91.3%)	
Asthma	10 (4.5%)	6 (4.7%)	4 (4.3%)	0.588
Bronchiectasis	5 (2.3%)	1 (0.8%)	4 (4.3%)	

Table 1: Baseline demographics of study population (results expressed in terms of mean and standard deviation or median and interquartile for continuous variable and in frequency for categorical values, [£] full list of other conditions can be found in annex 1, * n: 1096, ** n: 803

PaCO₂: Partial arterial carbon dioxide pressure, NIV: non-invasive ventilation, FEV1: Forced expiratory volume at 1 second, FVC: Forced vital capacity

Timing of NIV initiation and ventilator settings

Timing of NIV set up (post-acute and elective) and ventilator settings differed between centres. The Rouen group had a higher proportion of NIV setups following an acute admission (60.5% vs 53.9%; p<0.001) and had a longer length of stay regardless of whether NIV was set up acutely or electively (elective admission for NIV setup 2.0 days [2 – 4]; p<0.001 and non-elective admission for NIV set up

6.0 days [5 – 18]; $p < 0.001$). Ventilator device, mode, interface, pressure settings, back-up rate, and additional requirements varied significantly between centres (*Table 2*).

	Total population (n=1746)	London population (n=1118)	Rouen population (n=628)	p
NIV setup following an acute respiratory failure (yes)	824 (48.6%)	444 (53.9%)	380 (60.5%)	<0.001
Length of stay for NIV setup following an acute respiratory failure	10 [5-18]	7 [3-17]	13 [9-18]	<0.001
Length of stay for NIV setup following an elective admission	3 [2-4]	2 [2-3]	4 [3-4]	<0.001
Interface				
Full face mask	1,355 (77.6%)	882 (78.9%)	473 (75.3%)	
Nasal mask	238 (13.6%)	115 (10.3%)	123 (19.6%)	
Nasal pillows	64 (3.7%)	33 (3%)	31 (4.9%)	<0.001
Total face mask	47 (2.7%)	47 (4.2%)	0 (0%)	
Not available	42 (2.4%)	41 (3.7%)	1 (0.2%)	
Life support NIV (yes)*	609 (34.9%)	515 (46.1%)	94 (15%)	<0.001
NIV mode				
Pressure support	1,405 (80.5%)	859 (76.8%)	546 (86.9%)	
Pressure control	179 (10.3%)	144 (12.9%)	35 (5.6%)	
Spontaneous	89 (5.1%)	82 (7.3%)	7 (1.1%)	<0.001
Pressure support with target volume	40 (2.3%)	11 (1%)	29 (4.6%)	
Not available	33 (1.9%)	22 (2%)	11 (1.8%)	
Settings				
Positive inspiratory pressure (cmH ₂ O)	22±5	23±5	19±4	<0.001
Positive expiratory pressure (cmH ₂ O)	7±3	8±4	7±2	<0.001
Pressure support (cmH ₂ O)	14±5	15±5	12±3	<0.001
Back-up rate (/min)	13.2±2.5	13.4±2.8	12.8±1.6	<0.001
Additional oxygen (yes)	634 (36.3%)	247 (22.1%)	241 (38.4%)	<0.001

Table 2: Comparison of non-invasive ventilation setups and settings between London and Rouen (results expressed in terms of mean and standard deviation or median and interquartile for continuous variable and in frequency for categorical values - * defined by a ventilator with built-in battery and approved for invasive ventilation)

NIV: non-invasive ventilation

The level of pressure support was significantly different over the years ($p: 0.0069$) but with only a higher pressure support in 2011 and 2012 when compared to 2008: 13.5 [11.0 – 17.0] and 14.0 [10.0 – 17.0] vs. 13.0 [10.0 – 16.0] cmH₂O ($p: 0.049$ and 0.002 respectively) (eFigure 2). In each diagnostic group, ventilator settings used in the Rouen centre were lower than those used in London (*Figure 2*).

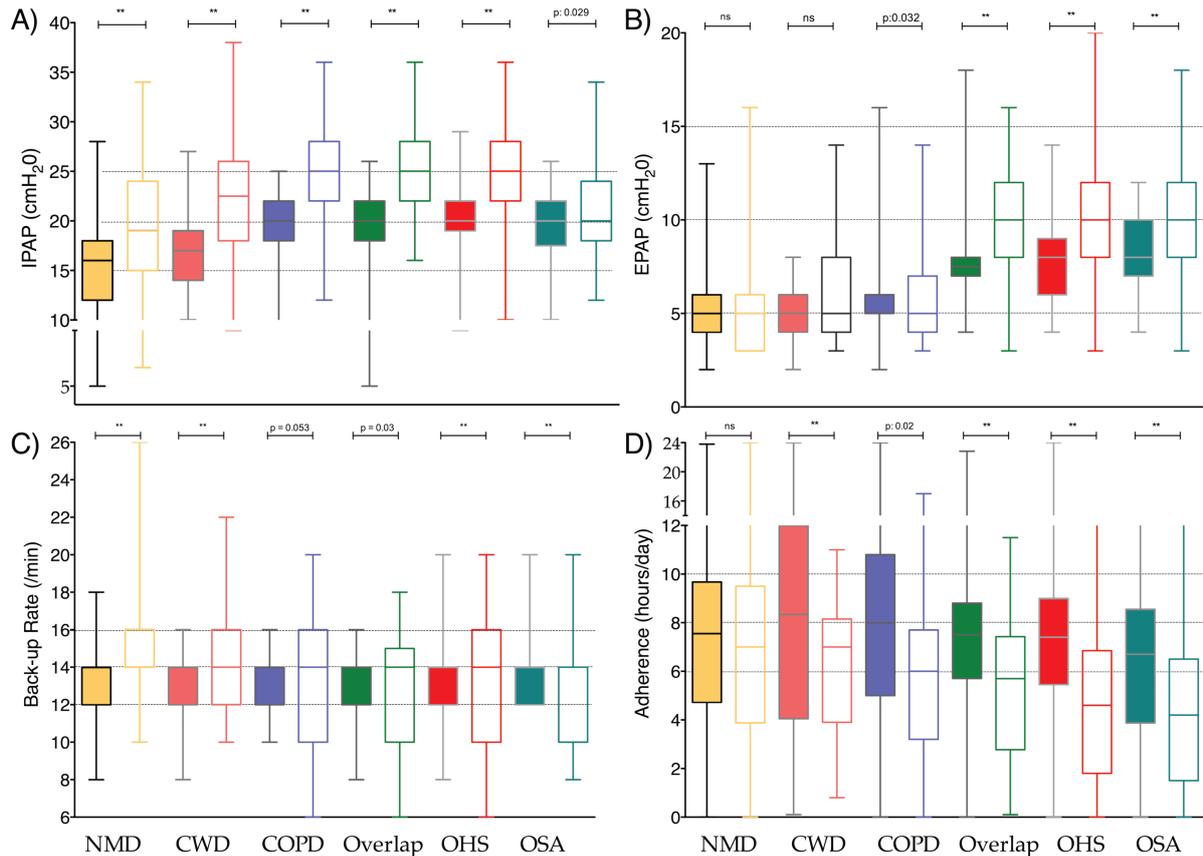


Figure 2: Comparison of NIV settings and adherence/day between London and Rouen according to diagnostic group. Panel A: Comparison of positive inspiratory pressure used. Panel B: Comparison of positive expiratory pressure used. Panel C: Comparison of back-up rate used. Panel D: Comparison of adherence

(IPAP: Inspiratory positive airway pressure, EPAP: Expiratory positive airway pressure, NMD : Neuromuscular disease group, CWD: Chest wall disease group, OAD: Obstructive airway disease group, Overlap: Overlap between OAD and obstructive sleep apnea group, OHS: Obesity hypoventilation syndrome, OSA: Obstructive sleep apnea group) (White box: London patients – Coloured box: Rouen patients, yellow: NMD), light red: CWD, blue: OAD, green: Overlap, red: OHS, grey-green: OSA, **: $p < 0.001$, ns: not significant)

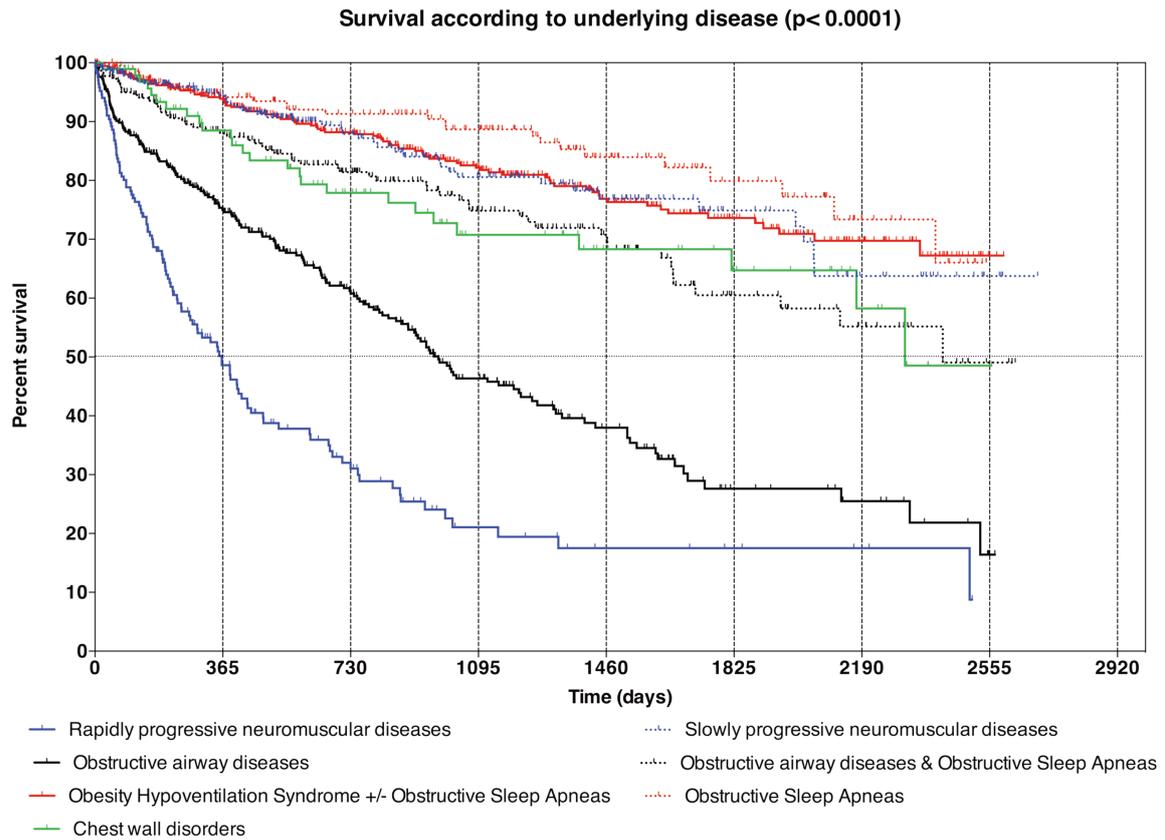
NIV adherence

NIV adherence to treatment was higher in the Rouen than the London centre (7.6 ± 4.6 hours/day vs. 5.5 ± 3.6 hours/day; $p < 0.001$). NIV adherence varied according to the underlying diagnostic group (NMD 7.1 [4.0 – 9.5] hours/day; CWD 7.5 [4.1 – 9.3] hours/day; OAD 6.5 [3.7 – 8.7] hours/day; OHS 5.8 [3.0 – 7.8]

hours/day; and OSA 5.5 [2.1–7.0] hours/day; $p < 0.001$). NIV adherence was higher in all diagnostic categories in the Rouen group, with the exception of the NMD category (*Figure 2*).

Survival

Following NIV initiation, overall survival was 6.63 years. Survival at 1 year, 3 years and 5 years were 85.9%, 68.7% and 58.3%, respectively, with a difference observed between the diagnostic categories ($p < 0.001$). Survival was 1.0 years in the rapidly progressive NMD category; 6.3 years in the CWD category; 2.7 years in the OAD category; and 6.6 years in the COPD-OSA overlap category. Median survival was not reached in the slowly progressive NMD, OHS and OSA groups (*Figure 3*).



	<i>Number of patients at risk</i>							
	365	730	1095	1460	1825	2190	2555	2920
Total	1229	876	613	392	228	118	18	0
Rapid MND	64	32	14	8	6	4	1	0
Slow MND	184	121	89	56	32	18	5	0
OAD	206	136	84	47	18	11	2	0
OAD-OAS	164	120	83	59	31	17	4	0
OHS	397	293	212	139	89	44	4	0
OSA	143	122	97	58	35	14	1	0
CWD	71	52	34	25	17	10	1	0

Figure 3: Survival curve after setup of home non-invasive ventilation depending on underlying disease.

Rapidly progressive neuromuscular disease group (Rapid NMD: continuous blue), slowly progressive neuromuscular disease group (Slow NMD: dashed blue), Obstructive airway disease group (OAD: continuous black), Overlap between COPD and obstructive sleep apnea group (COPD-OAS: dashed black), Chest wall disease group (CWD: light green), Obesity hypoventilation syndrome (OHS: continuous red), Obstructive sleep apnea group (OSA: dashed red)

In a univariate analysis, the centre of NIV initiation did not have any impact on prognosis (p=0.358), whereas an age > 60 years (p<0.001) and having NIV setup following an episode of acute respiratory

failure ($p < 0.001$) were both associated with a worse prognosis. In a multivariate analysis, age, gender, timing of NIV setup, and underlying disease were significantly correlated to survival (Table 3).

	Univariate analysis (Log-Rank)		Multivariate analysis (Cox regression)	
	HR [95%CI]	p	HR [95%CI]	P
NIV centre (Reference: Rouen)				
London	0.903 [0.756 - 1.079]	0.358	0.944 [0.778 - 1.145]	0.560
Gender (Reference: Male)				
Female	0.890 [0.749 - 1.058]	0.098	0.790 [0.652 - 0.959]	0.017
Age (Reference: Below 60 years old)				
Above 60 years old	3.131 [2.336 - 3.297]	< 0.001	2.398 [1.912 - 3.008]	< 0.001
Underlying respiratory disease (Reference: Overlap between obstructive airway disease and obstructive sleep apnea)				
Rapidly progressive neuromuscular disease	4.349 [4.095 - 7.906]	< 0.001	4.860 [3.432 - 6.881]	< 0.001
Slowly progressive neuromuscular disease	0.655 [0.442 - 0.977]	0.038	0.852 [0.550 - 1.320]	0.474
Obstructive airway disease	2.475 [1.771 - 2.988]	< 0.001	2.233 [1.623 - 3.073]	< 0.001
Chest wall disease	1.016 [0.639 - 1.616]	0.0946	1.169 [0.723 - 1.891]	0.524
Obesity hypoventilation syndrome with or without obstructive sleep apnea	0.633 [0.426 - 0.867]	0.006	0.721 [0.509 - 1.022]	0.066
Obstructive sleep apnea	0.469 [0.318 - 0.748]	0.001	0.516 [0.315 - 0.844]	0.008
Timing of NIV setup (Reference: Elective setup)				
Setup following an acute event	1.860 [1.545 - 2.203]	< 0.001	1.376 [1.161 - 1.731]	0.001
Adherence (Reference: Above 4 hours per night)				
Adherence below 4 hours per night	1.110 [0.903 - 1.376]	0.315	0.636 [0.512 - 0.790]	< 0.001

Table 3: Factors associated with mortality in univariate analysis (log-rank) and multivariate analysis (Cox regression)

NIV: non-invasive ventilation

NIV cessation

During the observation period, 680 patients discontinued the home NIV program. Reasons for cessation included death (503 patients, 74%); NIV withdrawal due to poor adherence (100 patients, 15%); reversal of chronic ventilatory failure and treatment cessation (42 patients, 6%); transfer to another centre (35 patients, 5%). There was no difference in distribution of follow up outcomes between centres ($p = 0.209$).

Discussion

These data represent the largest long-term outcome data of patients initiated on home NIV for the treatment of chronic ventilatory failure. The overall 5-year survival following initiation of home NIV was poor at 58%, however outcome varied according to diagnostic category of respiratory failure, timing of NIV initiation, gender and age at initiation of home NIV. A clinical approach of improving NIV adherence and elective timing of initiation of home NIV may enhance outcome.

Survival outcome

With an overall one-year survival rate of 86%, patients with chronic ventilatory failure have a worse prognosis than patients diagnosed with idiopathic pulmonary fibrosis receiving therapy who have a 1-year survival of 97% [24]. Following home NIV initiation, 5-year survival was 58%, similar to that reported for pulmonary hypertension with a 5-year survival of 57% [13]. As expected, survival varied depending on the underlying aetiology of chronic ventilatory failure. Patients with rapidly progressive motor neuron disease had a survival similar to the previous published clinical trial [3] with COPD patients observed to have a similar survival of patients in the fourth quartile of the BODE (body mass index, airflow obstruction, dyspnoea and exercise capacity) index [25]. In COPD patients, initiation of home NIV should trigger evaluation for lung transplantation or palliative care referral if lung transplantation is not appropriate [26].

Clinical implications

An important finding of the current study is the identification of two potentially modifiable factors associated with improved survival following initiation of home NIV. Firstly, we have shown that NIV initiation following an episode of acute decompensated hypercapnic respiratory failure was associated with an increase in mortality. It can be postulated that patients presenting with decompensated respiratory failure would be further through the natural history of the disease and thus would be expected to have a higher mortality with early detection by screening producing a lead time bias. An acute exacerbation of respiratory failure can cause further lung injury [27] and therefore lead to worse outcomes. Although, we still lack early predictors of the onset of chronic respiratory failure, it can be speculated that close monitoring of patients at high risk of chronic hypercapnia would allow for earlier

intervention and may therefore influence long-term outcomes. This is already established clinical practice in patients with NMD but could be extended to at risk patients with OSA and COPD.

Secondly, we have shown that an adherence to home NIV prescription of greater than 4 hours per night was associated with an improved survival. To the best of our knowledge, our results are the first to show a correlation between the adherence to home NIV prescription and mortality independently of the underlying disease. Interestingly, the cut-off of 4 hours home NIV use per night was based on routine clinical practice as previous studies in eucapnia OSA patients treated with CPAP with this level of adherence showed improvements in excessive daytime somnolence but not survival [28-30]. Our results support the use of a 4-hours per night target for minimal adherence in all patients with chronic ventilatory failure set up on home NIV, irrespective of underlying disease. Interventions that can facilitate patient home NIV adherence, such as telemonitoring [35], may have an impact on long-term outcome and should be the focus of future work.

Comparison with previous studies

Despite an increase in the total number of patients using home NIV [2], few data exist reporting long-term mortality. The only detailed dataset previously reported was based on historic data and included patients on long-term oxygen therapy and, thus, its relevance to the current population of home ventilation users is limited [14]. Indeed, in this previous cohort the median survival of patients with 'chronic bronchitis' was 3 years. Interestingly, this reported survival is comparable to the current data in the OAD patient category indicating little improvement in outcome in this patient group despite changes in pharmacotherapy and supportive care made over the last 20 years. Comparison with the study reported by Chailleux et al. [14] highlights the demographic change in of home NIV. Chronic ventilatory failure, secondary to tuberculosis or poliomyelitis, are increasingly uncommon but were previously a common indication for initiation of home NIV. The current data demonstrated that obesity related respiratory failure (OSA and/or OHS) was more prevalent and represents the most frequent indication for home NIV initiation to treat chronic ventilatory failure [9]. The use of CPAP may be considered as an alternative to NIV [31] [32]. However, in our cohort, the three years survival was slightly lower than that published by Masa and colleagues (82% vs. 89%) [32]. This could be explained by the fact that our

population was unselected and that patients were frequently established after acute respiratory failure who were excluded in the Pickwick study.

Increasing demand for home NIV

In the current study, the increase in NIV setup was 5% per annum. This growth has been described in France [10] and is explained by the increasing burden of obesity [33,34] and obesity related respiratory failure with this diagnostic category now representing the most common indication for home NIV setup. Changes in home NIV setup for COPD may have been influenced by the results of two recent randomized controlled trials demonstrating the clinical benefit of home NIV both in the chronic stable and post-acute state [6,7]. These data have been included in the update of a number of European [35] and European national guidelines [36,37] and it is expected that this would increase the referrals for home NIV in this patient group.

COPD-OSA overlap

Patients with COPD-OSA overlap syndrome have been shown to have significantly worse outcomes than patients with COPD alone [38]. However, these data are not confined to patients with respiratory failure. In the data reported here patients with respiratory failure caused by COPD-OSA overlap have an outcome that is between that of those patients with either obesity related respiratory failure or COPD alone. The provision of PAP therapy has been shown to improve outcomes in patients with COPD-OSA although the benefit on mortality may be confined to patients with hypercapnia [38,39]. These data support the screening of patients with COPD-OSA overlap for the presence of hypercapnia. Our results provide a useful insight for the design of clinical trials comparing NIV to CPAP in this patient population.

Difference between the home NIV centres

This study compared two expert home NIV centres, with different models of NIV management and integration with local healthcare organisations, albeit both university hospitals in urban areas. The data demonstrate variation in clinical practice between centres. Indeed, in the Rouen centre, more patients were set up following an acute event. This can be explained by the fact that the London centre is a tertiary referral centre, whereas the Rouen group is a secondary care hospital. The London centre

established significantly more patients on NIV in the study period as it covers a larger geographical area with more inhabitants than the Rouen centre. Ventilator settings also varied between the centres, with the London centre using higher average ventilator pressures than the Rouen. However, the level of pressure per se is not a marker of efficacy. Indeed, patients in London were significantly younger suggesting a more severe disease and the proportion of overweight patients was higher in England than in France impacting on ventilatory requirement. In both centres, NIV was titrated in order to target significant CO₂ reduction measured with nocturnal transcutaneous CO₂ monitoring or evening-morning ABGs. The similar long-term survival in both centres suggests adequate ventilator setup despite the variation in pressures delivered. This difference in the level of pressure may explain why a higher proportion of full-face mask was used in the London centre. However, in the combined population the proportion of full face mask is similar to that which has been previously reported [40].

Interestingly, patients that were set up in Rouen had a higher home NIV adherence, which may have been expected to influence mortality. These observations may be explained by different factors. Firstly, the lower pressures used to establish home NIV in the Rouen group may enhance comfort and tolerance. However, lessons learned from COPD trials and in neuromuscular disease [41] emphasise the need for a control of the level of carbon dioxide to achieve clinical benefits. Secondly, this discrepancy may also be explained by a longer length of stay during set up that may allow more time for training and education. Finally, this observation may be explained by the structure of the respective healthcare organization [42]. Indeed, all patients in Rouen had home follow-up by an external healthcare provider (ADIR Assistance, Asten Santé, France), whereas the London patients had hospital-based follow-up. Home visits may have facilitated greater patient understanding of the technique and the treatment promoting greater adherence.

Limitations of the study

The main limitation of the current study is the missing physiological data, in particular, the baseline arterial blood gas measurement and spirometric data as well as the arterial blood gas data after home NIV set up. These data were not always prospectively gathered and hence these data were not included in the analysis for long-term outcome. Indeed, as a significant proportion of patients were

initiated of home NIV following an acute episode of decompensated acute on chronic ventilatory failure treated with acute NIV, therefore arterial blood gas values in the stable state were not be available.

Conclusion

These data represent the largest long-term outcome data of patients initiated on home NIV for the treatment of chronic ventilatory failure. 5-year survival following initiation of home NIV was almost 60% with diagnostic category, gender and age of initiation as key determinants of long-term survival. Potentially modifiable factors impacting on survival were NIV adherence and elective setup of home NIV.

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Competing Interests statement:

Dr Patout reports personal fees from Resmed, grants and non-financial support from Fisher & Paykel, non-financial support from MSD, nonfinancial support and personal fees from Asten, grants from ADIR Association, grants from B&D Electromedical, personal fees from Philips Respironics, personal fees and non-financial support from Chiesi outside the submitted work.

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Drs. Kaltsakas, Declercq, Benattia, Ramsay, Arbane, Marino, Molano, Artaud-Macari, Viacroze, Steier, Muir, Cuvelier have nothing to disclose.

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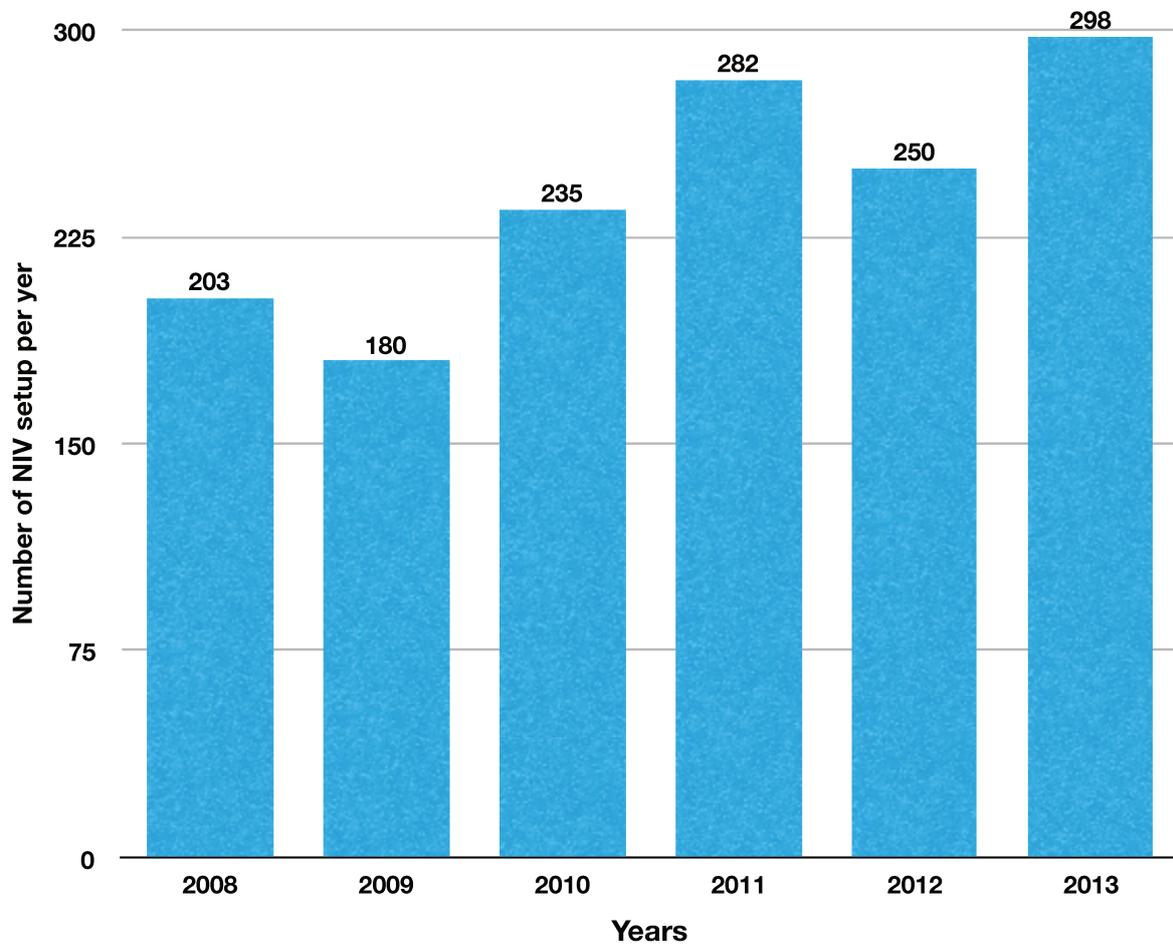
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**Long Term Survival Following Initiation of Home Non-invasive Ventilation
: A European Study – Online supplement**

eFigure 1: Number of NIV setups per year. (NIV: non-invasive ventilation)



eFigure 2: Level of pressure support set in patients from both centres per year (dashed line: median – dotted lines: quartile)

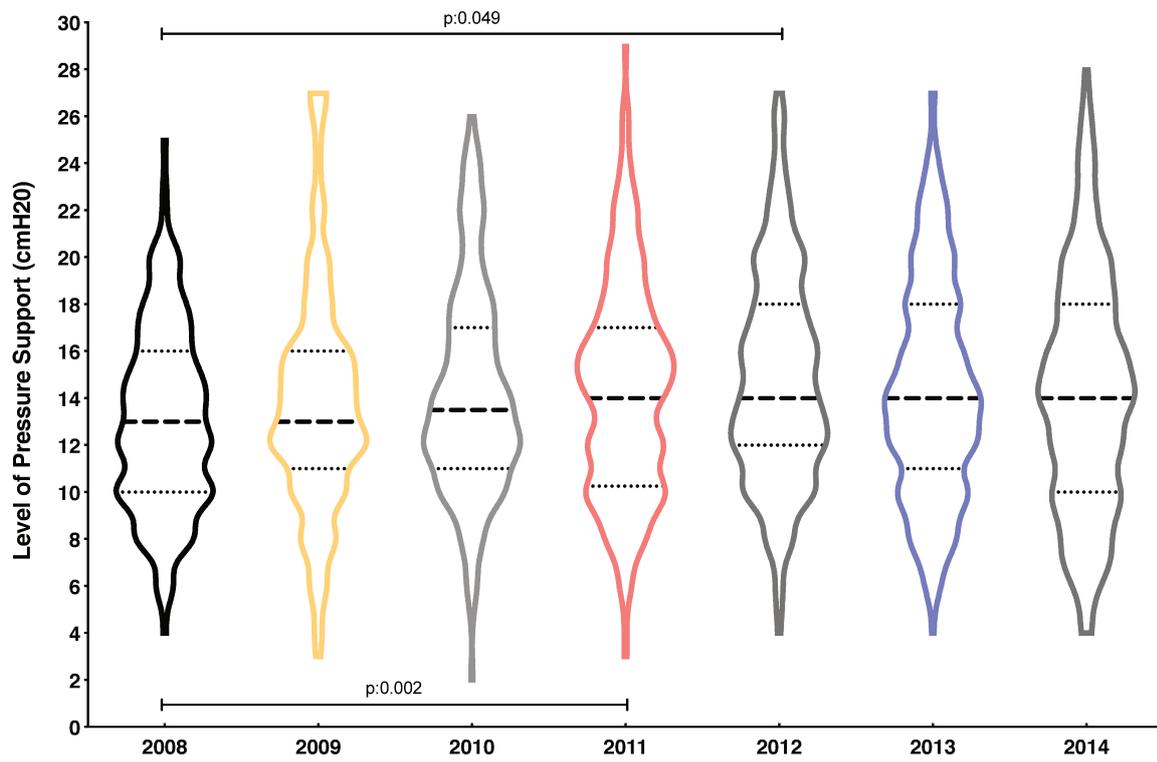


Table 1: Details of underlying chronic respiratory disorder for patients with neuromuscular disease (n=397).

	N (%)
Rapidly progressive neuromuscular disease	167 (42%)
Motor neuron disease	141 (84.4%)
Other rapidly progressive myopathy	17 (10.2%)
Auto-immune myositis	6 (3.6%)
Paraneoplastic syndrome	3 (1.8%)
Slowly progressive neuromuscular disease	230 (58%)
Duchenne's Muscular dystrophy	49 (21.3%)
Post-polio syndrome	40 (17.4%)
Type I myotonic dystrophy	27 (11.7%)
Tetraplegia	24 (10.4%)
Diaphragm palsy	21 (9.1%)
ICU neuro-myopathy	14 (6.1%)
Limb Girdle Dystrophy	13 (5.7%)
Kennedy's disease	7 (3.0%)
Guillain-Barré syndrome	5 (2.2%)
Myasthenia gravis	5 (2.2%)
Multiple sclerosis	4 (1.7%)
Charcot Marie Tooth disease	3 (1.3%)
Multiple System Atrophy	2 (0.9%)
Becker's disease	1 (0.4%)
Dyskinesia	1 (0.4%)
HTLV1 neuro-myopathy	1 (0.4%)
Myofibrillar myopathy	1 (0.4%)
Neuralgic amyotrophy	1 (0.4%)
Pompe's disease	1 (0.4%)
Rett syndrome	1 (0.5%)
Spina bifida	1 (0.4%)
Tetralogy of Fallot	1 (0.4%)
Type II myotonic dystrophy	1 (0.4%)
Unspecified congenital myopathy	1 (0.4%)

The main findings of this study were:

- An increasing number of patients is setup on home NIV
- Survival of patients following initiation of home NIV remains poor
- A compliance > 4 hours and an elective setup are modifiable factors that could be targeted to improve the outcome
- Despite differences in NIV setup and parameters and despite different healthcare organisations, there is no difference in the outcome of patients from Rouen and London.

II. *Established treatments for the management of chronic respiratory failure*

1. Oxygen therapy

Oxygen is a gas for medical use. In France, oxygen therapy is delivered to patients by a healthcare provider that has to provide all the equipment required to fulfil medical prescription to the patient.

a) Long-term oxygen therapy

Long-term oxygen therapy (LTOT) prescription has been used in patients with COPD since the late 60's⁹⁹. Its use has been validated in the early 80's by two randomised controlled trials^{100,101} that included patients with COPD. In these studies, patients could be included if daytime ABG performed in stable state showed a $P_aO_2 < 8\text{kPa}$ with peripheral oedema and/or a haematocrit $\geq 55\%$ or cor pulmonale on electrocardiogram. Oxygen flow was titrated to achieve a $P_aO_2 \geq 8\text{kPa}$ at rest. The clinical benefit of LTOT was only seen in patients using the O_2 for ≥ 15 hours per day.

Since these two randomised controlled trials, very little has changed regarding LTOT indications. As previously mentioned, LTOT prescription has been extended to other cause of type I CRF. More recent clinical trials aimed to assess the benefit of LTOT in COPD patients with moderate desaturation or hypoxemia. Both failed to show a benefit on survival^{102,103} or time to first severe exacerbation¹⁰³.

b) Nocturnal oxygen therapy

To date there is no data suggesting a benefit of isolated nocturnal hypoxemia in patients with type I CRF. In patients with COPD, no benefit was seen on pulmonary haemodynamic¹⁰⁴. No study has studied the long-term impact of such treatment in COPD patients with isolated nocturnal desaturation.

c) Use of oxygen during exercise

Portable oxygen during exercise has been used to improve exercise capacity since the 50's¹⁰⁵. In patients with severe hypoxemia meeting LTOT criteria, oxygen flow rate should be titrated and usually differ for the oxygen flow rate at rest. In patients that do not meet LTOT criteria, ambulatory oxygen improved breathlessness and tiredness¹⁰⁶. In patients with ILD, ambulatory oxygen has been

shown to improve quality of life but these benefits need to be confirmed by randomised controlled trials

15.

2. Non-invasive ventilation

Positive pressure non-invasive ventilation (NIV) has started to replace invasive ventilation through tracheostomy and negative-pressure ventilation in the 80's. Nowadays, NIV implies positive pressure NIV as negative-pressure ventilation has been withdrawn.

NIV is the treatment of choice of type II respiratory failure. NIV consists of a ventilator that is connected to a patient through a mask. To facilitate the home use, the circuit that connects the ventilator to the patient generally include an intentional leak to allow removal of exhaled CO₂.

During NIV, the ventilator generates a flow that varies during the respiratory cycle. The ventilator needs to detect patient's inspiratory effort to trigger an inspiratory flow and to detect the end of inspiration to let the patient breath out. The flow that is generated during inspiration will help the patient to produce a tidal volume at a low energetic cost for the patient. The flow generated by the ventilator during expiration generate an expiratory positive airway pressure (EPAP) that should overcome upper airway obstruction similarly as CPAP or intrinsic positive expiratory pressure in patients with COPD.

a) Standard mode for non-invasive ventilation

There is a wide range of NIV ventilators available ¹⁰⁷ and there is a lack of a standardised terminology of ventilatory modes and other settings that may induce some confusion.

Firstly, we can distinguish two different modalities to deliver NIV:

- Volume targeted ventilation where the ventilator delivers a fixed volume to the patient at each respiratory cycle and regardless of the pressure that is required to generate this volume. This modality is not frequently used anymore in patients with CRF as delivered volume delivered are negatively impact by frequent nonintentional leaks.
- Pressure targeted ventilation where the ventilator delivers a fixed pressure to the patient at each respiratory cycle. The volume therefore generated by the pressures varies according to patient efforts and the compliance of their respiratory system. The flow is adjusted to the level of leaks in order to deliver the pre-set pressures.

In pressure targeted ventilation, several parameters need to be setup:

- The onset of inspiration 1) can be controlled only by the patient (spontaneous mode), 2) can be controlled by the patient but with a fixed duration of the inspiratory time (assist mode), 3) can be controlled by the patient when its respiratory rate is above a pre-set limit (assist-control mode) or 4) can be fixed by the ventilator (controlled mode)
- The sensitivity of the trigger. It corresponds to the level of inspiratory effort that the patient has to achieve in order to trigger an inspiratory cycle from the ventilator. It should be set to minimise patients' effort whilst avoiding self-triggered ventilatory cycle that constitute a patient-ventilator asynchrony (PVA): auto-triggering.
- The level of EPAP that will aim to abolish upper airway obstruction and/or to match patient's intrinsic positive expiratory pressure to avoid ineffective efforts.
- The level of inspiratory pressure airway pressure (IPAP). The difference between the IPAP and the EPAP corresponds to the driving pressure. The driving pressure is proportional to the tidal volume and to the decrease in patient's work of breathing
- The cycling from inspiration to expiration that can be after a fixed duration or can depend on the inspiratory peak flow. In patients with COPD, cycling should be set to minimise the inspiratory time in order to avoid dynamic inflation.
- The minimal respiratory rate or back-up rate. This setting will ensure that the patient receive a minimal number of breaths if their respiratory rate is too low. This has been shown to be an effective way to optimise ventilation in patients with OHS ¹⁰⁸.

Given the variability of patients and the frequent overlap of sleep disordered breathing such as OSA, settings need to be tailored to the patients and the efficacy of ventilation checked.

More recently, hybrid modes of ventilation have been developed. The pressure targeted ventilation is combined to a target volume mode. With such mode of ventilation, the pressure is adjusted by the ventilator algorithm to achieve the pre-set volume. However, concerns have been raised regarding the consequences of these modes on sleep quality ¹⁰⁹.

b) Ventilation during exercise

As positive pressure ventilation decreases the work of breathing, NIV is used during pulmonary rehabilitation in COPD patients. Given the small sample size of published clinical trials, no significant benefit has been clearly demonstrated ¹¹⁰. This also may be explained by insufficient patient

phenotyping and also by the clinical challenges in order to adjust NIV to patients' respiratory demand during exercise.

Independently of its use during exercise, overnight NIV during pulmonary rehabilitation improves the outcome of such training in hypercapnic COPD patients ¹¹¹.

In COPD patients established on long-term NIV, NIV with a battery can be used during 6-minute walking tests (6MWT) and significantly improve the distance walked ¹¹². However, this technique has not spread into clinical practice mainly because of the technical and practical difficulties associated to the use of NIV during walks.

III. Established tools for the diagnosis and the management of chronic respiratory failure

1. Daytime tests

The diagnosis of CRF relies on ABG during stable state. They need to be repeated to assess the efficacy of the treatment (LTOT and/or NIV).

Clinical symptoms like sleepiness or altered quality of sleep may help clinicians to suspect CRF but these symptoms are not specific. In patients with regular medical follow-up, the onset of CRF can be detected using lung function tests.

a) Lung function tests

Spirometry and especially vital capacity is a useful tool to screen for CRF in patients with slowly or rapidly progressive NMD. Slow vital capacity is closely correlated to respiratory symptoms in ALS patients ¹¹³. The rate of decline of slow vital capacity has been shown to be a good marker of disease progression ⁴³. Similarly, in patients with DMD, forced vital capacity is correlated to survival ^{114,115}. In patients with restrictive respiratory disease, NIV may be initiated when forced vital capacity is below 50% ¹¹⁶.

In patients with mild to moderate COPD, the likelihood of chronic hypercapnia is low. Indeed, the negative predictive value of a FEV1 > 50% is 1 ¹¹⁷. However, chronic hypercapnia is also favoured by hyperinflation ¹¹⁸ and may also occur in milder stage of COPD in patients with COPD-OSA overlap ⁸⁵. Similarly, In COPD patients, occurrence of type I CRF is related to the degree of airflow obstruction ¹¹⁹.

b) Respiratory muscle testing

Respiratory muscle strength can be assessed by dedicated tests ¹²⁰. The most frequently used are the maximal inspiratory pressure (MIP), the maximal expiratory pressure (MEP), the sniff nasal inspiratory pressure (SNIP) and the cough peak flow. Amongst those, SNIP has been shown to be the best predictor non-invasive test for ventilator-free ^{121,122} and absolute survival in patients with ALS ^{121,123}. In patients with DMD, SNIP was an earlier marker of lung function decline than forced vital capacity ¹²⁴.

In patients with NMD, cough peak flow is also a marker of severity of the disease ¹²⁵. It is used to identify patients that require mechanical cough assistance ^{126,127}.

In patients with COPD, SNIP measurements are reliable ^{128,129}. Unlike patients with NMD, a decrease of SNIP values in COPD is related to hyperinflation ¹³⁰. Low SNIP values seems to be associated to a worse prognosis ^{131,132} but do not trigger NIV initiation.

To date, there is no data available on the evaluation of intercostal muscle and NIV.

c) Blood tests

The metabolic response of a chronically elevated level of P_aCO_2 is an increase in bicarbonates. As ABG are not commonly performed in general practitioners' medical practice, the use of venous blood bicarbonates may be a useful screening specifically in the obese population that may not have been referred to chest physicians. If a normal level of bicarbonates have a good negative predictive value ¹³³ but a poor sensitivity as the bicarbonates level can be increased by numerous factors commonly found in the obese population ¹³⁴.

2. Overnight tests

During sleep, the minute ventilation decreases ¹³⁵ as well as hypercapnic ventilatory response ¹³⁶. In addition to the screening of concomitant sleep apnoea, overnight studies give physician important information on respiratory mechanics overnight.

a) Oximetry

Overnight oximetry is widely used to screen for OSA ¹³⁷ even if not endorsed by French guidelines ¹³⁸.

In selected population at risk of CRF, overnight oximetry can be useful as it has been shown that there was no correlation between the forced vital capacity and overnight hypoxemia in ALS patients ¹³⁹. However, such screening has now been shown to be insufficient in patients with NMD as, in this population, significant hypoventilation can occur without prolonged desaturation given the absence of V/Q mismatch in the pathophysiology of these diseases ¹⁴⁰.

In patients with COPD, overnight desaturations are frequent but are not associated to an impaired quality of life ¹⁴¹, significant hemodynamic consequences ⁸⁶ neither to daytime gas exchange ¹⁴².

In patients established on home NIV, overnight oximetry is recommended as a first line monitoring tool in association with NIV data from built-in software ¹⁴³. Such monitoring can be imbedded in the ventilators to improve ventilation quality ¹⁴⁴. In patients with ALS, NIV is more likely to fail if overnight saturation are not normalised ¹⁴⁵. In patients with supplemental oxygen, oximetry performs poorly in detecting residual hypoventilation ¹⁴⁶. Therefore, overnight monitoring on patients established on NIV should not only rely on overnight oximetry.

b) Transcutaneous capnography

Overnight transcutaneous capnography can be performed at home ¹⁴⁷ or in hospital as a stand-alone monitoring or coupled with oximetry and / or polygraphy or polysomnography. It provides an overnight overview of transcutaneous CO₂.

In self-venting COPD with type II CRF, sleep hypoventilation is common ¹⁴⁸. In patients with restrictive CRF, overnight transcutaneous capnography performed better than overnight oximetry and morning ABG to diagnose nocturnal hypoventilation ¹⁴⁹. Nocturnal hypoventilation exists in 10 to 61% of patients with NMD ^{26,140,150}. Therefore, transcutaneous capnography is an important screening tool in this population.

In stable patients established on NIV, overnight transcutaneous capnography is a reliable tool when compared to ABG sampling ¹⁵¹. Moreover, its performance to diagnose residual hypoventilation is higher than daytime ABG and overnight oximetry ¹⁵². Adequate correction of overnight hypoventilation is key factor for NIV success ^{153,154}.

c) Polygraphy

Overnight polygraphy consists in a multiple channel sleep monitoring that includes abdominal and thoracic belts, nasal flow measurements and overnight oximetry. Overnight polysomnography (PSG) adds to the previous signal an electro-encephalography that allows sleep staging. These tests are essential for the diagnosis of sleep disordered breathing in patients with CRF. Indeed, COPD and OSA often overlap ⁸⁷, ALS patients frequently have upper airway obstruction ^{150,155} and patients with

type I myotonic dystrophy have complexed sleep abnormalities ¹⁵⁶. Given complexity, costs and limited availability, PSG's are not systemically performed before NIV setup and most centres use polygraphy or oxi-capnography overnight studies depending on local access to such tests ⁸⁰.

For NIV setup, the use of overnight PSG is recommended by the American Academy of Sleep Medicine. This recommendation will be discussed further in this thesis.

During NIV follow-up, in patients with insufficient control of their hypoventilation, overnight polygraphy is a useful tool. It allows a precise diagnostic of residual events and an identification of patient ventilator-asynchronies ^{157,158}. These events are frequent ¹⁵⁹⁻¹⁶². Their clinical consequences in the general population remained to be determined. However, overnight polygraphic monitoring is an effective tool in order to reduce their occurrence ¹⁶³ and can be beneficial in patients experiencing NIV side-effects ¹⁶⁴.

IV. Aims of the thesis

Since the outcome of CRF patients remains poor and that the number of patients developing CRF increases, our aims in this thesis are:

- To evaluate a novel diagnostic tool to assess the efficacy of NIV and their usefulness in order identify high-risk patients (Chapter 2). To do so, we will report three original research studies focusing on the use of parasternal surface electromyography (EMG) a non-invasive assessment of neural respiratory drive. These researches are entitled:
 - o “*Neural respiratory drive predicts long-term outcome following admission for exacerbation of COPD: a post hoc analysis*” that was published in Thorax in 2019¹⁶⁵
 - o “*Neural respiratory drive and cardiac function in patients with obesity hypoventilation syndrome following initiation of non-invasive ventilation*” that was published in Journal of Thoracic Disease in 2018¹⁶⁶
 - o “*Polysomnography versus limited respiratory monitoring and nurse-led titration to optimise non-invasive ventilation set-up: a pilot randomised clinical trial*” that was published in Thorax in 2019¹⁶⁷
- To identify how new treatments and better patient’s phenotyping can change healthcare organisation in order to still provide good quality of care to the increasing number of patients (Chapter 3). To do so, we will report two researches entitled:
 - o “*Step-down from noninvasive ventilation to continuous positive airway pressure: a better phenotyping is required*” that has been accepted in Respiriology in 2019.
 - o “*AVAPS-AE vs ST mode: A randomized controlled trial in patients with obesity hypoventilation syndrome*” that has been submitted to Respiriology in 2019
- To evaluate how tele-medicine could improve the care of patients with CRF (Chapter 4). To do so, we will report data from a review and 2 original researches entitled:
 - o “*Technological advances in home non-invasive ventilation monitoring: Reliability of data and effect on patient outcomes*” that was published in Respiriology in 2019¹⁶⁸
 - o “*Efficacy of a home discharge care bundle after acute exacerbation of COPD*” that was published in the International Journal of COPD in 2019¹⁶⁹

- *“Prediction of severe acute exacerbations using changes in breathing pattern of COPD patients on home non-invasive ventilation”* that was published in the International Journal of COPD in 2018 ¹⁷⁰
- To describe novel uses of existing device to meet patients' unmet needs with the current approach (Chapter 5). To do so, we will report two researches entitled:
 - *“Characteristics and outcome of patients set up on high-flow oxygen therapy at home”* that was published in Therapeutic Advances in Respiratory Disease in 2019 ¹⁷¹
 - *“Trial of Portable Continuous Positive Airway Pressure for the Management of Tracheobronchomalacia”* that was published in the American Journal of Respiratory and Critical Care Medicine in 2016 ¹⁷²

Chapter 2: Parasternal electromyography to predict the outcome of patients with chronic respiratory failure

In this chapter, we will review the principles of parasternal electromyography and its use to assess outcome and response to treatment.

1. Introduction to parasternal electromyography

1. Principles

Neural respiratory drive (NRD) is a physiological measurement that assesses the load applied on the respiratory system. The measurement is the electrical activity of respiratory muscle and can be performed during spontaneous breathing or respiratory manoeuvres such as SNIP, MIP or MEP or whilst a treatment such as NIV is applied.

NRD has initially been assessed by measuring the electrical activity of the diaphragm using oesophageal electrodes ¹⁷³. It has then been proposed to report the electromyography (EMG) results as the root mean square (RMS) of the highest EMG value during inspiration. As there is some inter-individual differences in signal acquisition of EMG signal (because of electrode position and attenuation of the electric signal), results of NRD are expressed as the percentage of the maximal RMS obtained during maximal manoeuvre (SNIP, MIP, MEP, inspiration to total lung capacity manoeuvres) ¹⁷⁴. It was shown that patients with chronic respiratory diseases (COPD and post-polio syndrome) had a mean RMS of 44% of the maximal RMS when it was 8% in healthy subjects ¹⁷⁴. These results were confirmed in a large cohort of stable patients that aimed to determine normal value of neural respiratory drive in healthy and COPD subjects ¹⁷⁵.

Diaphragmatic neural respiratory assessment has been shown to be a valuable tool to assess the consequences of respiratory diseases on clinical symptoms. In COPD patients, NRD is highly correlated to the level of breathlessness during exertion ¹⁷⁶. In this population, it could be a useful tool in complex patients to understand what is driving exercise limitation ¹⁷⁷. In patients with cystic fibrosis, NRD assessment is correlated to breathless and is an indicator of dynamic hyperinflation ¹⁷⁸. In morbidly obese patients, NRD is correlated to the BMI and significantly increases in the supine position suggesting that it could be a marker of intrinsic positive end-expiratory pressure ¹⁷⁹. However, despite

the important physiological information provided by diaphragm NRD, its use in daily care is limited. Indeed, oesophageal catheter insertion for diaphragmatic assessment is time consuming and can be unpleasant for patients.

The use of surface intercostal EMG is a non-invasive and easier approach to assess NRD. The electrical activity of the second space intercostal muscle is measured instead of diaphragm electrical activity. The parasternal NRD is closely correlated to diaphragm NRD, is reproducible and is sensitive to respiratory load changes ^{178,180,181}. Reference normal values of parasternal NRD have been reported ¹⁸².

2. Parasternal electromyography measurements

Here, we describe how parasternal EMG measurements were performed during our studies.

a) Equipment

All parasternal EMG measurements were performed using a Dual Bioamp amplifier (AD Instruments, Chalgrove, UK) connected to a data acquisition system: Powerlab (AD Instruments, Chalgrove, UK). Data were recorded using the data acquisition software: Labchart v7 (AD Instruments, Chalgrove, UK).

We used single Blue Sensor Q (Ambu, St Ives, UK) surface electrodes for our measurements. Before applying the surface electrode, the skin was cleaned using alcohol wipes. Then, NuPrep gel (DO Weaver and Co, USA) was applied and a gentle scrubbing of the skin was performed using sterile gaze. Excess of Nuprep gel was removed before surface electrode application.

A single use nasal bung was connected to a pressure transducer (GM instrument, Irvine, UK) that was calibrated before each recording. The size of the nasal bung was chosen to ensure sealing of patient's nostril. MIP and MEP were performed using a reusable mouthpiece.

When a measurement of parasternal EMG was planned on NIV and/or CPAP, a pneumotachograph was used. Three different pneumotachographs were used: a 3830 heated pneumotachograph (Hans-Rudolph, Shawnee, USA), a MLT1000L and a MLT300L pneumotachographs (AD Instruments, Chalgrove, UK). Pneumotachographs were connected to a pressure transducer spirometry pod (AD Instruments, Chalgrove, UK) which was connected to the PowerLab. Before each session, the pneumotachograph was calibrated using a 3L volume syringe

(Hans-Rudolph, Shawnee, USA). The pneumotachograph was used during quiet breathing self-venting, spirometric measurements and whilst on NIV and/or CPAP. When NIV or CPAP was used, the circuit was connected to a pressure transducer. The pneumotachograph was placed in the circuit between the mask and the tubing.

For the study on parasternal EMG outcomes ¹⁶⁵, no pneumotachograph was used. Inspiratory efforts were identified by an oxygen nasal cannula connected to a pressure transducer.

b) Measurements

All patients were positioned in a semi-recumbent position. When required, pillows were placed underneath their arms and/or neck to limit tonic activity of non-respiratory muscles. The second intercostal space was identified by palpation of the bony structures. Two electrodes were placed on immediately lateral to the left and right edge of the sternum. A third electrode was placed on a bony structure of the shoulder and was used as a reference. The electrode position is illustrated in Figure 2.



Figure 2: Position of surface electrode for parasternal EMG on a healthy subject.

After equipment setup, patients were asked to breath quietly for 5 minutes. Then, we performed SNIP manoeuvres.

For patients that had a recording with NIV/CPAP, we then performed MIP and MEP manoeuvres as well as we measured forced vital capacity, forced expiratory volume at 1 second. Then, we initiate the NIV/CPAP and measured the parasternal EMG activity under ventilation.

During data acquisitions, all meaningful information was timed and recorded in the LabChart software. Quality of the acquired data was constantly verified visually. When the signal was of poor quality, the recording was stopped and the cause of the abnormal signal corrected.

c) Analysis

After data acquisition, data were analysed using the LabChart software. The analysis were performed manually. The analysed variables were:

- Parasternal EMG (EMG_{para}) (μV). EMG_{para} was analysed from the RMS of the raw signal EMG. The EMG_{para} was calculated during quiet breathing by selecting its maximal value during the inspiratory phase. The value was the mean results of EMG_{para} breaths over at least one minute of stable breathing during self-ventilation or, on NIV or, on CPAP. No filter was applied to the electrocardiogram signal, therefore, the maximal value of the EMG_{para} was only calculated when it occurred outside of any electrocardiogram artefact. Respiratory efforts with movement artefacts were discarded.
- Maximal parasternal EMG ($EMG_{paraMax}$) was calculated by measuring EMG_{para} during maximal maneuvers such as SNIP, MIP and MEP. The maximal EMG_{para} value of all maximal maneuvers was recorded at the $EMG_{paraMax}$ (μV).
- $EMG_{para\%max}$ which was calculated as the mean EMG_{para} value divided by the $EMG_{paraMax}$.
- Tidal volume (V_t) was calculated using the integral of the inspiratory flow when a pneumotachograph was used.
- Respiratory rate was calculated as breaths per min using the flow signal when a pneumotachograph was used or inspiratory depression in the nasal canula when not.
- Neural respiratory drive index (NRDI) was calculated by the product of $EMG_{para\%max}$ and respiratory rate and expressed in arbitrary unit (AU).
- Respiratory efficiency was calculated when tidal volume was available as the average of EMG_{para} divided by the tidal volume over one minute of stable breathing.
- Respiratory offload by NIV or CPAP was calculated as follow: $(EMG_{para}$ on NIV or CPAP – EMG_{para} during tidal breathing)/ EMG_{para} during tidal breathing and expressed as percentage of change.

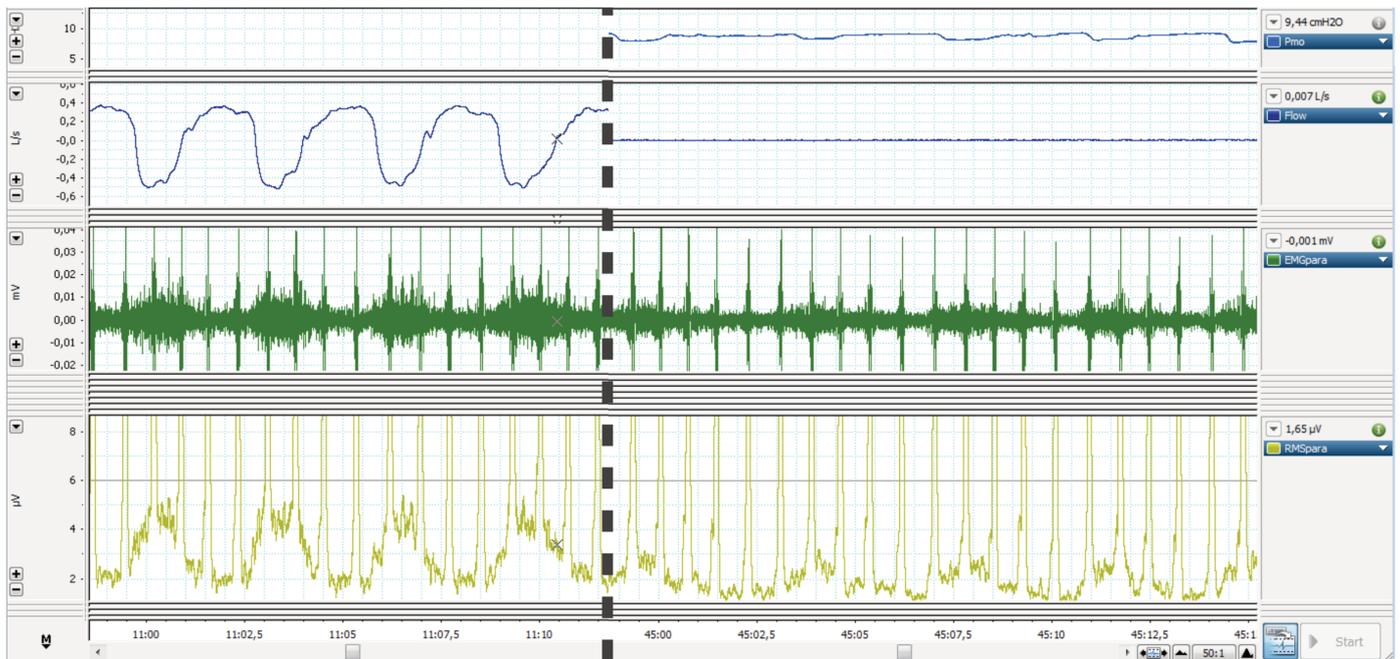


Figure 3: Screenshot of patient's NRD recording.

On the left side of the panel, recording during self-ventilation with inspiratory flow (flow and dark blue line), raw parasternal EMG signal (EMGpara and green trace) and RMS parasternal EMG (RMSpara and yellow trace). On the right side of the panel, decrease of EMGpara is seen whilst patients established on CPAP (Pmo: pressure in CPAP circuit and light blue line)

3. Usefulness of parasternal electromyography

As parasternal EMG is easier to assess NRD, larger scale studies that included patients with COPD exacerbations have been conducted.

Firstly, an observational study recruited patients admitted for severe acute exacerbation of COPD (AECOPD) and assessed the change in parasternal EMG during their stay. This study showed that parasternal EMG could be repeated on a daily basis. Parasternal EMG results changed over the course of admission. Moreover, it showed that parasternal EMG could differentiate patient who improved with a decrease of their parasternal EMG from those who deteriorated who had an increase of their parasternal EMG ¹⁸³. Then, a larger cohort study focusing on the same population showed that parasternal EMG could predict safe discharge following admission for a severe exacerbation of COPD. Change in parasternal EMG from admission to discharge was correlated to 14-days readmission in the cohort and 28-days readmission in patients under 85 years-old ¹⁸⁴. Results from these two studies are highly relevant to help identify patients at risk of 28-days readmission. As parasternal NRD is an

evaluation of the load on the respiratory system, it may be a useful tool to tailor care following discharge but during the long-term management of patients. As we lack data regarding the impact of NRD on the long-term outcome of COPD patients, such strategy cannot be implemented yet.

NIV is a treatment that aims to reduce the work of breathing and thus, NRD. The use of parasternal EMG provides a non-invasive tool to assess work of breathing on NIV. Duivermann *et al.* have shown that in patients with COPD, offload of NRD assessed by parasternal EMG was correlated to the decrease of transcutaneous CO₂ ¹⁸⁵. However, there is no data available in other populations.

II. *Parasternal electromyography to predict long term outcome of patients with COPD*

C. *Original research: Neural respiratory drive predicts long-term outcome following admission for exacerbation of COPD: a post hoc analysis (Thorax, 2019)*

As highlighted before, NRD reflects the load on the respiratory system and could therefore a marker of disease severity. Yet, no study has reported any correlation between NRD and mortality.

In COPD patients, the outcome can be predicted using simple tools such as spirometry, anthropometrics and exercise capacity ¹⁸⁶. However, this index does not take into account exacerbations that are an identified factor of poor prognosis ¹⁸⁷.

In our study, we aimed to evaluate if a NRD evaluation could help identify patients at high-risk of mortality.

The study that was published in Thorax in 2019 ¹⁶⁵:

Patout, M., Meira, L., D’Cruz, R., Lhuillier, E., Kaltsakas, G., Arbane, G., et al. (2019). Neural respiratory drive predicts long-term outcome following admission for exacerbation of COPD: a post hoc analysis. Thorax, 74(9), 910–913. <http://doi.org/10.1136/thoraxjnl-2018-212074>

Neural respiratory drive predicts long-term outcome following admission for exacerbation of COPD: a post hoc analysis

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2018-212074>).

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ABSTRACT

Neural respiratory drive (NRD), as reflected by change in parasternal muscle electromyogram (EMGpara), predicts clinical deterioration and safe discharge in patients admitted to hospital with an acute exacerbation of COPD (AECOPD). The clinical utility of NRD to predict the long-term outcome of patients following hospital admission with an AECOPD is unknown. We undertook a post hoc analysis of a previously published prospective observational cohort study measuring NRD in 120 patients with AECOPD. Sixty-nine (57.5%) patients died during follow-up (median 3.6 years). Respiratory failure was the most common cause of death (n=29; 42%). In multivariate analysis, factors independently associated with an increased mortality included NRD (HR 2.14, 95% CI 1.29 to 3.54, p=0.003), age (HR 2.03, 95% CI 1.23 to 3.34, p=0.006), PaCO₂ at admission (HR 1.83, 95% CI 1.06 to 3.06, p=0.022) and long-term oxygen use (HR 2.98, 95% CI 1.47 to 6.03, p=0.002). NRD at hospital discharge could be measured in order to assess efficacy of interventions targeted to optimise COPD and reduce mortality following an AECOPD.

Original clinical trial number: NCT01361451

INTRODUCTION

Following a severe acute exacerbation of COPD, patients are at high risk of readmission and death.^{1,2} Neural respiratory drive (NRD) can be estimated using parasternal muscle electromyogram (EMGpara). EMGpara is a non-invasive physiological measurement which has demonstrated utility in determining the trajectory of recovery during hospital admission as well as predicting readmission following a hospital admission.³ Indeed, Suh *et al* showed that NRD can predict early 14-day readmission in 120 unselected patients with acute exacerbations of COPD.⁴ Although there are composite measures that predict long-term outcome based on disease severity in stable COPD,^{5,6} there are few factors predicting the long-term outcome at the end of a severe exacerbation of COPD. The aim of the current study was to assess if NRD at hospital discharge following an admission due to an exacerbation of COPD could predict long-term mortality.

METHODS

The original study was registered as an observational cohort study (NCT01361451). The study was conducted between January 2011 and September

2013. Full details of the protocol are available in the cohort manuscript.⁴ In brief, consecutive patients admitted to a UK urban teaching hospital with acute exacerbations of COPD were recruited and had daily measurements of NRD, using EMGpara, from admission until discharge.⁴ In May 2017, we collected data from electronic medical records to assess the mortality status of all recruited patients. Cause of death was obtained from the medical cause of death certificate. EMG data are expressed as EMGpara (which corresponds to the measured EMGpara during tidal breathing), EMGpara%max (which corresponds to the ratio between EMGpara during tidal breathing and EMGpara during a maximal sniff manoeuvre) and NRD index (NRDI) (which corresponds to EMGpara%max*RR).

Data were assessed for normality using the Shapiro-Wilk test. Results are expressed as number and percentages, means and SD when normally distributed or medians and IQR when not normally distributed. Comparisons were performed using the t-test for normally distributed continuous variables and a Mann-Whitney U test for non-normally distributed continuous variables. Survival data were analysed using Kaplan-Meier method and log-rank test. Prognostic factors were identified using a multivariate Cox model. Prognostic factors with a p value <0.1 in univariate analyses were included in the multivariate Cox model. EMGpara%max was the only variable included in the model given its collinearity with NRDI. For the Cox model, all continuous variables were divided into two groups based on their median. For admission PaCO₂, the study population was divided into two groups: ≥6 or <6 kPa. Receiver-operator characteristic (ROC) analyses were used to assess performance of predictors of 5 years mortality. A predictive model was produced using logistic regression with variables from the Cox model. All tests were two-sided with the level of significance set at 0.05. Analyses were performed using GraphPad Prism V.6 for Mac OS X (GraphPad Software, La Jolla, California, USA) and IBM SPSS Statistics V.20.0 (IBM Corp, Armonk, New York, USA).

RESULTS

Of the 120 patients involved in the clinical trial, 69 (57.5%) had died by 1 May 2017, mean duration of follow-up was 3.4±1.8 years. Patients' clinical and physiological characteristics obtained during hospital admission are reported in [table 1](#). During inpatient stay, eight (6%) received acute



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Table 1 Population characteristics

	Patients alive at follow-up (n: 69) Mean±SD/median (IQR)	Patients dead at follow-up (n: 51) Mean±SD/median (IQR)	p value
Age (years)	66.3±10.0	72.5±8.9	<0.001
Male (%)	26 (51.0%)	32 (46.4%)	0.713
Body mass index (kg/m ²)	27.7 (23.3 to 33.6)	20.9 (18.2 to 27.7)	0.713
COPD history			
Current smoker (%)	23 (33.3%)	24 (41.1%)	0.136
Smoking history (pack-years)	40 (20 to 50)	40 (30 to 56)	0.213
Use of long-term oxygen therapy (%)	1 (2.0%)	12 (17.4%)	0.007
Exacerbation frequency (/12 months)	2 (0 to 4)	4 (1 to 6)	0.079
Hospital admission frequency (/12 months)	0 (0 to 1)	1 (0 to 2)	0.007
Comorbidities			
Ischaemic heart disease (%)	14 (27.5%)	20 (29.0%)	1
Cerebrovascular disease (%)	5 (9.8%)	8 (11.6%)	1
Hypertension (%)	25 (49.0%)	28 (40.6%)	0.457
Diabetes mellitus (%)	12 (17.4%)	8 (11.6%)	0.091
Admission			
MRC dyspnoea grade at admission	4 (3 to 5)	5 (4 to 5)	0.045
Respiratory rate at admission (/min)	25 (20 to 29)	26 (20 to 31)	0.670
DECAF score at admission	1 (0 to 1)	1 (0 to 2)	0.044
CAT at admission	30 (26 to 34)	27 (23 to 31)	0.022
Admission arterial blood gas			
pH	7.41 (7.37 to 7.45)	7.40 (7.35 to 7.42)	0.029
PaO ₂ (kPa)	8.22 (7.46 to 8.91)	8.37 (7.42 to 9.84)	0.3756
PaCO ₂ (kPa)	5.05 (4.61 to 5.91)	6.09 (4.96 to 7.24)	0.002
Bicarbonates (mmol/L)	24.4 (23.0 to 26.3)	26 (23/5 to 29.4)	0.023
At discharge			
CAT	24 (17 to 28)	24 (17 to 29)	0.507
Saint-Georges Respiratory Questionnaire	65.0 (59.5 to 75.4)	62.8 (56.8 to 72.2)	0.275
Hospital Anxiety and Depression Scale	15.5±7.5	15.7±7.7	0.775
FEV ₁ (L)	0.85 (0.63 to 0.98)	0.62 (0.46 to 0.85)	<0.001
FVC (L)	1.62 (1.62 to 2.12)	1.40 (1.14 to 1.96)	0.067
Readmission or death within 28 days (%)	11 (26.6%)	18 (26.1%)	0.668
Baseline EMG			

Continued

Table 1 Continued

	Patients alive at follow-up (n: 69) Mean±SD/median (IQR)	Patients dead at follow-up (n: 51) Mean±SD/median (IQR)	p value
EMG para (µV)	8.80 (6.46 to 14.7)	10.88 (7.43 to 17.55)	0.048
EMG para%max	15.1 (11.0 to 22.0)	16.5 (11.2 to 22.2)	0.446
Respiratory rate (/min)	21 (17 to 26)	21 (18 to 24)	0.885
NRDI (/min)	313 (221 to 438)	344 (228 to 456)	0.403
Discharge EMG			
EMGpara (µV)	8.17 (5.77 to 10.85)	11.33 (8.09 to 17.02)	<0.001
EMGpara%max	12.8 (9.1 to 17.4)	15.7 (11.8 to 22.6)	0.008
Respiratory rate (/min)	20 (18 to 23)	19 (17 to 22)	0.120
NRDI (/min)	228 (151 to 368)	319 (232 to 458)	0.004
EMG change from baseline to discharge			
ΔEMGpara (µV)	-0.74 (-5.06 to 0.36)	0.73 (-3.53 to 2.48)	0.016
ΔEMGpara%max	-1.96 (-7.61 to 0.79)	-0.95 (-4.44 to 3.24)	0.054
ΔRespiratory rate (/min)	-2 (-4 to 1)	-1 (-3 to 3)	0.043
ΔNRDI (/min)	-61 (-173 to 8)	-9 (-112 to 73)	0.039

Δ, change in; CAT, COPD assessment tool; DECAF, dyspnea, eosinopenia, consolidation, acidemia, fibrillation; EMG, electromyography; MRC, medical research council; NRDI, neural respiratory drive index.

non-invasive ventilation. Medical cause of death was reported as respiratory failure for 29 (42.0%) patients, cardiac failure for five (7.2%), cancer for five (7.2%) and from other cause for two (2.9%). Cause of death could not be verified in 26 (37.7%) patients.

Regardless of the cause of death, an EMGpara%max at discharge ≥15% was associated with a worse prognosis with a median survival of 998 days versus 2002 days when compared with an EMGpara%max at discharge <15% (HR 1.89, 95% CI 1.19 to 3.08, p=0.009, log rank) (figure 1). Other prognostic factors

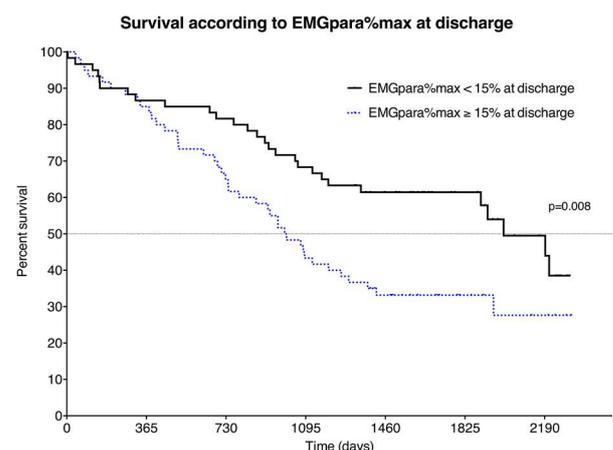


Figure 1 Survival according to EMGpara%max at discharge (continuous line: patients with EMGpara%max <15% at discharge, dot: patients with EMGpara%max ≥15% at discharge) (p=0.008, log rank). EMGpara, parasternal muscle electromyogram.

in the univariate analysis are reported in the online supplement table 1. A post hoc analysis of respiratory-specific mortality indicated a stronger association with long-term outcomes with an EMGpara%max at discharge $\geq 15\%$ being associated with a three-fold risk of respiratory-specific mortality when compared with an EMGpara%max $< 15\%$ (HR 3.18, 95% CI 1.52 to 6.46, $p=0.002$, log rank, online supplement efigure 1).

In the multivariate analysis, factors associated with a poor prognosis were an EMGpara%max at discharge $\geq 15\%$ (HR 2.14, 95% CI 1.29 to 3.54, $p=0.003$), an age ≥ 71 years (HR 2.03, 95% CI 1.23 to 3.34, $p=0.006$), a PaCO₂ at admission ≥ 6 kPa (HR 1.83, 95% CI 1.06 to 3.06, $p=0.022$) and previous long-term oxygen use (HR 2.98, 95% CI 1.47 to 6.03, $p=0.002$). In the multivariate analysis, FEV₁ at discharge and hospital admission frequency were not associated with long-term outcome ($p=0.606$ and 0.720 , respectively).

ROC analysis for the prediction of 5 years mortality gave an area under the curve of 0.649, 0.626, 0.701 for EMGpara%max, age and admission PaCO₂, respectively ($p=0.02$, 0.006 , <0.001 , respectively). An individual risk score of all significant factors associated with poor prognosis was produced to predict 5-year mortality and provided an area under the curve of 0.747 ($p<0.001$) (online supplement table 2 and online supplement efigure 2). The individual risk score performed better than the isolated predictors (EMGpara%max, $p<0.001$; age, $p<0.020$; admission PaCO₂, $p=0.201$). The regression model provided an individual risk score correctly classifying 74% of patients (online supplement table 3).

DISCUSSION

This post hoc analysis has demonstrated that NRD, as reflected by EMGpara, is an independent predictor of long-term mortality in patients following an admission for an acute exacerbation of COPD. NRD, as reflected by EMGpara%max, at admission was similar between patients who died and those who remained alive at follow-up, as was early readmission within 28 days and 12-month mortality, indicating that the difference was likely not due to the severity of the index exacerbation. However, those who remained alive appear to have responded more favourably to treatment during the acute exacerbation with a reduction in EMGpara, EMGpara%max and NRDI indicating a favourable effect on the load–capacity–drive relationship of the respiratory system. Conversely, patients who died during follow-up demonstrated smaller changes in measures of NRD and therefore high levels at discharge, indicating either less reversible disease or more severe baseline COPD. This lack of improvement associated with a higher NRD at discharge highlights the severity of their respiratory disease more accurately than traditional markers such as FEV₁, the number of admissions for acute exacerbation of COPD or symptom-related questionnaires. The importance of an imbalance in the load–capacity–drive relationship of the respiratory system is highlighted by the fact that the principal cause of death was from respiratory failure rather than cardiovascular causes as is common in mild COPD.⁷

In our cohort, factors associated with poor survival were prescription of long-term oxygen therapy, age, admission PaCO₂ and EMGpara%max. Interestingly, the last two parameters can be treated with non-invasive ventilation providing a possible physiological rationale for recently demonstrated benefits of this therapy.^{8,9} Our findings are consistent with those of Esteban¹⁰ and colleagues who demonstrated a link between 1-year survival and patient characteristics (age), clinical severity of COPD (presence of hypercapnia) and comorbidities in a large multicentre

study. These findings demonstrate a potential role for NRD in the risk stratification of patients following a hospital admission secondary to an acute exacerbation of COPD. Future work will need to focus on strategies to reduce NRD to evaluate whether these can alter disease progression, risk of re-exacerbation and hospitalisation and long-term mortality.

CONCLUSION

In addition to the short-term value of using NRD to predict safe hospital discharge following a severe acute exacerbation of COPD, NRD at hospital discharge could be measured in order to assess efficacy of interventions targeted to optimise COPD and to reduce mortality following an acute exacerbation of COPD.

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Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement There are no additional unpublished data from the study.

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Neural respiratory drive predicts long term outcome following admission for exacerbation of COPD: A post-hoc analysis

Online supplement

eResults

Table 1 reports univariate and multivariate analysis of factors associated to death. Only factors with a p-value < 0.1 were included in the multivariate analysis.

As EMG measurements are correlated, the only EMG measurements included in the multivariate analysis is the discharge EMG%max. Similarly, bicarbonates and pH were not included given their correlation with PaCO₂.

The regression analysis can produce a risk score which can be translated to individual risk using the following equation:

$$\text{risk of death} = \frac{e^{\text{risk score}}}{1 + e^{\text{risk score}}}$$

eDiscussion

We have shown that a discharge EMG%max ≥15% was associated to a worst outcome. When compared to reference values, in healthy subjects [1], it corresponds to a three-fold increase of the neural respiratory drive. Therefore, such value corresponds to a significant increase in the neural respiratory drive. This result is line with previously measured neural respiratory drive in COPD patients admitted for acute exacerbation [2].

eTable 1: Factors associated with mortality in univariate and multivariate analysis (HR: hazard-ratio, CI: confident interval, MRC: medical research council, DECAF: dyspnea, eosinopenia, consolidation, acidemia, fibrillation, CAT: COPD assessment tool, NRDl: neural respiratory drive index, FEV₁: forced expiratory volume at 1 second)

	Univariate analysis (log rank)		Multivariate analysis (Cox regression)	
	HR [95%CI]	p	HR [95%CI]	p
Age ≥ 71 years old	1.94 [1.21 - 3.11]	0.007	2.03 [1.23 – 3.34]	0.006
Prescription of long term oxygen therapy	3.40 [3.14 - 23.53]	<0.001	2.98 [1.47 – 6.03]	0.002
Number of admissions for acute exacerbations of COPD in the previous year ≥ 1	2.26 [1.40 - 3.72]	<0.001	2.98 [0.94 – 1.23]	0.292
Admission MRC ≥ 4	1.25 [0.71 - 2.15]	0.451	Not included	
Admission DECAF ≥ 1	1.29 [0.79 - 2.09]	0.316	Not included	
Admission CAT ≥ 29	0.73 [0.46 - 1.18]	0.207	Not included	
Admission pH ≥ 7.398	0.633 [0.39 - 1.00]	0.055	Not included	
Admission PaCO ₂ ≥ 6kPa	1.85 [1.17 - 3.02]	0.010	1.83 [1.06 – 3.06]	0.022
Admission Bicarbonates ≥ 25.2mmol/L	1.56 [0.97 - 2.50]	0.066	Not included	
Discharge EMGpara ≥ 9.53μV	1.66 [1.03 – 2.76]	0.039	Not included	
Discharge EMGpara%max ≥ 15%	1.89 [1.19 - 3.08]	0.008	2.14 [1.29 – 3.54]	0.003
Discharge NRDl ≥ 110	3.08 [1.91 – 5.13]	<0.001	Not included	
Discharge FEV ₁ ≥ 0.71L	0.578 [0.37 - 0.95]	0.031	0.91 [0.53 – 1.58]	0.739
Change in EMGpara%max during inpatient stay ≥ 1.53%	0.69 [0.43 – 1.23]	0.139	Not included	
Change in respiratory rate during inpatient stay ≥ 1/min	1.32 [0.83 – 2.14]	0.244	Not included	
Change in NRDl during inpatient stay ≥ 42.07	0.57 [0.35 – 0.91]	0.019	Not included	

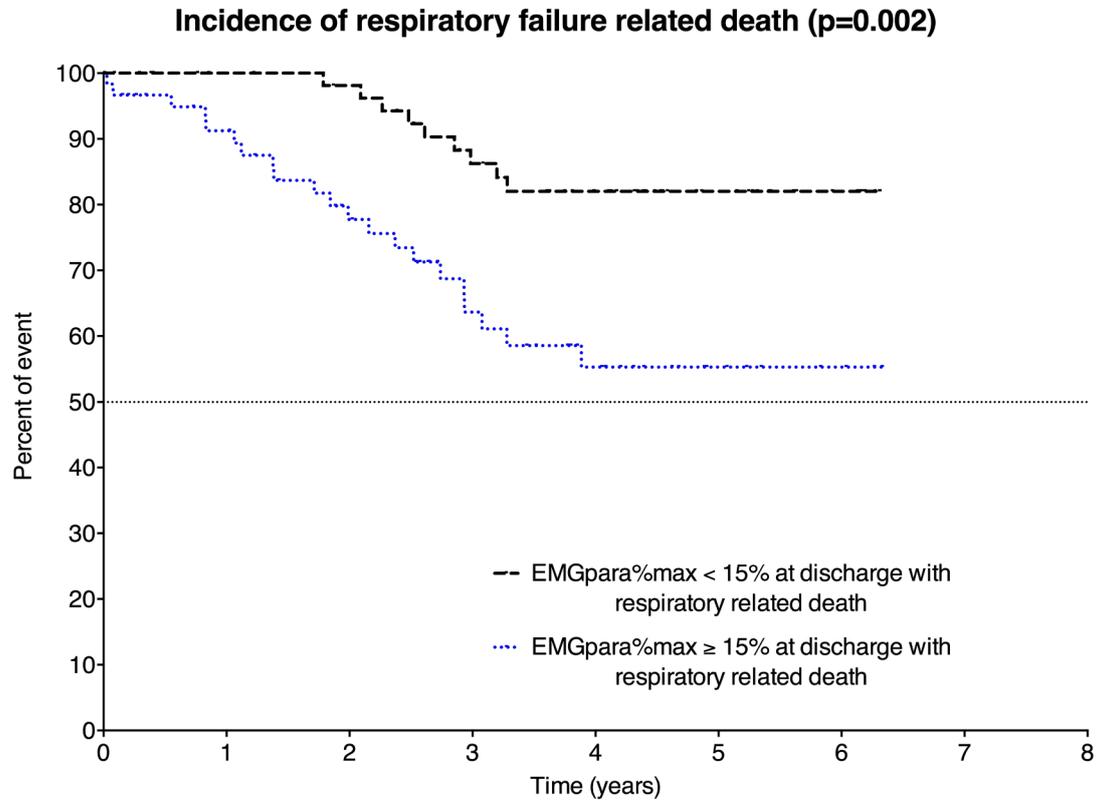
eTable 2: Diagnostic performance for prediction of 5-years mortality at optimal cut-off values (PPV: positive predictive value, NPV: negative predictive value, AU: arbitrary unit)

	Cut-off value	Sensitivity	Specificity	PPV	NPV	Youden index	AUC
EMGpara%max at discharge (%)	>15.5	60.3	70.2	69.1	61.5	0.30	0.656
Age (years)	>63	82.5	43.9	61.9	69.4	0.26	0.639
PaCO ₂ at admission (kPa)	>6.15	53.3	86.0	80.0	63.6	0.39	0.701
Individual risk score (AU)	88.1	81.8	58.8	70.7	71.1	0.41	0.747

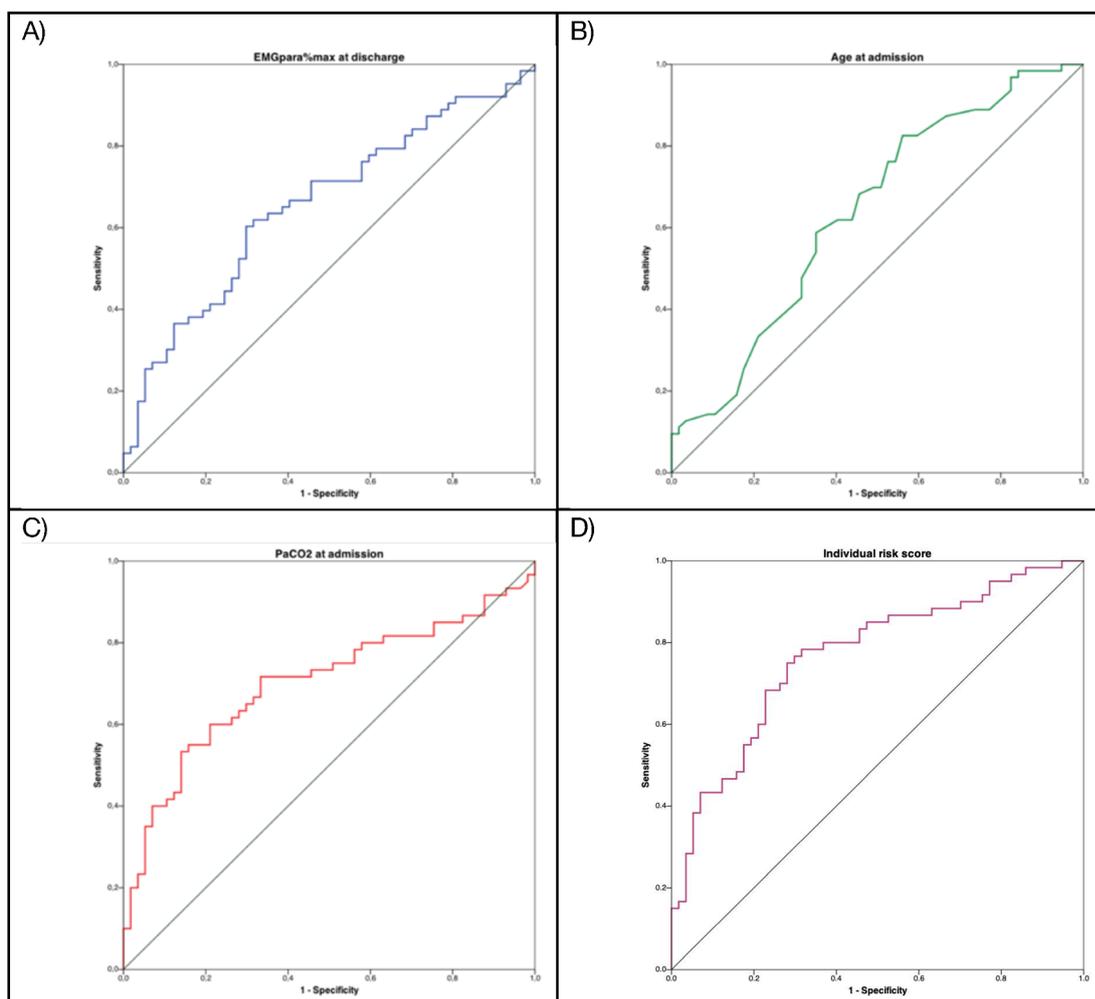
eTable 3: Logistic regression results for prediction model (C.I.: Confidence interval)

	B	p	Exp(B)	Lower 95% C.I. for Exp(B)	Lower 95% C.I. for Exp(B)
Age (years)	.079	.002	1.083	1.030	1.138
PaCO ₂ at admission (kPa)	.572	.001	1.771	1.253	2.504
EMGpara%max at discharge (%)	.075	.034	1.078	1.006	1.155
LTOT (yes)	1.932	.083	6.900	.778	61.196
Constant	-9.816	.000	.000		

eFigure 1: Incidence of respiratory failure related death according to EMGpara%max at discharge (p=0.002, log-rank)



eFigure 2: Receiver-operator characteristic (ROC) curve for predictions of 5-years mortality: A) EMGpara%max at discharge (AUC: 0.649) B) Age at admission (AUC:0.626) C) PaCO₂ at admission (AUC:0.701) D) Individual risk score (AUC:0.768) (AUC: area under the curve)



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The main findings of this study ¹⁶⁵ were:

- NRD non-invasively assessed at discharge could predict the long-term outcome of COPD patients hospitalised for acute exacerbation
- NRD at discharge could predict respiratory related mortality
- NRD may be an early marker of disease severity that is targeted by NIV similarly than P_aCO_2 .

Results from our study confirm the usefulness of NRD evaluation in the risk-stratification and therefore resource allocation of COPD patients admitted with severe exacerbation.

III. *Parasternal electromyography to assess the effect of non-invasive ventilation*

D. *Original research: Neural respiratory drive and cardiac function in patients with obesity hypoventilation syndrome following initiation of non-invasive ventilation (Journal of Thoracic Disease, 2018)*

It has been previously shown that NRD is increased ¹⁷⁹ in patients with OHS. The application of a positive airway pressure can reduce NRD when the treatment is applied ¹⁷⁹, *i.e.* overnight in daily clinical practice.

To date, no study has evaluated the consequences of NIV treatment on daytime NRD. With the ongoing debate regarding the first line treatment of OHS ⁵⁷, such data are of particular interest ⁵⁹. Indeed, NIV improved significantly lung function and walking distance in patients with OHS in comparison to CPAP ⁵². Other data support the benefit of NIV on exercise capacity and weight loss ^{188,189}.

In the following study, we aimed to investigate the change in NRD following 3-months of NIV in patients with OHS. In parallel, we investigated the change in their cardiac function.

This study that was published in the Journal of Thoracic Diseases in 2018 ¹⁶⁶:

Onofri, A., Patout, M., Kaltsakas, G., Lhuillier, E., Mushemi-Blake, S., Arbane, G., Pengo M., Marino P., Steier J. (2018). Neural respiratory drive and cardiac function in patients with obesity hypoventilation syndrome following initiation of non-invasive ventilation. *Journal of Thoracic Disease*, 10(Suppl 1), S135–S143. <http://doi.org/10.21037/jtd.2017.12.129>

Neural respiratory drive and cardiac function in patients with obesity hypoventilation syndrome following initiation of non-invasive ventilation

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Contributions: (I) Conception and design: A Onofri, G Arbane, MF Pengo, P Marino, J Steier; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Chronic hypercapnic respiratory failure (HRF) in obesity hypoventilation syndrome (OHS) is commonly treated using non-invasive ventilation (NIV). We hypothesised that treatment of OHS would improve neural respiratory drive index (NRDI) and cardiac function.

Methods: Fourteen patients (8 females) with OHS, who were admitted for initiation of domiciliary NIV, were prospectively studied. Patients had (mean \pm SD): age (53 \pm 10 years), body mass index (BMI) (50.1 \pm 10.8 kg/m²), and pCO₂ (7.3 \pm 0.9 kPa). NRDI was assessed by surface electromyogram of the parasternal intercostals. Cardiac function was assessed by transthoracic echocardiography (TTE). All measurements were performed at baseline, 6 weeks, and 3 months.

Results: NRDI improved on day one following NIV set-up comparing to baseline (484.2 \pm 214.8 *vs.* 316.5 \pm 106.5 AU) and this improvement was maintained at 6 weeks (369.1 \pm 173.2 AU) and at 3 months (351.2 \pm 167.1 AU) (P=0.004). No significant differences were identified in terms of cardiac function between baseline and 3 months [tricuspid annular plane systolic excursion (TAPSE) (24.6 \pm 5.8 *vs.* 23.0 \pm 4.0 mm, P=0.317); systolic pulmonary artery (PA) pressures (36.7 \pm 15.2 *vs.* 44.5 \pm 23.9 mmHg, P=0.163].

Conclusions: NIV improves NRDI in patients with OHS, while the cardiac function over a three-month period remains unchanged.

Keywords: Obesity hypoventilation syndrome (OHS); neural respiratory drive (NRD); sleep-disordered breathing; non-invasive ventilation (NIV); respiratory muscle function; pulmonary hypertension (PH)

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Introduction

The prevalence of obesity has increased continuously over recent decades reaching epidemic proportions (1). Obesity increases the load on the respiratory system and the work of breathing (2), leads to high levels of neural respiratory drive (NRD) (3), and is associated with a high prevalence of

sleep-disordered breathing (4). An imbalance in the load-to-capacity ratio of the respiratory muscles (2) leads to increased levels of NRD (3); in turn, nocturnal loss of NRD may first lead to hypercapnic respiratory failure (HRF) while asleep and, subsequently, breathlessness in patients with obesity hypoventilation syndrome (OHS) while awake

(5-7).

Obesity-related respiratory failure, the OHS, is an increasingly common problem (8). Current estimates suggest that between 0.3% to 0.4% of the general population may develop OHS (9). Patients with morbid obesity are more likely to develop significant sleep-disordered breathing and OHS (10). However, it remains unclear why some obese patients develop OHS over time (11), while others remain unaffected: approximately a third of morbidly obese patients develop hypercapnia (12).

In addition to the respiratory constraints, pulmonary hypertension (PH) and cardiac impairment, particularly right ventricular (RV) dysfunction, are associated with adverse health outcomes in OHS (13-16). The prevalence of PH in obese patients is higher than in the general population, 5% of all individuals with a body mass index (BMI) greater than 30 kg/m² have some degree of PH, while 48% of patients with severe PH are obese (17,18). Moreover, there is a strong correlation between BMI and RV dysfunction, with congestive heart failure being two-fold more common in obese patients (19).

Non-invasive ventilation (NIV) is commonly used to treat HRF in OHS and its impact on mechanical indices of respiratory function and blood gas homeostasis has been previously described (20-24). However, the effect of NIV on NRD and RV function remains largely unexplained (22-24). The aim of this study was to assess the impact of NIV on respiratory and cardiac function in patients with HRF caused by OHS. We hypothesised that NIV improves not only respiratory but also cardiac function, and that this functional improvement would contribute to better oxygenation, quality of life and exercise capacity.

Methods

This was a prospective observational study assessing patients with OHS prior to and immediately following NIV setup, followed up at 6 weeks and 3 months; it was approved by London City & East NHS Research Ethics Committee (reference: 15/LO/1,390). OHS was defined as obesity (BMI >30 kg/m²) with associated daytime hypercapnia (pCO₂ >6 kPa) and sleep disordered breathing. Patients were recruited at Guy's and St Thomas' NHS Foundation Trust, London (UK) from November 2015 to November 2016. Patients were enrolled within 24 hours of admission to the hospital; follow up was arranged at six weeks with an outpatient review and at three months with a planned inpatient review. Informed and written consent was obtained from

all patients. The study was registered on ClinicalTrials.gov (CARE-NIV, NCT02699112).

Primary and secondary outcomes

Primary outcome parameters were NRD and tricuspid annular plane systolic excursion (TAPSE) score. These were used to assess the impact of NIV on the cardiorespiratory system, using markers of NRD, as measured by the electromyography of the parasternal intercostals (EMGpara). These were measured prior to, during and after NIV initiation and at 6 weeks and 3 months. In addition, transthoracic echocardiography (TTE) to assess cardiac function was performed at baseline and 3 months. Secondary outcomes were oxygenation (SpO₂), arterial blood gas analysis including pO₂, pCO₂ and pH, quality of life, and exercise capacity.

Inclusion and exclusion criteria

Inclusion criteria were a confirmed diagnosis of OHS with HRF and the need to commence on NIV (pCO₂ >6 kPa), age ≥18 and <80 years, BMI >30 kg/m², confirmed sleep-disordered breathing, and clinical stability without acute deterioration for ≥4 weeks.

Exclusion criteria were patients already established on NIV, patients with an overlap syndrome (OHS and COPD), inability to tolerate NIV, a low compliance with NIV during the hospital stay (usage <4 hours/day), any contraindication to NIV, acute respiratory deterioration, other acute pathology or critical illness, and psychological or social factors that would impair compliance with the protocol (Figure 1).

Measurement of NRD

The EMGpara was recorded whilst the patient was awake, at rest and in semi-recumbent position in bed, as previously described (25). EMG electrodes were applied 3cm from the midline in the 2nd intercostal space; a reference electrode was placed on the right clavicle. The skin was prepared using NuPrep abrasive skin preparation gel (D.O.Weaver, Aurora, CO/USA) and alcohol solution. The signal was amplified and processed using a high differential amplifier with band pass filters set at 10 and 2,000 Hz (1902, Cambridge Electronic Design, Cambridge, UK). Additional analogue 50 Hz notch filter and AC coupling were used. Amplified signals were passed to an analogue to

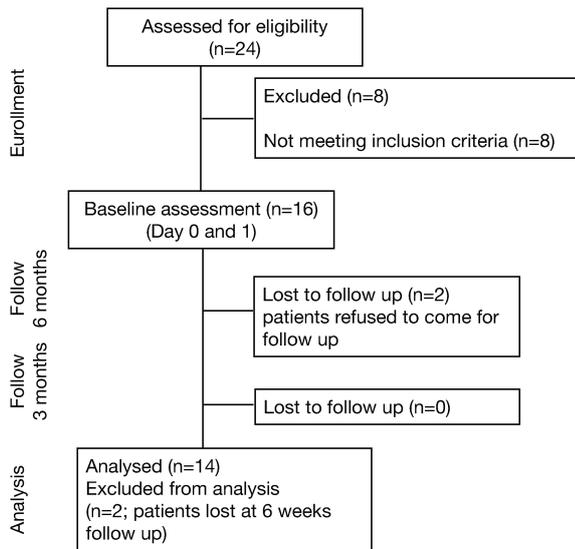


Figure 1 Consort diagram of the study.

digital convertor (Powerlab, ADInstruments, Chalgrove, UK) and passed to a personal computer. Further digital filtering occurred at 20Hz after data acquisition (LabChart v7.1, ADInstruments, Chalgrove, UK). At baseline, EMGpara was recorded during maximal inspiratory and expiratory manoeuvres: sniff, maximal inspiratory pressure (P_Imax), maximal expiratory pressure (P_Emax), and inspiratory capacity. The average EMGpara of two minutes tidal breathing was calculated (mean EMGpara) with a time constant of 100 ms. EMGpara%max was calculated as the mean of EMGpara divided by the maximum EMGpara ×100%; neural respiratory drive index (NRDI) was obtained from EMGpara%max × respiratory rate.

TTE

All TTEs were performed by the same trained technician of the cardiology department of Guy's and St Thomas' NHS Foundation Trust while patients were awake, at rest and supine in bed. The assessment followed the American Society of Echocardiography guidelines (26) using an IE-33 device and an ×5–1 probe (Phillips, Amsterdam/Netherlands). The following cardiac chamber dimensions and pressures were recorded: RV systolic pressure (RVSP), RV diameters [RV basal (RVD1), mid-cavity (RVD2) and longitudinal dimension (RVD3) and RV outflow tract (RVOT)], right atrium major and minor dimension, right atrial pressure (RAP) and inferior vena cava (IVC) diameter.

Pulmonary artery (PA) diameter was measured between the valve and the bifurcation point, while the PA pressures [mean, PAP_M and systolic, pulmonary artery pressure (PAP_S)] were derived by measuring the PA acceleration time and tricuspid regurgitation. RV systolic function was assessed by recording the TAPSE score. Left ventricular (LV) systolic and diastolic functions were defined by the ejection fraction (Simpson's rule) and E/E' ratio (between early mitral inflow velocity and mitral annular early diastolic velocity), respectively.

Study protocol

Baseline measurements were taken on the day prior to (day 0) and following NIV set up (day 1), at follow up assessment at six weeks (outpatient; W6) and at three months (inpatient; M3). Demographics and anthropometric parameters were recorded including age, gender, height, weight, BMI, hip, waist and neck circumference, office blood pressure (average of three measurements), oxygen saturation, temperature, respiratory rate and heart rate. The patients filled in the Medical Research Council (MRC) dyspnoea scale (27), the COPD assessment test (CAT) (28), the St George's Respiratory Questionnaire (SGRQ) (29) and the Severe Respiratory Insufficiency Questionnaire (SRI) (30). Electrocardiogram (ECG) and chest X-ray were performed routinely and were reviewed to exclude ischaemic heart disease, arrhythmias, cardiomegaly, signs of acute heart failure and respiratory co-morbidities like fibrosis or emphysema. All subjects underwent standard spirometry (31). Blood tests included the full blood count, the renal profile, thyroid stimulating hormone (TSH), N-terminal pro-brain natriuretic peptide (NT-proBNP), glucose and a radial artery blood gas (ABG) analysis. At baseline, a nocturnal transcutaneous oximetry and capnography (TCM TOSCA, Radiometer Medical ApS, Bronshoj/Denmark) and a walking test (4-metre gait speed) were performed (32). EMGpara and TTE were measured prior to NIV setup.

NIV setup followed established guidelines of the Lane Fox Unit for NIV in OHS, as described elsewhere (33). The aim was to control snoring, avoid chest wall paradox with oxygen desaturations, to maintain oxygen saturation (SpO₂) >88% and transcutaneous CO₂ <7.0 kPa, while using nocturnal NIV. Oxygen supplementation was applied, if indicated, to maintain SpO₂ >88%. NIV modes used were spontaneous/timed (S/T) and volume-assured pressure assistance (AVAPS-AE). A full face mask was used as standard interface. Following the first night of NIV usage

Table 1 Demographics, spirometry, respiratory muscle strength, and exercise capacity at baseline and follow up

Parameters	Baseline	6 weeks	3 months	P value
Height (m)	1.64 (1.60–1.66)	–	1.64 (1.60–1.66)	1.000
BMI (kg/m ²)	50.1±10.8	50.8±10.0	50.0±10.2	0.382
FEV ₁ (% predicted)	43±13	42±12	43±19	0.738
FVC (% predicted)	40±13	42±15	41±16	0.892
FEV ₁ /FVC (%)	85±8	82±12	82±13	0.745
SNIP (cmH ₂ O)	–44.9±18.6	–59.9±14.3	–45.1±31.4	0.239
PI, max (cmH ₂ O)	–38.6±20.2	–47.7±13.2	–48.9±15.7	0.089
PE, max (cmH ₂ O)	92.5±55	81.5±50.3	83.8±49.8	0.773
4-metre gait speed (sec)	5.02±2.10	–	4.24±1.85	0.258

Values are presented as mean ± SD or median (IQR) unless otherwise stated. 6 weeks, follow up at 6 weeks; 3 months, follow up in 3 months. BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; SNIP, maximal sniff nasal inspiratory pressure; PI, max, maximum inspiratory mouth pressure; PE, max, maximum expiratory mouth pressure; SD, standard deviation; IQR, interquartile range.

(within 4 hours) the ABG was repeated, and EMGpara (EMGpara%max) and NRDI were measured and compared to baseline. At six weeks' outpatient follow-up, NIV settings and usage were recorded, the patient was clinically reassessed and NRDI measurements performed. Adherence to NIV (hours/day) and percentage of nights used were retrieved from NIV built-in software at 6 weeks and 3 months follow-up. Anthropometrics, questionnaires, ABG, spirometry and NRDI measurements were repeated. At three months inpatient follow-up, all baseline measurements and an overnight assessment were repeated, including NRDI measurements and TTE.

Sample size calculation

The sample size was calculated with an alpha of 5% and a statistical power of 90%. A standard deviation was available from previous studies using the TAPSE score (standard deviation of 3.5 and a minimum clinical significant difference of 6 mm) (26). With these parameters, a total number of 14 patients were required for this observational pre-/post-comparison study design.

Statistics

Normal distribution of the data was checked with the Shapiro-Wilk test. Data were expressed as mean (± standard deviation) for normally distributed variables, while median

(interquartile range with 25th–75th percentile) were used for non-normally distributed data. Comparisons were made using paired *t*-test, Wilcoxon signed rank test, one way and two way repeated measures ANOVA, and McNemar's test. Holm-Sidak and Dunn's post hoc correction methods were used where appropriate. A P value <0.05 was considered significant. Statistical analysis was performed using SigmaPlot V13.0 statistical software (Systat Software Inc., CA, USA).

Results

Sixteen patients were recruited at baseline with two drop-outs (*Figure 1*). The anthropometric, demographic, and respiratory function data (spirometry, respiratory muscle strength, and exercise capacity) of the 14 patients (8 females, age 53.3±9.9 years) who completed the study did not change during the observation period (*Tables 1* and *S1*).

Arterial blood gas analysis

The arterial blood gas analysis confirmed chronic compensated HRF at baseline with an improvement in the pCO₂ and bicarbonates at 3 months (*Table 2*).

Venous blood tests

The patients were not anaemic, had no significant infection

Table 2 Arterial blood gas analysis at baseline and follow up

Parameters	Baseline	6 weeks	3 months	P value
SpO ₂ (%)	92.9±4.6	93.8±4.1	94.0±2.0	0.560
pO ₂ (kPa)	8.1±0.8	8.8±0.9	8.7±1.1	0.064
pCO ₂ (kPa)	7.3±0.9*	6.8±0.9	6.7±0.8*	0.045
pH	7.39±0.02	7.38±0.04	7.38±0.04	0.351
HCO ₃ (mmol/L)	31.7±2.9*	29.6±2.8	29.2±2.7*	0.036

Values are presented as mean ± SD or median (IQR) unless otherwise stated. 6 weeks, follow up at 6 weeks; 3 months, follow up in 3 months; *, significantly different. SpO₂, oxygen saturation; pO₂, partial pressure of oxygen; pCO₂, partial pressure of carbon dioxide; HCO₃, bicarbonates; SD, standard deviation; IQR, interquartile range.

Table 3 Nocturnal transcutaneous capnography data at baseline and during follow up

Parameters	Day 0	Day 1	3 months	P value
Mean SpO ₂ (%)	87±8*	91±4	94±4*	0.024
4%ODI (hour ⁻¹)	69.1±51.8* [#]	38.6±28.9*	21.2±19.7 [#]	0.002
Mean tCO ₂ (kPa)	7.4 (7.1–7.9)	7.2 (6.8–7.9)	6.7 (5.9–7.6)	0.174
Max tCO ₂ (kPa)	8.7 (8.0–9.6)*	9.1 (7.4–9.6)	7.3 (7.1–8.4)*	0.023

Values are presented as mean ± SD or median (IQR) unless otherwise stated. Day 0, day pre non-invasive titration; day 1, day post non-invasive titration; 3 months: follow up in 3 months; *[#], significantly different. SpO₂, oxygen saturation; 4%ODI, 4% oxygen desaturation index; tCO₂, transcutaneous carbon dioxide levels; SD, standard deviation; IQR, interquartile range.

or renal problems; one patient had an abnormal elevated serum creatinine level. The NTpro BNP levels were increased in 6 patients. Although the TSH changed slightly, it remained within the normal range during the study period (*Table S2*).

NIV and nocturnal transcutaneous capnography

At baseline, 12 patients received NIV with an S/T mode, while two patients were set up on AVAPS-AE; the pressure settings were not significantly altered over the three months follow up period. Three patients required supplemental oxygen (1 L/min by day and 2 L/min by night) at initial discharge, but were weaned off oxygen over the follow up period. At six weeks and three months follow up, only 6 patients used NIV longer than 4 hours/day (compliant patients). There were no differences in adherence at 6 weeks and 3 months. Two patients did not use NIV at all at three months, and one patient utilised NIV less than 1 hour daily, while 4 patients used the NIV 3–4 hours daily. One patient was non-compliant at six weeks and became more compliant during further follow up.

Night-time ventilation improved respiratory control over time with higher average oxygenation, whilst oxygen desaturations were diminished. Transcutaneous CO₂ monitoring indicated that the maximal tCO₂ was lower at three months than the mean tCO₂ at baseline (*Table 3*). Efficacy of the ventilation was also confirmed by the improved daytime ABG results (*Table 2*) and the weaning of supplemental oxygen in all patients.

Dyspnoea and quality of life

The MRC dyspnoea and SGRQ scores did not change over time, but the SRI indicated an improvement in “attendant symptoms and sleep” at 6 weeks and 3 months (*Table S3*).

Parasternal intercostal electromyography

NRDI improved significantly over time (*Table 4*). NIV successfully offloaded the work of breathing, when comparing the electromyographic activity of the inspiratory muscles on NIV *vs.* off NIV. EMG raw (D1 P=0.002, W6 P=0.016, M3 P=0.004), EMG %max (D1 P=0.001, W6

Table 4 Respiratory muscle activity on and off NIV at baseline and during the follow up period

Parameters	Day 0	Day 1	6 weeks	3 months	P value
EMGpara (μ V) off NIV	5.5 \pm 1.3	5.0 \pm 1.1	5.5 \pm 1.6	5.1 \pm 1.8	0.699
EMGpara (μ V) on NIV	–	2.7 \pm 0.7	3.8 \pm 1.1	3.4 \pm 0.9	0.324
EMGpara (%max) off NIV	21.7 \pm 8.5	16.2 \pm 4.6	18.7 \pm 7.9	17.5 \pm 7.5	0.080
EMGpara (%max) on NIV	–	8.94 \pm 4.1	12.9 \pm 5.7	12.0 \pm 5.9	0.481
NRDI (a.u.) off NIV	484.2 \pm 214.8 ^{*,#,%}	316.5 \pm 106.2 [*]	369.1 \pm 173.2 [#]	351.2 \pm 167.1 [%]	0.004
NRDI (a.u.) on NIV	–	166.8 \pm 99.4	219.6 \pm 105.3	221.2 \pm 116.4	0.626

Values are presented as mean \pm SD or median (IQR) unless otherwise stated. Day 0, Day pre non-invasive titration; Day 1, Day post non-invasive titration; 3 months: follow up in 3 months; ^{*,#,%}, significantly different. EMGpara, parasternal intercostal electromyography; NRDI, neural respiratory drive index; NIV, non-invasive ventilation; SD, standard deviation; IQR, interquartile range.

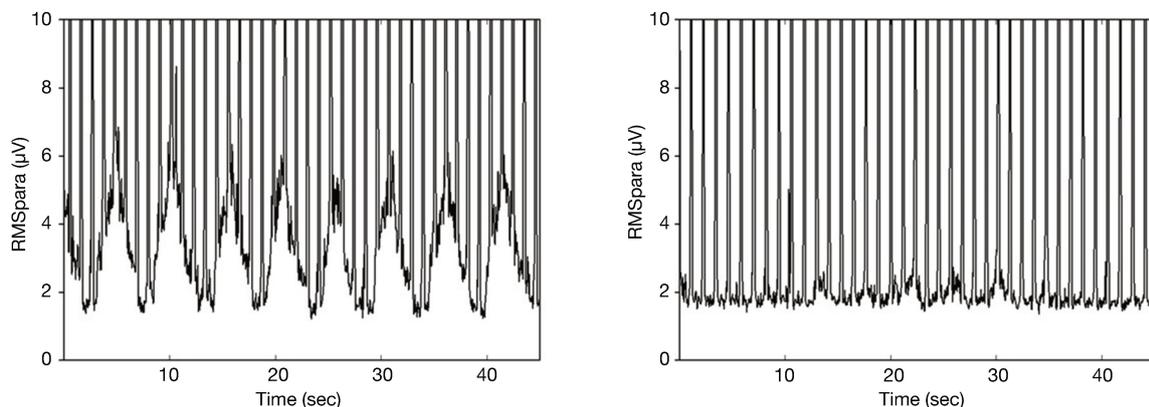


Figure 2 Root mean square (RMS) of the parasternal electromyography (EMG) during self-ventilation (Left) and when on NIV (Right). The QRS complex artefacts of the ECG (truncated) are clearly visible superimposed on the activity of the EMG trace. sec, seconds; ECG, electrocardiogram.

P=0.011, M3 P=0.002), and EMG NRDI (D1 P=0.014, W6 P=0.021, M3 P=0.014) significantly improved at all follow up assessments (*Figure 2*).

TTE

The systolic pulmonary artery pressure (PAP_s) could only be assessed in 7 patients, 3 of which had a PAP_s >40 mmHg. Five patients had dilated RV dimensions at baseline and at 3 months, while five had E/E' Ratio impairment (correlated with LV diastolic dysfunction) at baseline and two at 3 months follow up; all three patients that required oxygen at baseline had LV diastolic dysfunction. LV systolic function was normal in all patients, whereas LV diastolic function was impaired in 3 patients at baseline and in 2 patients at follow up. One patient had RV impairment (*Table 5*).

Discussion

NIV in patients with OHS improves the NRD, sleep-disordered breathing and arterial blood gases over a three-month period by offloading the work of breathing. Furthermore, it positively impacts symptoms and sleep quality. However, cardiac function, spirometry, respiratory muscle strength, and exercise capacity do not change significantly.

NIV in OHS reduces the NRD. The NRD was reduced while patients were on NIV comparing to self-ventilating. Furthermore, our data suggests that the initiation of nocturnal use of NIV reduces the NRD while self-ventilating, and this effect remains unchanged during a 3 months period. A possible explanation for this is that NIV offloads the respiratory muscles and as a result reduces the work of breathing. The effect of NIV on respiratory neural

Table 5 Transthoracic echocardiography results at baseline and follow up

Parameters	Baseline	3 months	P value
RVSP (mmHg)	32.0 (24.0–48.0)	36.0 (26.5–65.8)	0.313
RVD1 (mm)	41.0 (35.5–49.8)	41.0 (38.0–44.5)	0.839
RVD2 (mm)	36.6±11.4	37.6±8.8	0.806
RVD3 (mm)	74.9±11.8	74.1±12.5	0.958
RVOT (mm)	32.0 (24.5–35.0)	35.5 (27.0–41.8)	0.413
RAP (mmHg)	6.8±4.4	5.9±3.9	0.379
RA major diameter (mm)	42.0±8.7	37.0±9.4	0.298
RA minor diameter (mm)	40.1±8.6	38.5±9.0	0.796
IVC diameter (mm)	20.3±4.2	19.4±6.4	0.913
PA diameter (mm)	25.1±3.6	23.4±5.5	0.342
PAP _s (mmHg)	36.7±15.2	44.5±23.9	0.163
PVAT (ms)	88.5±18.2	73.7±44.5	0.372
E/E' ratio	6.0±4.2	5.4±2.2	0.819
Tricuspidal regurgitation (cm/m ²)	2.65±0.62	2.97±0.73	0.110
TAPSE score (mm)	24.6±5.8	23.0±4.0	0.317
LVEF (%)	59.0±7.2	58.8±7.4	0.880

Values are presented as mean ± SD or median (IQR) unless otherwise stated. 3 months, follow up in 3 months. RVSP, right ventricular systolic pressures; RVD, right ventricular diameter; RVOT, right ventricular outflow diameter; RAP, right atrium systolic pressures; RA, right atrial; IVC, inferior vena cava; PA, pulmonary artery; PAP_s, systolic pulmonary pressure; PVAT, pulmonary velocity acceleration time; E/E', ratio between early mitral inflow velocity and mitral annular early diastolic velocity; TAPSE, tricuspid annular plane systolic excursion; LVEF, left ventricular ejection fraction; SD, standard deviation; IQR, interquartile range.

drive has been previously demonstrated in neuromuscular disease and COPD (34). To the best of our knowledge, this is the first study showing the positive effect of NIV on NRD in OHS, acutely and in the long term.

In this context, cardiac function remained unchanged. Our data show that any potential effect of NIV on the cardiovascular may be less profound than on the respiratory system. In contrast with these findings, Castro-Añón *et al.* screened OHS patients established on positive airway pressure therapy for PH and followed them for 6 months, using TTE (35). They demonstrated a significant decrease in pulmonary arterial pressure at 6 months. Moreover, Kauppert *et al.* demonstrated in 21 OHS patients established on NIV using right heart catheterization and echocardiography that pulmonary pressures decreased with better NIV compliance (36). Held *et al.*, retrospectively identified 18 patients with hypoventilation and PH who were treated with PAP

therapy (37). They assessed PA pressure and cardiac function using right heart catheterization and echocardiography, and found significant improvements in mean and systolic PA pressures, pulmonary vascular resistance, right ventricular systolic function and improvements in walking distance at 3 months follow up. Possible explanations for the discrepancy with the aforementioned studies are the use of right heart catheterization, different compliance and follow up periods.

The data of this study support the hypothesis that the positive treatment effect of NIV on the respiratory system does not significantly impact on the pathophysiology of the cardiovascular system in the short term. This is limited by the relatively short follow up, limited sample size, lack of invasive PA pressure measurement and observation of patients who had relatively preserved RV function. Larger cohort studies of patients with OHS will be necessary to define improved clinical outcomes on NIV, particularly in patients who have significant right heart strain due to

PH. Moreover, as there are sparse data regarding long-term NIV treatment (38-39) in OHS, extended observation periods are needed. Furthermore, invasive measurements of pulmonary pressures and cardiac function might better elucidate the role of right ventricular function and PH in the pathophysiology of OHS in order to identify relevant future treatment targets and outcomes. This could include specific targeting of patients who have an insufficient response to NIV therapy beyond the initial treatment period, as right heart failure significantly impacts on long-term outcomes and can, potentially, be modified using drug specific treatment for PH.

Conclusions

NIV controls HRF and improves NRD in OHS in the domiciliary setting. Any potential impact on the cardiovascular system might be less responsive to NIV than the respiratory system.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: It was approved by London City & East NHS Research Ethics Committee (reference: 15/LO/1,390). Informed and written consent was obtained from all patients.

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Supplementary

Table S1 Anthropometrics, demographics, and cardiorespiratory measurements at baseline and follow up

Parameters	Baseline	6 weeks	3 months	P value
Weight (kg)	134.1±34.3	136.1±33.9	134.2±34.5	0.388
Neck circumference (cm)	44.5±5.0	44.7±5.2	44.8±4.8	0.851
Waist circumference (cm)	130.6±14.9	130.9±17.6	133.4±16.5	0.346
Hip circumference (cm)	146.8±17.1	141.1±16.1	145.5±16.5	0.055
Waist/hip ratio	0.82±0.06	0.81±0.05	0.81±0.06	0.740
SpO ₂ (%)	92.9±4.6	93.8±4.1	94.0±2.0	0.560
Heart rate (min ⁻¹)	80.0±11.3	74.7±16.2	74.8±13.3	0.309
Respiratory rate (min ⁻¹)	19.9±2.7	19.9±4.1	20±4.5	0.996
Systolic BP (mmHg)	128.4±17.7	129.7±19.6	131.6±22.7	0.804
Diastolic BP (mmHg)	77.7±14.2	77.5±14.6	77.1±12.1	0.987

Values are presented as mean ± SD or median (IQR) unless otherwise stated. 6 weeks, follow up at 6 weeks; 3 months, follow up in 3 months. BMI, body mass index; SpO₂, oxygen saturation; BP, blood pressure; SD, standard deviation; IQR, interquartile range.

Table S2 Blood test results at baseline and follow up

Parameters	Baseline	3 months	P value
Hb (g/dL)	13.6±1.9	13.3±1.5	0.368
Hct (%)	45.9±9.0	44.0±6.8	0.357
White blood cells (x10 ³ /mm ³)	7.9±2.0	8.7±2.8	0.147
Platelets (x10 ³ /mm ³)	223.3±70.0	191.9±89.6	0.327
Urea (mg/dL)	6.0±1.9	5.7±1.9	0.780
Creatinine (µmol/L)	80.3±20.7	78.3±19.0	0.337
Clearance creatinine (mL/min)	79.5±22.1	79.4±17.7	0.875
TSH (mUI/L)	2.16±1.14	2.11±1.07	0.033
NT-proBNP (pg/mL)	70.5 (35.0–178.0)	107.0 (23.0–352.0)	0.067
Glucose (mmol/L)	6.98±2.14	6.53±2.22	0.871

Values are presented as mean ± SD or Median (IQR) unless otherwise stated. 3 months, follow up at 3 months. Hb, haemoglobin; Hct, haematocrit; TSH, thyroid stimulating hormone; NT-proBNP, n-terminal pro-brain natriuretic peptide; SD, standard deviation; IQR, interquartile range.

Table S3 Dyspnoea and quality of life scores at baseline and follow up

Parameters	Baseline	6 weeks	3 months	P value
MRC (points)	3.8±1.3	3.4±1.15	3.5±1.0	0.345
CAT (points)	23.5±7.5	20.8±10.0	20.5±10.1	0.287
SGRQ summary (points)	63.8±19.7	49.9±27.1	54.0±22.6	0.093
Symptoms (points)	61.3±31.1	54.3±32.8	51.7±27.5	0.443
Activity (points)	89.0 (69.4–92.7)	80.3 (50.4–92.2)	92.5 (54.7–92.5)	0.091
Impact (points)	57.6 (27.5–69.2)	40.0 (24.9–60.2)	49.3 (18.2–66.0)	0.173
SRI, summary (points)	39.1(26.5–65.4)	54.0 (32.8–74.7)	43.5 (31.5–70.5)	0.092
Respiratory complaints (points)	44.6±24.2	60.9±26.6	50.2±24.1	0.060
Physical functioning (points)	36.3±24.3	45.5±22.9	40.7±30.5	0.115
Symptoms and sleep (points)	35.3±15.5 ^{*,#}	53.8±24.3	50.0±16.5 [#]	0.011
Social relation (points)	61.3±23.3	65.2±18.2	67.0±18.0	0.410
Anxiety (points)	36.1±31.3	46.1±36.0	33.9±30.9	0.488
Psychological well-being (points)	45.8 (32.6–68.7)	47.2 (35.4–78.5)	52.8 (34.7–72.2)	0.926
Social functioning (points)	46.9 (27.3–79.7)	73.9 (31.2–88.3)	59.4 (28.1–82.8)	0.487

Values are presented as mean ± SD or median (IQR) unless otherwise stated. 6 weeks, follow up at 6 weeks; 3 months, follow up in 3 months; ^{*}, [#], significantly different. MRC, medical research council dyspnoea scale; CAT, Chronic Obstructive Pulmonary Disease assessment test; SGRQ, Saint George's respiratory questionnaire; SRI, severe respiratory index questionnaire SD, standard deviation; IQR, interquartile range.

The main findings of this study were:

- Parasternal EMG measurements are feasible in morbidly obese patients.
- The use of NIV effectively offloaded the respiratory system by reducing the NRD by 55%.
- The use of NIV improves NRD rapidly as the improvement was seen after only one night under NIV.
- The improvement in respiratory mechanics is more rapidly achieved than any change in haemodynamic.

IV. *Parasternal electromyography to assess compliance to non-invasive ventilation*

E. *Original research: Polysomnography versus limited respiratory monitoring and nurse-led titration to optimise non-invasive ventilation set-up: a pilot randomised clinical trial (Thorax, 2019)*

Given the obesity epidemic ⁵⁶, patients with COPD are progressively more likely to suffer from concomitant OSA. In this population of overlap patients, a good compliance to overnight treatment is associated to a lower mortality ¹⁹⁰. However, the use of a positive airway pressure to overcome upper airway obstruction may have deleterious effects. If some level of positive expiratory pressure is helpful to decrease work of breathing when counterbalancing intrinsic positive end-expiratory pressure ¹⁹¹, the level of pressure reached to treat upper airway obstruction could contribute to lung hyperinflation ¹⁹².

Therefore, in this population, NRD evaluation could be a useful tool to assess NIV efficacy and adequate offloading. Hence, as part of a clinical trial designed to assess the usefulness of overnight PSG for NIV setup in COPD-OSA, we conducted a nested physiological study that include assessment of NRD in this population and its correlation with patients' outcome.

The study that was published in Thorax in 2019 ¹⁶⁷:

Patout, M., Arbane, G., Cuvelier, A., Muir, J. F., Hart, N., & Murphy, P. B. (2019). Polysomnography versus limited respiratory monitoring and nurse-led titration to optimise non-invasive ventilation set-up: a pilot randomised clinical trial. *Thorax*, 74(1), 83–86. <http://doi.org/10.1136/thoraxjnl-2017-211067>

Polysomnography versus limited respiratory monitoring and nurse-led titration to optimise non-invasive ventilation set-up: a pilot randomised clinical trial

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ABSTRACT

Polysomnography (PSG) is recommended for non-invasive ventilation (NIV) set-up in patients with chronic respiratory failure. In this pilot randomised clinical trial, we compared the physiological effectiveness of NIV set-up guided by PSG to limited respiratory monitoring (LRM) and nurse-led titration in patients with COPD–obstructive sleep apnoea (OSA) overlap. The principal outcome of interest was change in daytime arterial partial pressure of carbon dioxide (PaCO₂) at 3 months. Fourteen patients with daytime PaCO₂ >6 kPa and body mass index >30 kg/m² were recruited. At 3 months, PaCO₂ was reduced by –0.88 kPa (95% CI –1.52 to –0.24 kPa) in the LRM group and by –0.36 kPa (95% CI –0.96 to 0.24 kPa) in the PSG group. These pilot data provide support to undertake a clinical trial investigating the clinical effectiveness of attended limited respiratory monitoring and PSG to establish NIV in patients with COPD–OSA overlap.

Trial number Results, NCT02444806.

INTRODUCTION

Patients with COPD–obstructive sleep apnoea (COPD–OSA) overlap syndrome have a greater incidence of chronic respiratory failure compared with patients with OSA alone.¹ Non-invasive ventilation (NIV) has been demonstrated as an effective treatment² and current guidelines recommend polysomnography (PSG) accompanied by waveform analysis and retrospective NIV modification on the following day to direct NIV titration.³ However, access to PSG is limited and, combined with a rising numbers of patients requiring investigation for sleep-disordered breathing, clinical capacity is unable to match demand. Simple overnight transcutaneous measurements of gas exchange with nurse-led titration according to a protocol has been used as an alternative to PSG-directed set-up.^{4–6} The aim of the current study was to determine the physiological efficacy of limited respiratory monitoring (LRM) using transcutaneous oximetry and nurse-led titration, compared with PSG and retrospective NIV modification, for the set-up of NIV in patients with chronic respiratory failure secondary to COPD–OSA overlap.

METHODS

The study protocol was approved by Guy's and St Thomas' Research Ethics Committee (14/EM/1257)

and the trial registered in a publicly accessible database (NCT02444806).

Inclusion and exclusion criteria

Patients naive to home NIV use were recruited if they met the following criteria: diagnosis of COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease criteria,⁷ OSA defined by a 4% oxygen desaturation index >7.5 events/hour or an apnoea–hypopnoea index >5 events/hour, a daytime arterial PaO₂ of carbon dioxide (PaCO₂) >6 kPa and a body mass index (BMI) >30 kg/m². Exclusion criteria included decompensated respiratory failure with a pH <7.35, inability to tolerate NIV (<4 hours usage during titration), contraindication to NIV, pregnancy, age <18 years and any significant physical or psychiatric comorbidity that would prevent adherence to the trial protocol. Patients were randomised 1:1 to have NIV set-up using LRM or PSG. All overnight titrations in the PSG arm were performed by a single specialist trained respiratory physician. In the LRM arm, the overnight NIV titration was performed by a specialist trained nurse from the ward clinical team, which was not always the same member of staff. Final assessment was performed 3 months after NIV set-up.

Outcomes

Principal outcome of interest was daytime arterial partial pressure of carbon dioxide (PaCO₂) at 3 months. Other relevant outcomes were daytime PaO₂, adherence to ventilation (measured hours of use recorded by device software), health-related quality of life (measured by severe respiratory questionnaire; SRI), sleep quality (measured by Pittsburgh Sleep Quality Index; PSQI) and physiological efficacy of NIV demonstrated by change in neural respiratory drive.

Full methodology including the nurse-led titration protocol and NIV modification protocol and statistical analysis plan have been placed in the online (supplementary material and methods, pages 1–4 OLS; figure E1, page 9 OLS).

RESULTS

Baseline

Recruitment was performed between 25 February and 7 November 2015. Forty-two patients were screened for study participation and 14 included



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Table 1 Baseline characteristics of study population

	Overall population (n=14) Mean±SD/median (IQR)/number (%)	LRM (n=7) Mean±SD/median (IQR)/number (%)	PSG (n=7) Mean±SD/median (IQR)/number (%)
Age (years)	62.4±9.3	64.1±11	60.7±8
Gender (male)	11 (79%)	6 (86%)	5 (71%)
Anthropometrics			
BMI (kg/m ²)	37.2±5.7	35.5±4	38.9±7
Neck circumference (cm)	47.3±5	45.3±5.5	49.4±3.7
COPD severity			
Medical Research Council Dyspnoea scale* (/5)	4.7±0.5	4.9±0.4	4.6±0.5
Borg Scale† (/10)	2.5 (0.6–3.8)	3.0 (0.0–5.0)	2.0 (0.5–3.0)
FEV ₁ (L)	1.00±0.7	0.93±0.2	1.07±0.9
FEV ₁ (% predicted)	30.1±15.3	31.4±12.3	28.7±18.8
FVC (L)	1.7±0.8	1.6±0.3	1.8±1.2
FVC (% predicted)	40.8±15.4	42.3±10.7	39.3±19.8
FEV ₁ /FVC	56.7±10	58.2±12.2	55.3±8.1
Smoking history (p/y)	42 (31–58)	40 (20–58)	50 (35–60)
No of acute exacerbations over the last 12 months	1.5 (0.0–2.0)	2.0 (0.0–2.0)	1.0 (0.0–3.0)
Daytime arterial blood gas on room air			
pH	7.38±0.03	7.39±0.03	7.37±0.02
PaO ₂ (kPa)	7.72±0.72	7.36±0.8	8.08±0.4
PaCO ₂ (kPa)	7.18±0.78	7.03±0.4	7.33±1
Health-related quality of life questionnaires			
COPD Assessment Tool‡ (/40)	24.4±4.7	22.9±2	25.9±6
Severe Respiratory Insufficiency Questionnaire§ (/100)	48.4 (40.9–59.7)	47.3 (40.2–62.1)	49.5 (28.3–61.1)
Sleep-related questionnaires			
Epworth Sleepiness Scale¶ (/10)	10 (7–14)	7 (5–16)	11 (8–15)
Pittsburgh Sleep Quality Index**	11 (±3.2)	11 (8–14)	12 (8–13)
Baseline sleep study (respiratory polygraphy)			
4% Oxygen desaturation index (/h)	36.4 (26.8–53.3)	33.6 (17.1–46.7)	51.1 (26.0–55.0)
Apnoea–hypopnoea index (/h)	19.7 (17.6–23.4)	19.3 (11.6–37.8)	19.7 (12.8–25.1)
Mean SpO ₂ (%)	88.2 (86.9–88.9)	87.4 (85.0–89.0)	88.6 (87.4–89.4)
Percentage of time spent with SpO ₂ <90%	66.4 (41.1–81.2)	73.8 (35.7–89.0)	63 (39.7–73.0)
Mean tCCO ₂ (kPa)	7.8±0.9	7.4±0.6	8.1±1

*Medical Research Council Dyspnoea score—0–5 with higher levels indicating more severe limitations due to dyspnoea.

†Borg score—0–10 categorical rating of perceived exertion with higher ratings indicating more severe dyspnoea.

‡COPD assessment tool—higher scores indicate worse quality of life.

§Severe Respiratory Insufficiency Questionnaire—higher scores indicate better quality of life.

¶Epworth Sleepiness Score—0–24 scale with higher scores indicating more severe daytime somnolence.

**Pittsburgh Sleep Quality Index (PSQI)—0–21. PSQI above 5 indicates poor quality of sleep.

BMI, body mass index; LRM, limited respiratory monitoring; PSG, full polysomnography; SpO₂, oxygen saturation of pulsatile haemoglobin; tCCO₂, transcutaneous carbon dioxide.

(online supplementary figure E2, page 10 OLS). No patients withdrew or were lost to follow-up. Three (43%) patients in each group were established on long-term oxygen therapy. Baseline characteristics are shown in table 1. Length of stay for baseline assessments and NIV set-up was similar between both groups; 2 (2–2) nights in the LRM arm versus 2 (2–3) nights in the PSG arm. NIV settings were similar between both groups (table 2). Visual analogue scales of ease of falling asleep, comfort of sleep and comfort of breathing were similar between both groups.

Outcomes of ventilation at 3 months

At trial completion (3 months), there was a reduction in PaCO₂ of –0.88 kPa (95% CI –1.52 to –0.24 kPa) in the LRM group

and of –0.36 kPa (95% CI –0.96 to 0.24 kPa) in the PSG group. Mean adherence was 4.4 hours/night (95% CI 2.8 to 6.0) in the LRM group and 2.3 hours/night (95% CI 0.91 to 3.8) in the PSG group. Within the 7 days preceding final evaluation, NIV was used for more than 4 hours for 4.7 nights (95% CI 2.7 to 6.7) in the LRM group and 0.7 nights (95% CI 0.0 to 2.4) in the PSG group. Changes in other relevant outcome variables were similar (table 2).

In the overall study population, there was a significant improvement in daytime PaCO₂ (mean difference of –0.62 (95% CI –1.02 to –0.22)), in SRI (mean difference 10.8 (95% CI –2.6 to 19.0)), Epworth Sleepiness Scale (mean difference –1.9 (95% CI –3.6 to –0.1)) and PSQI (mean difference –4.3

Table 2 NIV set-up data and secondary outcomes 3 months after initiation of NIV

	Overall population (n=14) Mean±SD/median (IQR)/ mean difference (95% CI)	LRM (n=7) Mean±SD/median (IQR)/ mean difference (95% CI)	PSG (n=7) Mean±SD/median (IQR)/ mean difference (95% CI)
IPAP (cmH ₂ O)	25.8±2.9	25.7±3.5	26.0±2.3
EPAP (cmH ₂ O)	10±1.9	9.1±1.9	10.9±1.6
Pressure support (cmH ₂ O)	15.9±2.9	16.6±2.8	15.1±3
BUR (breaths/min)	15.7±1.7	15.1±1.1	16.3±2.1
Ti (s)	1.06±0.1	1.06±0.1	1.06±0.1
Average use per day (hours)	3.5 (1.5 to 4.6)	4.5 (3.5 to 5.6)	2 (1 to 3.6)
Patient triggered breaths (%)	37 (31 to 50)	34 (31 to 44)	48 (15 to 56)
Expiratory Vt (mL)	654±142	653±125	657±169
Respiratory rate (/min)	17.1±1.2	16.8±1.1	17.4±1.4
Average non-intentional leak (L/min)	18.1 (15.1 to 26.2)	19.6 (14.8 to 38.8)	17.5 (10.1 to 24.9)
Residual apnoeic event according to NIV built-in software	2.2 (1.6 to 7.5)	2.8 (1.5 to 8.7)	2.0 (0.8 to 21.1)
Change in Severe Respiratory Insufficiency Questionnaire	10.8 (2.6 to 19.0)	14.0 (−1.0 to 28.9)	7.6 (−3.6 to 19.0)
Change in COPD Assessment Tool	−3.9 (−7.8 to 0.1)	−1.3 (−7.1 to 4.6)	−6.4 (−12.8 to 0.0)
Change in Epworth Sleepiness Scale	−1.9 (−3.6 to −0.1)	−1.9 (−3.2 to −0.5)	−1.9 (−5.7 to 2.0)
Change in Pittsburgh Sleep Quality Index	−4.3 (−6.5 to −2.1)	−6.1 (−9.2 to −3.1)	−2.4 (−5.5 to 0.7)
Subjective sleep quality (1: poor/2: average/3: good)	2.2 (2 to 2.7)	2.5 (2 to 2.8)	2.1 (1.5 to 2.5)
Total sleep time (min)	380 (352 to 420)	346 (223 to 433)	400 (375 to 465)
Wake after sleep onset (min)	144 (105 to 181)	142 (42 to 210)	144 (109 to 174)
Sleep latency (min)	11 (7 to 24)	11 (6 to 21)	15 (6 to 37)
Sleep efficiency (%)	64 (56 to 77)	61 (57 to 71)	71 (55 to 81)

Objective sleep quality measured by 2-week actigraphy following NIV set-up.

BUR, back-up rate; EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; LRM, limited respiratory monitoring; NIV, non-invasive ventilation; PSG, full polysomnography; Ti, inspiratory time.

(95% CI −6.5 to −2.1)).

Results detailing the NIV set-up and the nested physiological study are available in the online supplement (results pages 4–6 OLS).

DISCUSSION

This pilot randomised physiological effectiveness trial demonstrated that LRM using transcutaneous oximetry and nurse-led NIV titration, in patients with COPD–OSA with chronic respiratory failure, resulted in a greater fall in daytime PaCO₂ at 3 months compared with gold-standard PSG monitoring and retrospective NIV modification. The improvements in health-related quality of life and daytime somnolence were in line with previous published data and of a similar magnitude to those achieved in patients with obesity-related respiratory failure.⁸

Despite randomisation, patients allocated to the PSG-directed titration had more severe COPD–OSA overlap when compared with patients allocated to LRM-directed titration. BMI, neck circumference, smoking history and baseline daytime PaCO₂ were all numerically higher in the PSG arm. These differences may have contributed to the higher EPAP in the PSG group, which in turn could be responsible for adverse pulmonary mechanics with reduced respiratory muscle unloading and subsequent poor comfort and reduced adherence. However, the comfort scores at NIV set-up were the same. The lower NIV adherence in the PSG arm may explain,

in part, the lower reduction of daytime PaCO₂ at follow-up.⁹ The small sample size of the study prevents the completion of an adjusted analysis to try and account for the differences in NIV adherence or any other baseline differences between the two groups. The results from this pilot proof-of-concept clinical trial need to be interpreted with caution and are hypothesis generating rather than hypothesis testing, which is the role of a multicentre clinical trial.

Despite these limitations, our data support the use of transcutaneous combined oximetry monitoring, in combination with a nurse-led titration protocol to safely establish NIV in patients with chronic respiratory failure secondary to COPD–OSA overlap syndrome. Both LRM and PSG groups achieved similar clinical effectiveness in terms of change in daytime PaCO₂, health-related quality of life and sleep quality. These data support the safety and efficacy of limited respiratory monitoring and nurse-led titration as a simpler alternative approach to PSG for home NIV set-up. The next step will be to proceed to a multicentre clinical trial that will investigate the clinical and cost-effectiveness of limited respiratory monitoring with a nurse-led titration protocol. This is in line with the current direction of home NIV delivery with the use of auto-titrating devices, which have been shown to be safe and effective in patients with COPD–OSA overlap syndrome.⁶ Indeed, the built-in ventilator software may offer additional data, including Vt, leak flow and volume, triggered breaths¹⁰ and residual events.¹¹

Correction notice This article has been corrected since it was published Online First. A sentence in the Abstract and the Outcome section has been corrected.

Contributors MP: conception of the work, acquisition, analysis, interpretation of data, drafting of the work. GA: acquisition of data, critical revising of the draft. AC, JFM, NH: conception of the work, critical revising of the draft. PBM: conception of the work, acquisition, analysis, interpretation of data, drafting and critical revising of the draft.

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Competing interests MP reports grants from ADIR Association, from B&D Electromedical, during the conduct of the study; personal fees from Fisher & Paykel and ResMed, non-financial support from Antadir and Asten, outside the submitted work. JFM reports grants from ADIR Association, during the conduct of the study; personal fees from Philips-Respironics, personal fees from ResMed, personal fees from Air Liquide Santé, personal fees from Breas, personal fees from Boehringer, outside the submitted work. NH reports grants from Guy's and St Thomas' Charity, during the conduct of the study; grants from Philips-Respironics, non-financial support from Philips-Respironics RT Meeting (MYOTRACE), personal fees from Fisher & Paykel, grants from ResMed, grants from B&D Electromedical, grants from Fisher & Paykel, outside the submitted work. In addition, NH has a patent MYOTRACE pending and MP is on the Pulmonary Research Advisory Board for Philips. NH's research group has received unrestricted grants (managed by Guy's and St Thomas' Foundation Trust) from Philips-Respironics, Philips, ResMed, Fisher & Paykel, and B&D Electromedical. Philips-Respironics are contributing to the development of the MYOTRACE technology. PBM reports grants and personal fees from Philips-Respironics, grants from ResMed, grants from B&D Electromedical, outside the submitted work. Other authors have no competing interests to declare.

Patient consent Obtained.

Ethics approval Guy's Research Ethics Committee.

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Author note MP is the guarantor of the content of the manuscript, including the data and analysis.

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**On-line supplement - Polysomnography vs. Limited Respiratory Monitoring
and Nurse-Led Titration To Optimise Non-Invasive Ventilation Set Up:
A Pilot Randomised Clinical Trial**

Material and methods

Subjects

Patients referred to the Lane Fox Respiratory Unit, St Thomas' Hospital, Guy's and St Thomas' Foundation Trust, London, UK for NIV setup with a background of COPD and suspected OSA were screened for eligibility. Inclusion criteria were a known diagnosis of COPD as defined by GOLD criteria [1], OSA defined by a 4% oxygen desaturation index > 7.5 events/hour or an apnoea-hypopnea index > 5/hours, a daytime PaCO₂ > 6kPa and a body mass index (BMI) > 30kg/m². Exclusion criteria were decompensated respiratory failure with a pH < 7.35, inability to tolerate NIV (< 4 hours usage during titration), contraindication to NIV, pregnancy, age < 18 years and any significant physical or psychiatric co-morbidity that would prevent compliance with the trial protocol. Written consent was obtained for all eligible patients.

Study design

The study was an open-label, single-centre randomised clinical trial. Patients were allocated to have NIV setup with an overnight titration using a full montage polysomnography (PSG) or using attended limited respiratory monitoring with transcutaneous oxi-capnometry and protocol-based titration (LRM). Randomisation was performed using dedicated software with minimisation based on gender and use of long term oxygen therapy (LTOT).

Study protocol

The trial was registered and submitted on clinicaltrial.gov prior to patient recruitment. For administrative reasons, the study was not released until 12th May 2015. Study protocol remained unchanged.

All included patients underwent baseline spirometry, daytime arterial blood gas sampling, overnight inpatient study using combined transcutaneous oxi-capnometry (Tosca 500, Radiometer, Crawley, UK) and baseline respiratory polygraphy (Embletta, Resmed, Abingdon, UK). Anthropometrics: weight, height, BMI, neck circumference were collected. Subjects were asked to complete health related quality

of life questionnaires: COPD Assessment Test (CAT), Pittsburgh Sleep Quality Index (PSQI) [2] and Severe Respiratory Insufficiency questionnaire (SRI) [3,4]. Subjects were asked to assess their breathlessness using the modified Medical Research Council dyspnoea score and Borg Scale and their sleepiness using Epworth Sleepiness Scale (ESS). Quality of sleep and of overnight breathing during baseline sleep study and during overnight titration was assessed using visual analogue scales (VAS) (0: very easy / comfortable – 100: very difficult / uncomfortable). Comfort of breathing and breathlessness were assessed on NIV using the same VAS. All patients were initiated on NIV in the Lane Fox Respiratory Unit in which they received the same structured training for home NIV use.

Overnight NIV titration was performed using A30 ventilators (Philips-Respironics, Murrysville, Pennsylvania, USA) on spontaneous-timed mode with an oro-nasal interface adjusted to optimise comfort and minimise unintentional leaks (Quattro, Quattro FX and Airfit F10 masks (Resmed, Abingdon, UK)).

For patients randomised to the limited respiratory monitoring, overnight titration was performed using a nurse-led protocol (*Figure E1*) based on transcutaneous oximetry signal and clinical examination. All titrations were performed by trained nurses with clinical observation at the bedside performed at least every 30 minutes. Not all titrations were performed by the same nurse. Overnight titration aimed to achieve sufficient control of apnoeic events and of hypoventilation. This assessment was performed by a consultant with a special interest in respiratory failure and home mechanical ventilation. Assessment of ventilation was based on the results of the oximetry monitoring, nursing notes regarding the overnight titration and their clinical assessment.

For patients randomised to PSG led NIV setup, all overnight titration were performed by a chest physician (MP) with the guidance of polysomnography (ALICE 5; Philips-Respironics, Murrysville, PA, USA) with continuous recording of electro-encephalogram (EEG), electro-oculogram (EOG), submental electromyogram (EMG), anterior tibialis EMG, oxygen saturation (SpO₂), electrocardiogram (ECG), pulse rate, mask pressure, respiratory inductance plethysmography (thoracic and abdominal) and transcutaneous oximetry (Tosca 500, Radiometer, Crawley, UK) and clinical examination. Overnight titration aimed to abolish apnoeic events, control nocturnal hypoventilation and minimise patient-ventilator asynchronies. Polysomnographic analysis of sleep was performed using ASM guidelines [5]. Polysomnographic analysis of respiratory events was performed according to SomnoVNI guidelines [6]. Patient-ventilator asynchronies were defined as follows: auto-triggering (breath delivered

by ventilator in the absence of any respiratory effort at a different rate from the set back-up rate), multiple triggering (repeated (at least once) breaths delivered by the ventilator associated with shorten inspiratory time and desynchronization from patient respiratory efforts), ineffective triggering (presence of an inspiratory and expiratory respiratory movement not associated with any pressure delivery by the ventilator), trigger delay (breath delivered by ventilator after more than 25% of the inspiratory effort produced by the patient), early cycling (interruption of pressure generation despite the persistence of an inspiratory effort produced by the patient), late cycling (maintenance of pressure to IPAP level despite initiation of expiration by the patient), and leaks (sudden loss of mask pressure during expiration or inspiration resulting in more than 25% reduction of the pressure) [7]. Given the study design, patient ventilator asynchronies could only be assessed in the PSG arm. Analysis was performed in 30s-epochs, if an apnoea occurred during an epoch the period was scored as apnoeic. In the absence of an apnoeic event the epoch was examined for evidence of patient ventilator asynchrony. Only one patient ventilator asynchrony was scored per epoch. If multiple asynchronies occurred in a single epoch, the predominant asynchrony was scored. Frequency of patient ventilator asynchrony (PVA) was calculated for each NIV setting used during the titration process. For patients in the PSG arm, home settings were further adjusted before discharge according to results from the full PSG analysis. Chosen settings were those under which the patient had satisfactory control of sleep disordered breathing with lowest level of PVA. Patients were discharged once satisfactory control of sleep disordered breathing was obtained, as determined by the supervising consultant. If after the first night, the supervising consultant judged that control of sleep disordered breathing was insufficient, patients had a further titration night with the same monitoring as their first night. Following discharge, patients completed a sleep diary that included subjective assessment of sleep quality (1: poor, 2: average, 3: good) for 2 weeks. Objective sleep quality was assessed by 2-week wrist worn actigraphy (Actiwatch spectrum; Philips, Murrysville, PA, USA) at 3 month follow up.

Patients attended a 6 weeks outpatient follow-up as part of standard care to optimise NIV compliance. Final follow-up was performed at 3 months with baseline measures repeated.

Nested physiological study

After NIV initiation, all patients underwent an assessment of their pulmonary mechanics including: sniff nasal inspiratory pressure (snip), maximal inspiratory pressure (mip), maximal expiratory pressure

(mep), forced expiratory volume at 1 second (FEV₁), forced vital capacity (FVC), vital capacity (VC) and self-ventilating tidal volume (V_t). During respiratory manoeuvres, neural respiratory drive (NRD) was measured using surface electrodes applied in the parasternal area of the second intercostal space (EMG_{para}) as previously described [8]. A measurement of EMG_{para} was also performed whilst on NIV. Unloading of the respiratory muscles was calculated [(EMG_{para} on NIV – EMG_{para} during tidal breathing)/EMG_{para} during tidal breathing] and expressed as percentage change [9]. All physiology measurements were performed in line with ATS/ERS guidelines [10]. Data were acquired using an analogue to digital converter (Powerlab, ADInstruments, Chalgrove, UK) and analysed using specialist software (Labchart v7.2, ADInstruments, Chalgrove, UK).

Statistical analysis

Based on prior results from our group [11] in a similar population, we designed this pilot study to include 12 patients. To allow for a dropout rate of 15%, we targeted 14 patients for randomisation and 14 patients were analysed.

Normal distribution was assessed by visual inspection and using the Shapiro-Wilks test. Results are expressed as number and percentages, means and standard deviation (SD) when normally distributed or medians, and inter quartile range (IQR) when not normally distributed. Estimates of effect size are provided with 95% confidence intervals (95%CI) but due to the small sample size inferential statistics were not employed on the clinical study. The nested physiological study used paired and unpaired t-test or non-parametric alternative as appropriate for comparison using a level of 0.05 to denote significance. Correlations were assessed using the Spearman correlation coefficient. The analyses were performed using GraphPad Prism 6[®] for Mac OS X[®] (GraphPad Software, La Jolla, CA, USA) and IBM SPSS[®] Statistics v20.0 (IBM Corp, Armonk, NY, USA).

Ventilation setup and nested physiological study

Results

NIV titration

Length of stay for baseline assessments and NIV setup was similar between both groups: 2 [2 – 2] nights in the limited arm vs. 2 [2 – 3] nights and the PSG arm. NIV settings were similar between both groups with comparable rate of control of sleep breathing disorder, although with a trend to higher EPAP

in the PSG arm (*Table E1*). PSG monitoring for overnight titration did not significantly altered the perceived ease of sleep onset or sleep comfort as compared to limited monitoring. Overnight comfort of breathing on NIV was similar in both groups (*Table E1*).

PSG results

Subjects in the PSG arm had a median duration of sleep of 307min [201 – 431]. Duration and proportion of N1, N2, N3 and REM sleep were 35min [3 – 43] (9%), 161min [140 – 234] (74%), 11min [0 – 85] (5%), 9min [4 – 19] (5%), respectively. Median arousals occurrence was 12.1 [6.6 – 20.3] per hour. During overnight titration, residual AHI was 14.6 ± 16 /hour with the majority of events occurring prior to achieving final therapeutic pressure (*Table E2*). Mean PVA occurrence was 27.2 ± 19.4 /hour. PVA were associated with a 3% desaturation in 278 (15%) epochs and with an arousal in 195 (11%) epochs. Predominant type of PVA varied for each patient (*Table E3*). Incidence of PVA and residual apnoeic events was significantly lower when subjects were ventilated using final therapeutic settings as compared to the rest of the night: 19.3 ± 14.9 vs. 35.4 ± 18.2 ($p=0.0045$) (*Figure E3*). For the patients in PSG arm, there was no significant correlation between the frequency of PVA and compliance ($p=0.071$).

Nested physiological study

There was no significant difference between groups with respect to their respiratory muscle strength (*Table E4*). Although raw EMGpara during self-ventilation was similar between groups, once normalised for maximum muscle strength, subjects in the PSG arm used a higher proportion of their NRD during tidal breathing than those in the limited arm. In the total study population, fall in NRD from self-ventilation to NIV (respiratory muscle offload) was correlated with NIV adherence ($\rho = -0.581$, $p=0.029$) (*Figure E4*). At a cut-off value of 20%, NRD offloading was able to identify patients with a compliance below 3 hours/day with a sensitivity of 80%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 90%.

Discussion

Value of PSG during titration

As previously described in COPD population [12] and reflecting the complexity of ventilation management in COPD-OSA overlap, PVA are frequent. Whilst PVA appear deleterious during acute

NIV [13], their consequences during long-term NIV are not clear. Fanfulla *et al* reported a lower control of PaCO₂ in stable patients established on home NIV with high PVA. However, this impact was only found in patients experiencing more than 100 PVA/hour, in a heterogeneous population and with low pressure ventilation in patients with COPD alone [14]. In patients admitted for overnight NIV titration, no correlation was found between PVA and control of PaCO₂ [15]. Ramsay *et al* demonstrated a similar incidence of PVA to Fanfulla and colleagues [14]. In line with previous data, the most frequent PVA was ineffective triggering [14,15] but interestingly, each of the seven patients randomised to PSG setup had a different predominant type of PVA. Variability in PVA can be explained by the use of different ventilators [16], but in this study the same ventilator was used for all the patients in the trial, therefore this variability is likely explained by patients intrinsic characteristics.

Relevance of neural respiratory drive for NIV setup

Use of neural respiratory drive provides physiologically coherent and clinically useful data in COPD patients [17,18] and in patients with OSA [19] undergoing CPAP therapy [20,21]. Neural respiratory drive can be assessed easily and non-invasively using parasternal EMG [8,9,15,22]. In the overall study population, we have seen that an offload of respiratory muscle activity during NIV was associated with improved adherence to NIV. The use of EMGpara could allow identification of patients at risk of poor adherence and thus offer the opportunity to assess whether targeted support to the most at risk patients would improve subsequent adherence. Patients randomised to the PSG arm trended to have a higher EPAP when compared to those in the limited respiratory monitoring arm. We hypothesise that this higher EPAP resulted in a higher degree of hyperinflation leading to discomfort, as suggested by a higher EMGpara activity and to a lower compliance in that group. In that context, lack of offload of respiratory muscles may reflect hyperinflation caused by EPAP. In patients with COPD-OSA overlap, this physiological assessment is particularly relevant given the dose response to therapeutic efficacy demonstrated in this group [23].

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Figure E1: Nurse led protocol for NIV titration in COPD-OSA overlap patients (COPD-OSA: Chronic obstructive pulmonary disease and obstructive sleep apnoea, ST: spontaneous timed, IPAP: inspiratory positive airway pressure, EPAP: expiratory positive airway pressure, Ti: inspiratory time, BUR: back-up rate, TcCO₂: transcutaneous carbon dioxide, Sat O₂: Oxygen saturation)

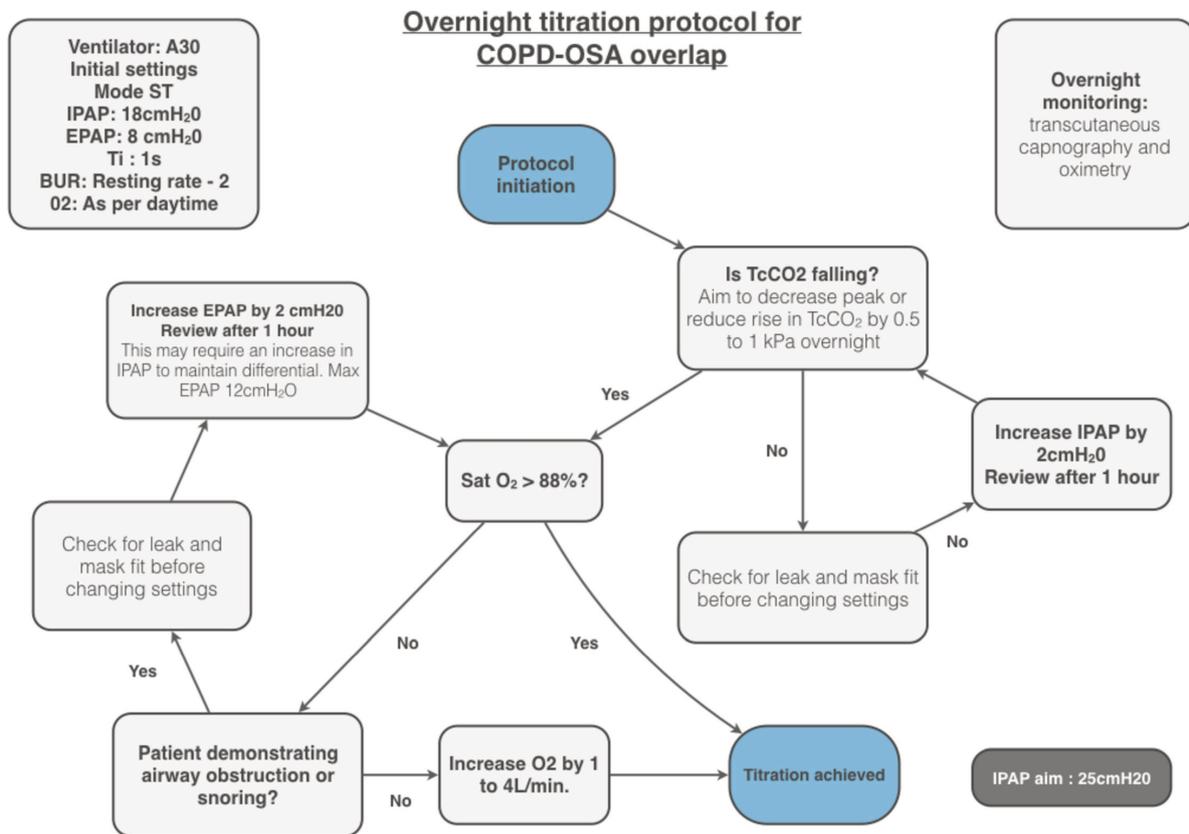


Figure E2: Consort recruitment diagram for enrolment and follow-up. (OSA: obstructive sleep apnoea, BMI: body mass index – NIV: non-invasive ventilation - PSG: polysomnography)

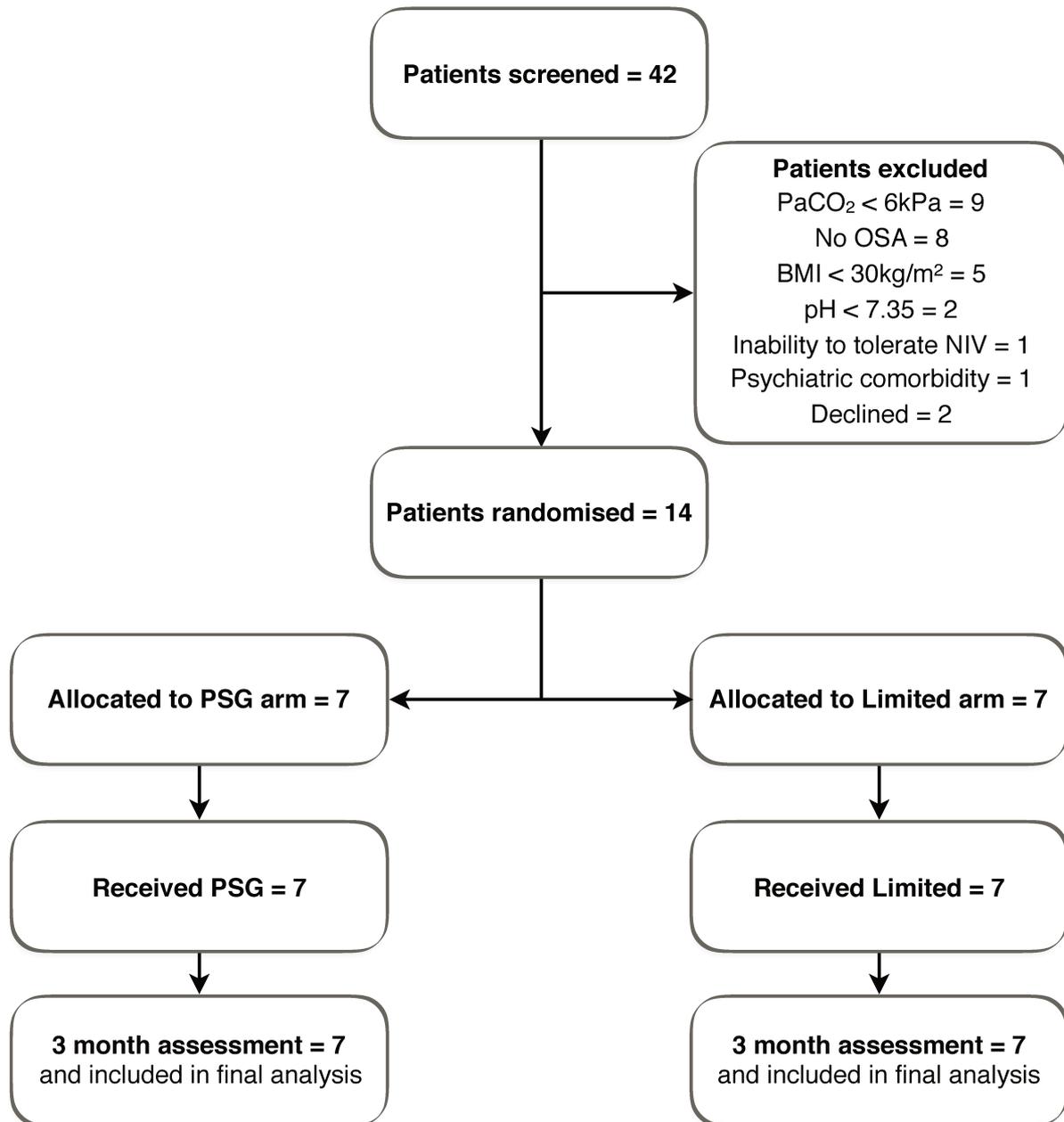


Figure E3: Frequency of PVA during overnight titration and on discharge settings ($p=0.0045$) (PVA: patient-ventilator asynchrony)

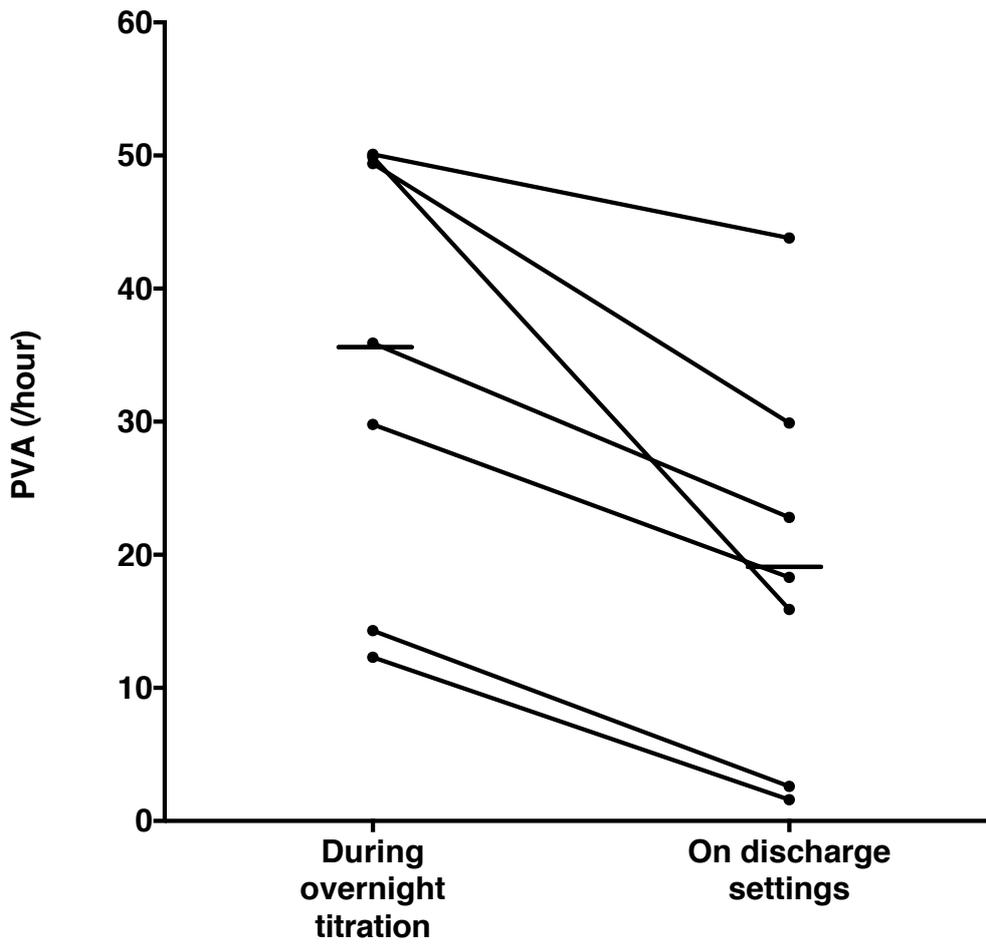


Figure E4: Correlation between offload of respiratory muscles and adherence to NIV (rho:-0.581, p:0.029) (NIV: noninvasive ventilation, EMGparasternal: parasternal surface electromyography)

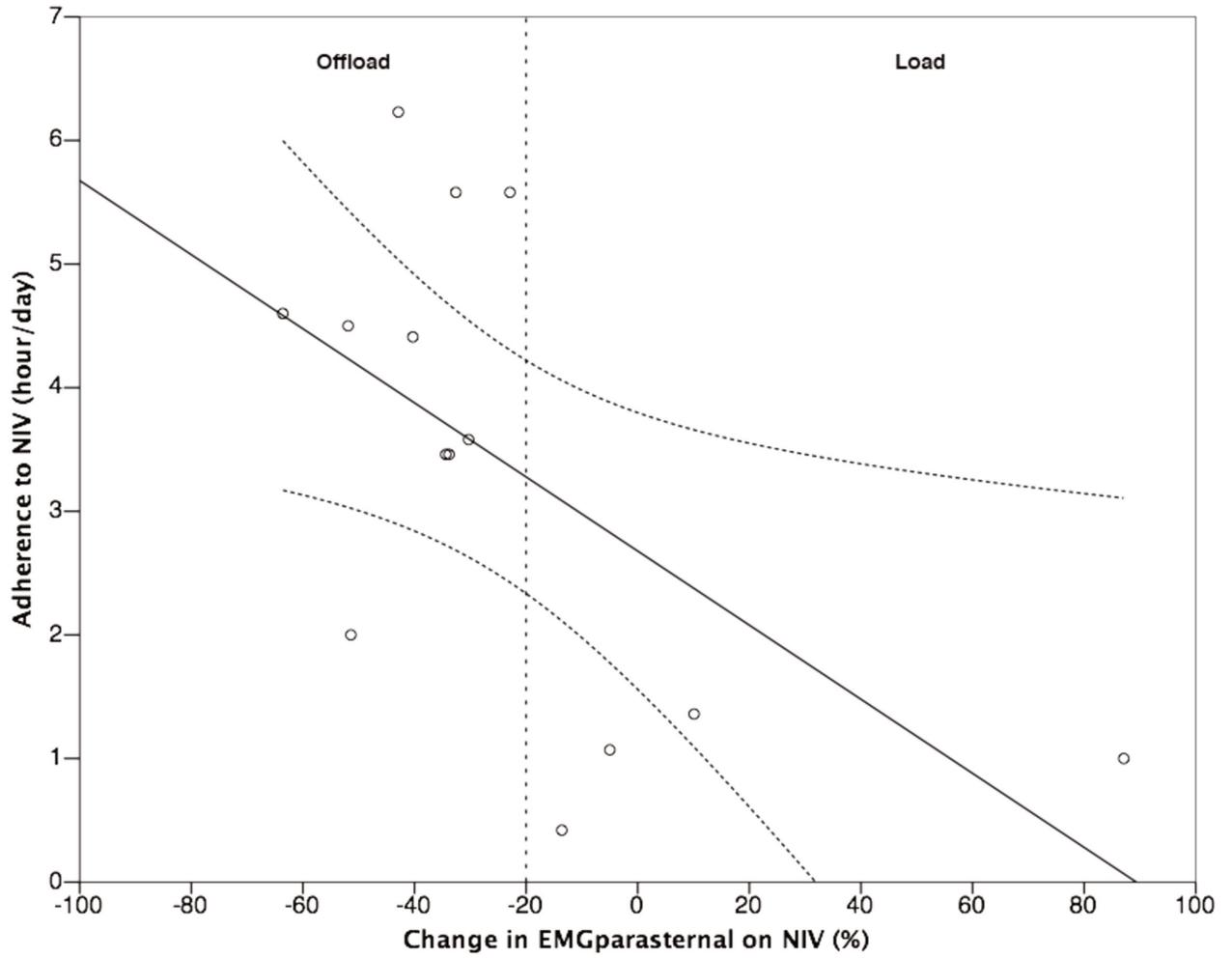


Table E1: Results from overnight NIV titration.

	Total	LRM	PSG	p
NIV settings at discharge				
IPAP (cmH2O)	25.8 (±2.9)	25.7 (±3.5)	26.0 (±2.3)	0.66
EPAP (cmH2O)	10 (±1.9)	9.1 (±1.9)	10.9 (±1.6)	0.17
Pressure support (cmH2O)	15.9 (±2.9)	16.6 (±2.8)	15.1 (±3)	0.37
BUR (/min)	15.7 (±1.7)	15.1 (±1.1)	16.3 (±2.1)	0.45
Ti (s)	1.06 (±0.1)	1.06 (±0.1)	1.06 (±0.1)	1
Overnight sleep monitoring during NIV titration*				
4% oxygen desaturation index (/h)	18.1 (±8.9)	19 (±6.6)	17.2 (±11.3)	0.68
Mean saturation O2 (%)	90.6 (±2.7)	89.8 (±2.9)	91.5 (±2.3)	0.3
Percentage of time spent < 90%	31.7 (±22)	35.1 (±26)	28.4 (±18.6)	0.78
Mean TcCO2 (kPa)	7.34 (±0.7)	7.33 (±0.7)	7.35 (±0.7)	1
Sleep quality during titration				
Easiness to fall asleep (0: very easy to 100: very difficult)	29.9 (±25)	22.1 (±22.7)	37.6 (±26.6)	0.26
Comfort of sleep (0: very uncomfortable to 100: very comfortable)	36.5 (±24.1)	38.7 (±26)	34.3 (±23.5)	0.75
Comfort of breathing overnight on NIV (0: very uncomfortable to 100: very comfortable)	37.9 (±24.2)	44.1 (±24.7)	31.7 (±26)	0.37

*Results are expressed in terms of mean (standard deviation) and number (percentage) *Whole night results including initial NIV settings through to optimal discharge settings. (LRM: protocol-based titration, PSG: polysomnography, NIV: noninvasive ventilation, IPAP: inspiratory positive airway pressure, EPAP: expiratory positive airway pressure, Ti: inspiratory time, BUR: back-up rate, TcCO2: transcutaneous carbon dioxide, Sat O2: Oxygen saturation)*

Table E2: Results of polysomnography performed during NIV overnight titration.

	Sleep staging						Residual AHI (/hour)
	Sleep duration min	N1 min (%)	N2 min (%)	N3 min (%)	REM Min (%)	Arousals per hour (/hour)	
Patient 1	478	376 (79%)	23 (5%)	0 (0%)	79 (16%)	27.1	2.7
Patient 2	432	37 (9%)	392 (90%)	3 (1%)	0 (0%)	5.6	41
Patient 3	244	43 (18%)	182 (74%)	11 (5%)	9 (3%)	25.8	2.8
Patient 4	201	3 (1%)	148 (74%)	42 (21%)	9 (4%)	14.7	3.4
Patient 5	307	15 (5%)	161 (52%)	116 (38%)	16 (5%)	7.5	31.3
Patient 6	144	0 (0%)	140 (97%)	0 (0%)	4 (2%)	12.1	4
Patient 7	372	35 (9%)	234 (63%)	85 (23%)	19 (5%)	4.2	7.5

Results are expressed in terms of mean and/or percentage. (NIV: noninvasive ventilation, REM: rapid eye movement, AHI: apnoea-hypopnoea index)

Table E3: Patient-ventilator asynchrony during NIV overnight titration in the PSG group.

	PVA per hour	Arousals related to PVA n (%)	Typology of patient-ventilator asynchrony per patient						
			Auto-triggering	Multiple triggering	Early cycling	Ineffective triggering	Late cycling	Leaks	Trigger delay
Patient 1	31.5	79 (34%)	6 %	16 %	13 %	21 %	12 %	7 %	26 %
Patient 2	22.6	25 (63%)	46 %	19 %	6 %	5 %	3 %	18 %	3 %
Patient 3	9.4	9 (9%)	7 %	73 %	0 %	10 %	11 %	0 %	0 %
Patient 4	65.8	33 (67%)	4 %	13 %	0 %	72 %	3 %	0 %	9 %
Patient 5	12.6	16 (41%)	17 %	21 %	14 %	10 %	9 %	24 %	6 %
Patient 6	51.2	13 (45%)	2 %	40 %	0 %	8 %	46 %	3 %	1 %
Patient 7	13	4 (15%)	9 %	29 %	1 %	12 %	48 %	1 %	0 %

Results are expressed in terms of mean and/or percentage. (PVA: patient-ventilator asynchrony)

Table E4: Neural respiratory drive and respiratory muscle strength assessment.

	Total	LRM	PSG	p
Respiratory muscle strength				
Sniff Nasal Inspiratory Pressure (cmH ₂ O)	55.7 (±17.7)	62.6 (±19)	53.2 (±16.6)	0.34
Maximal Inspiratory Pressure (cmH ₂ O)	54.6 [41.2 – 66.4]	63.9 [41.2 – 66.4]	49.2 [27 - 56.6]	0.16
Maximal Expiratory Pressure (cmH ₂ O)	-98 (±33.3)	103.8 (±27.7)	86.8 (±8)	0.33
Neural Respiratory Drive				
EMG _{para} during tidal breathing (µV)	8.3 (±2.7)	8.0 (±1.8)	8.1 (±2.8)	0.96
EMG _{para} %max (%)	17.1 (±7.2)	12.8 (±4.3)	20.6 (±7.5)	0.033
EMG _{para} during NIV (µV)	5.3 [4.6 - 6.7]	5.4 [3.8 - 7]	5.2 [4.7 - 7.7]	0.47
Change in EMG _{para} from tidal breathing to NIV (%)	-23.4 (±39.7)	-32.8 (±15.3)	-13.7 (±50.6)	0.36

Results are expressed in terms of mean (standard deviation), median [interquartile] and number (percentage). (LRM: protocol-based titration, PSG: polysomnography, EMG_{para}: parasternal surface electromyography, NIV: noninvasive ventilation).

The main findings of this study ¹⁶⁷ were:

- NIV contributes to a significant offload of the respiratory drive in patients having COPD and OSA, as the NRD decreased by 23% under NIV.
- Offload of NRD is correlated to compliance to the treatment.
- NIV setup using the Gold-Standard PSG was effective to achieve successful setup but that it does not seem to be superior to a nurse-led titration protocol.

This last result is of main interest in terms for organizing healthcare provision during NIV setup and, in a more general way, for the organisation in order to deliver care efficiently in patients with CRF.

Chapter 3: Improving care delivery for patients with chronic respiratory failure

In this chapter, we will focus on healthcare organisation for CRF patients. We will then discuss the strategies that could be used in order to face the increasing number of patients with CRF and to maintain the same, or even higher quality of care in an economic and policy driven environment characterised by limited resources.

I. Current organisation of home ventilation service in France and in the Netherlands

F. Book chapter: Chronic ventilator service (CRC Press, 2018)

In this book chapter, we have reviewed how our chronic ventilator service is organised as well as in a leading European home ventilation centre in Groningen, the Netherlands.

The main difference in the organisation of home NIV care in France and in Netherlands is the fact that, in the Netherlands, only 4 centres can provide home NIV. Such situation is facilitated by the country size. However, these 4 centres had to change their organisation in order to be able to provide NIV to the increasing number of patients with CRF. Moreover, the Dutch colleagues have validated their management in two randomized controlled trial in patients with restrictive CRF ¹⁹³ and in patients with COPD ¹⁹⁴.

The book chapter is included in the book edited by Profs M. Elliot, S. Nava and B. Schönhofer in: *Non-Invasive Ventilation and Weaning – Principles and Practice*, Second Edition 2018 (CRC Press).

Chronic ventilator service

MAXIME PATOUT, ANTOINE CUVELIER, JEAN-FRANÇOIS MUIR AND PETER WIJKSTRA

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KEY MESSAGES

- Patients with chronic respiratory failure are best initiated on home mechanical ventilation, and their treatment regularly assessed, in a specialist chronic ventilation service (CVS).
- The care of these patients requires a sometimes very large, multi-disciplinary team; all the necessary components must be in place.
- The provision of home ventilation is complex and involves much more than just the purchase of a machine and ancillary equipment; home mechanical ventilation should not be delivered on an occasional basis by general pulmonology units.
- The CVS may be hospital-based or delivered at home by a mobile team.
- Training, and expertise, of medical, nursing and physiotherapy staff are key to the success of a CVS.
- The CVS must provide a 24 h service, either itself or through a home care service – there must be access to clinical advice and technical support, in case of equipment malfunction.

INTRODUCTION

Home mechanical ventilation (HMV) delivered either non-invasively or via a tracheostomy is the key treatment for patients with chronic respiratory failure and hypercapnia. Non-invasive ventilation (NIV) has progressively replaced tracheotomy ventilation, although this last modality still has some specific indications, especially during difficult weaning.

The overall prevalence of HMV in Europe is around 6.6/100,000, but this varies greatly between countries.¹ The increasing prevalence of severe COPD and severe obesity, better identification of adult neuromuscular diseases and the increasing lifespan of the general population point to a major increase in the disease burden associated with chronic

respiratory failure in the next 20 years. The development of NIV by chest physicians during the early 1990s has led to the growth of centres delivering NIV to patients with chronic or acute-on-chronic respiratory failure. The wide variations between local organisations, from the technical, administrative and economic points of view, including the variable investment of chest physicians in the field of chronic respiratory failure and the relationships with the local intensive care units, have led to heterogeneous management. The need to rationalise healthcare costs and the development of more sophisticated technological tools imposes the obligation for better structures for the management of patients receiving HMV, beginning with titration and long-term monitoring and including rehabilitation and the management of acute episodes.² Clinical research in chronic respiratory failure

patients is difficult to perform, but we can take advantage of the experience acquired in sleep laboratories. In a slightly different setting, clinicians in these units have developed a rational management structure and have produced quality research on ventilator assistance, titration and monitoring.

In this chapter, we describe a chronic ventilation service (CVS) that was set up in a university hospital in the early 1990s in France. This structured network manages around 200 new chronic respiratory failure patients each year, in connection with a non-profit provider for domiciliary management. This way of working is probably not valid for all healthcare organisations but is an example of how to organise the management of such patients. This chapter will describe the two components of a CVS: the specific activities provided in the hospital and the support provided at home. At the end of this chapter, the unique organisation of a CVS in the Netherlands will be described to illustrate an alternative model.

CVS IN THE HOSPITAL

Creation of a CVS first requires a sustained collaboration between physicians and the hospital administration, beginning with the identification of the number of NIV or tracheostomy-ventilated patients who may enter the CVS. This calculation clearly influences the subsequent choices about location, the medical and nursing staffing requirements and the technical equipment required to run the CVS. Our experience is that offering such a CVS immediately leads to an increase in the number of patients utilising such a service compared with the predicted needs. The different components of a CVS may be schematised as shown in Figure 19.1.

It is still not known if a CVS in the hospital improves the management of patients as compared with conventional management in the ward or with domiciliary-based management. Its impact should be assessed through objective

endpoints, such as waiting time for initiation of HMV and the length of stay in the facility to initiate HMV, the number or unplanned hospitalisations or hospital-based assessments, the number of acute hypercapnic respiratory failure episodes, long-term ventilatory compliance and the effect on symptoms and quality of life. It is plausible that a CVS has some economic justifications because of longer-term savings, by reducing future healthcare costs despite the numbers of medical and nursing staff required to run it and the complexity of the technologies involved.

Organisation

The CVS is integrated into a network of departments of different competencies (Figure 19.2). The heart of the CVS is the place where patients are received and routinely assessed in the hospital. New patients enter the CVS through the titration unit, where planned HMV may be started and settings chosen and adjusted. The titration unit organises planned hospitalisations, usually after a chest physician consultation or after referral from a sleep laboratory. The relationship with the sleep laboratory is crucial since many chronic respiratory failure patients are diagnosed during investigations for sleep respiratory disturbances, particularly sleep apnoea. NIV is initiated over 3 to 5 days. Beds from the intermediate respiratory care unit or the pulmonary ward may be used to initiate HMV; our approach has the advantage that admissions are not delayed by the constant pressure to get available beds for unplanned pulmonary patients. In most centres, the expertise in invasive ventilation and NIV is available in intensive care units, and one of the challenges for the CVS is to take advantage of this expertise for patients with chronic respiratory failure on a long-term basis.

The second part of a CVS is the monitoring unit. This unit is dedicated to scheduled and sometimes unplanned

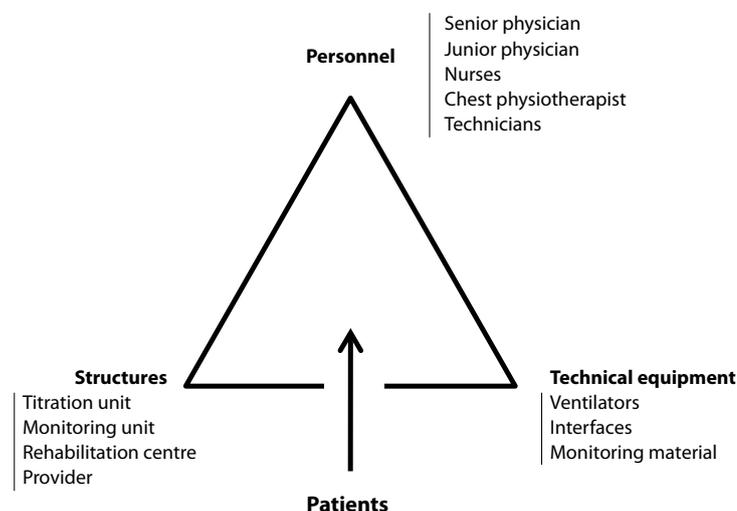


Figure 19.1 Organisation of a CVS.

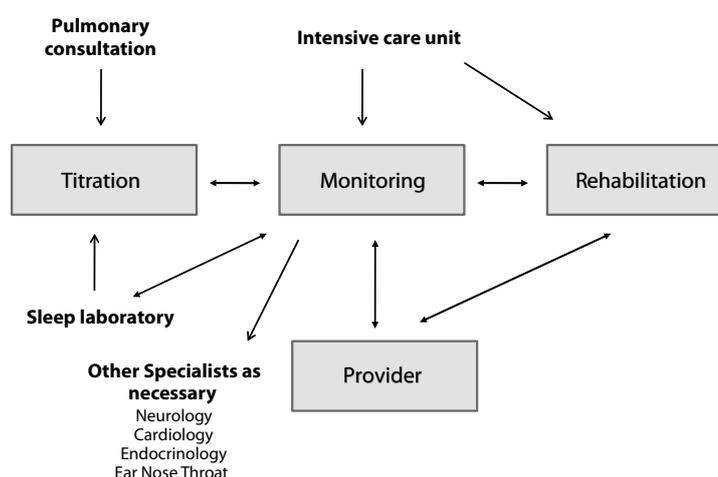


Figure 19.2 Network organisation of the clinical management of patients with chronic respiratory failure requiring HMV. The network is organized around the chronic ventilator service (in grey) and its correspondents.

assessments of long-term chronic respiratory failure patients having NIV or tracheostomy ventilation at home. These assessments are performed at regular intervals that vary according to the aetiology of the chronic respiratory failure; in some situations, the assessments may also be performed irregularly, owing to an unpredicted change, for instance, if HMV becomes less tolerated or is less efficient. It is probably better if the monitoring unit is localised in the same place as the titration unit, and both units may be under one administrative structure. However, both units are very different in their operational functioning, especially regarding the duration of patient stay. In our department, the titration unit accepts patients from 2 to 5 days, and the monitoring unit accepts patients for only 8 h long daytime assessments. If a patient requires more than this, he or she has to be transferred to the titration unit for one to several nights in order to modify the ventilator settings. Respiratory events have been reported in a significant proportion of patients treated by domiciliary NIV,³ and night-time ventilatory assessments may be then justified in chronically ventilated patients. Such assessments may be performed at home through the provider, but their consequences on the treatment and the course of the disease still need to be evaluated on an immediate and a long-term basis. The recent characterisation of polysomnography during NIV^{4,5} will perhaps modify the nature of these assessments and may lead to a larger number of one-night hospitalisations in selected patients. A high proportion of patients treated with NIV or tracheostomy ventilation are introduced to their ventilatory treatment during an episode of acute hypercapnic respiratory failure, managed in an intensive care or an intermediate care unit. Therefore, these patients enter the CVS via the monitoring unit and are subsequently managed like all other chronic respiratory failure patients. This unit should be accessible to patients with reduced mobility. It should also be organised to receive input from various professionals such as non-respiratory physicians, dieticians,

occupational therapists, social services, etc. The multidisciplinary approach is key to the success of such a program. Regular reports from the monitoring unit should be sent to the patients' general practitioners (GPs), nurses and chest physiotherapists in the community.

The third component of a CVS organisation is the rehabilitation unit. Pulmonary rehabilitation is a major component of the management of chronic obstructive pulmonary disease (COPD), even in those severe patients requiring domiciliary NIV⁶ and is now used in domiciliary ventilated patients with other diseases.⁷ Pulmonary rehabilitation improves clinical symptoms and quality of life in patients with chronic respiratory failure⁶ and may be performed in the hospital or in the home. It should always be delivered by dedicated staff, usually a chest physiotherapist, who can visit the patients in their homes.

Finally, the last component of the CVS is the equipment provider, which should be integrated in the activities of the centre, in order to provide and manage the ventilatory equipment at home. The importance of a high-quality coordination between the CVS and the provider will be described later.

Dedicated staff

The success of a CVS largely depends on the availability of dedicated medical, nursing and physiotherapy staff. The ratio of patients to staff varies greatly between centres and between different healthcare organisations. The nursing staff should be distinct from the staff in the pulmonary ward and should have competencies in NIV initiation and monitoring, not only during the day but also during sleep. Medical staff and the physiotherapists should be trained in the management of these patients, but there is no need that they are exclusively dedicated to the CVS. Technical support from the provider, which should be able to establish the link between the CVS and the home, is also very important.

The role of the provider's technicians begins as soon as the titration is finished and is followed by an iterative supervision/renewal of the ventilator and ancillary equipment, as well as all notifications and alerts about these devices.⁸

STAFF TRAINING (SEE ALSO CHAPTER 11)

Undoubtedly, the success of a CVS largely depends on its medical, nursing and physiotherapist staff competence. In our view, the best training is based on regular caregiver teaching at bedside and is therefore largely dependent on the number of patients managed and experience from encountering and resolving various problems. This competence is also improved by regular teaching about the basis of mechanical ventilation and also through ventilator workshops using domiciliary devices and/or simulators. This is particularly true for learning how to set a ventilator and manipulate the interfaces, to install the ventilator circuits and the humidification devices. A low level of training will decrease the efficiency of the whole healthcare team and probably affect the short- and long-term benefits for the patient. Also, every component of training should be regularly reinforced, probably twice a year, but there is no consensus at present regarding the schedule of learning. Training for physicians should be organised in a similar way, but they should also keep abreast of the medical literature, current technological advances and availability and the various guidelines that may be published by health agencies. These guidelines should be adopted after being suitably adapted for the local needs by all the members of the CVS. Finally, it is recommended that the physicians involved in a CVS should have basic knowledge about intensive care and should be able to perform an endotracheal intubation as quickly as possible.

Training, which has to be tailored to all the different caregivers in the CVS team, should also include a good level of theoretical knowledge about ventilation physiology, ventilatory modes and the indications and contraindications for domiciliary ventilation. It should also include bedside practice, including examination of the patient and also the technical skills necessary to set the ventilator and interpret the effects of different modes and settings, especially during sleep. These competencies should be complemented by the appropriate skills for communicating with the patient and their family, in order to make treatment acceptable to them and to achieve high compliance. Training should also aim to develop the capacity for clinical reasoning and problem solving, for instance, intolerance of long-term NIV, patient-ventilator asynchronies, persistent nocturnal hypoxaemia or diurnal hypercapnia.

Equipment

The third component of a CVS is a stock of up-to-date equipment.

VENTILATORS

An active CVS inventory should consist of most domiciliary ventilators available on the market, and the staff should be

trained to use them. Bench tests have shown great performance variability between different domiciliary ventilators, especially about triggering response,⁹ battery duration,⁹ tidal volumes, cycling off and airways pressurisation.¹⁰ A ventilator may behave differently when applied to patients with different conditions,¹¹ in the presence of leaks,^{12,13} and the comfort during ventilation may also vary greatly according to the machine.¹⁴ Today, such discrepancies between ventilators are rarely due to hardware differences, but rather to software algorithm differences.¹⁰ Moreover, large variations about ventilator characteristics and software navigation may also be perceived as a barrier to the training of physicians, nurses and physiotherapists. This is not the case in our experience, especially for people who are already familiar with one type of ventilator and if theoretical knowledge about triggering, cycling and pressurisation has been acquired. Therefore, careful attention should be paid to the teaching of ventilatory modes and the associated nomenclature, which is unfortunately very heterogeneous and confusing from one machine to another. Specific teaching should be provided to new staff, and regular courses should be aimed at strengthening the knowledge and skills of younger healthcare workers.

In order to titrate the patients with their domiciliary ventilators, the CVS should have the capacity to collect and interpret a substantial amount of monitoring data like clinical tolerance and compliance, evolution of signs of respiratory failure and the secondary effects due to pressure delivery or the effect of the interface (see Chapter ***). Dedicated ventilators are no longer needed for the titration step, because most bi-level domiciliary ventilators can now display nightly reports about flow/pressure variations, cycle rates, leaks and even an integrated SpO₂ curve. Regarding batteries, French legislation obliges the physician to prescribe a domiciliary ventilator with an internal or an external battery, once the prescribed ventilation is ≥ 12 h/day.

INTERFACES (SEE CHAPTER **)

Interfaces are another factor influencing the efficacy and compliance with treatment. Their management by the CVS is largely the same as for the ventilators, as discussed in the previous section. The large number of masks (nasal, facial or nasal plugs) available allows management of most, if not all, adult patients. Custom-moulded interfaces still have a place in very specific situations such as older children with facial deformities. Seventy-five per cent of all our domiciliary ventilated patients are treated with only two models of nasal or facial interface. The difficulty therefore arises in the case of the minority of patients in whom several interfaces should be tested to get a balance between tolerance and efficacy. This phenomenon is still poorly understood because of the various related factors such as the amount of intentional leaks according to the delivered pressure, the configuration of intentional leaks on the mask or the circuit and the gas trajectory into the interface.^{15,16} Also, an additional psychological factor cannot be excluded,

including claustrophobia or treatment reluctance that may be expressed as interface intolerance. Any attempt by a hospital administration to provide only one standardised interface in their centres will compromise the care for around 25% of patients. Accordingly, a large variety of interfaces should be available in an expert CVS, both in the titration and the monitoring units. In France, the home care providers are not allowed to modify the ventilator model, the ventilator settings nor the interface. Finally, caregivers should be able to detect any complication and intolerance related to an interface and should be able to suggest a solution to the patients and their family: counselling about interface utilisation, trying out another interface, optimisation of humidification devices, etc. This approach is different for tracheostomised ventilation patients since tracheostomy cannulas have roughly similar technical characteristics, and their clinical performance is less influenced by the ventilatory mode.

Monitoring

The third technical component of a CVS is its monitoring capacity, including regular clinical monitoring of the underlying respiratory disease, regular identification of secondary effects of flow/pressure delivery or NIV interfaces and also patient-ventilator adaptation that is best evaluated at night, since most domiciliary ventilatory treatments are used during sleep. This topic is detailed in another part of this book, especially in Chapter **.

CVS IN THE COMMUNITY

Definition and goals

The role of the respiratory home care service (RHCS) is to provide health services to patients and caregivers at home (Figure 19.3), to restore and maintain an acceptable clinical status and to minimise the consequences of chronic hypoventilation and disability and to reduce the number of episodes of acute respiratory events or failure. When they are discharged from the in-hospital CVS, and thus are considered as clinically stable, patients on long-term

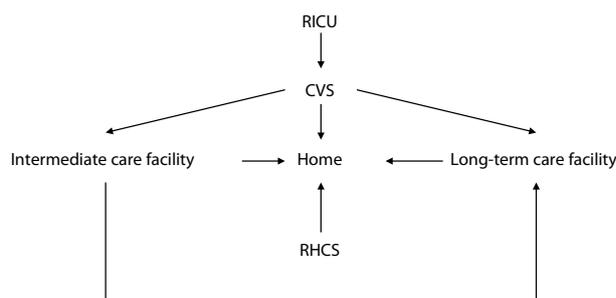


Figure 19.3 Place of the RHCS among other in- and out-hospital facilities. RICU: Respiratory intermediate care unit.

mechanical ventilation need an adequate environment to continue their treatment. They may be orientated towards either a long-term in-hospital facility or more often stay at home. At home, they need a structure to get adequate monitoring and maintenance of their equipment. As chronic respiratory failure patients are becoming older and more and more frail, with frequent comorbidities, they must be under the charge of not only respiratory technicians for their equipment but also other home care services as they are frequently dependent of them.

Thus, RHCS organisations represent a complex set of medical, ethical and social issues that involve multiple interest groups¹⁷: ventilator-assisted individuals, those who are completely dependent upon assisted ventilation for life support, those needing tracheostomy (generally neurological or neuromuscular patients, or severe end-of-life COPD patients) and partially dependent patients with varying degrees of severity and different aetiologies for respiratory failure treated by NIV.

Transition to home (see also Chapters 21 and 22)

The transition between the CVS and home is a crucial period. It is important that the first days at home are successful as they will impact on the long-term acceptance of HMV by the patient. The keys for success are discussed below.

CONTINUUM OF THE IN-HOSPITAL EDUCATION PROGRAM FOR THE PATIENT AND THEIR FAMILY

Discharge from the CVS to home must be anticipated by in-hospital education involving a dedicated team consisting of physicians, nurses, respiratory therapists and social workers on one hand, and technicians and nurses of the RHCS who made contact with the patient in the hospital, on the other hand.¹⁸ According to the aetiology of chronic respiratory failure, other professionals should be consulted, such as psychologists, dieticians and speech therapists. Prior to discharge, the RHCS team should meet the patient and their family, perform a home visit to plan the installation of the equipment and discuss potential improvement of the home setting in order to optimise the transfer and settling in of the patient.¹⁹

The training of patient and his or her family has to start as soon as possible during the stay in hospital and is continued after the patient has returned home.²⁰ The home nursing staff who are directly involved in the day-to-day care of the patient have the task to demonstrate and repeat, as needed, the instructions to the patient and their caregivers on medication and nasal/face mask use.²¹ Another important item is to ask the RHCS technician to check, at home, the level of knowledge of the patient and their family with regard not only to the equipment for its 'chronic' use but also the equipment and procedures to be used at home in case of an emergency (self-inflating manual resuscitator) for the most severe.²¹

The follow-up scheme and the 24 h free telephone line must be explained, as well as the therapeutic protocol indicating the timing and duration of night ventilation, and daytime oxygen therapy, sometimes interrupted by NIV sessions. The follow-up scheme must be planned with adequate frequency of follow-up. It is also important to ensure a 24 h free helpline for emergency telephone calls. A physician should be contactable concerning any information about treatment or other management problems. This same arrangement should also be in place for contacting the device manufacturing companies and technicians.

Finally, the patient should be made aware that the main goals of RHCS are to enhance their quality of life, to reduce hospital admissions and to be cost-effective, and also to supervise compliance with therapy. These goals are achieved by ensuring that the clinical and physiological functions (mainly adequate ventilation) and the patient's safety are maintained (see also Chapter 24).

SOCIAL CONSIDERATIONS

An important factor for success is to coordinate the social assistance that will be available at home. The spectrum ranges from the simplest case where the patient has numerous, motivated, available family members to no relatives in proximity. If the patient wants to go back home and if his or her clinical status permits it, collaboration with social workers must be organised according to the financial possibilities of the society and the social network. In France, for instance, patients with established chronic respiratory failure benefit from 100% reimbursement for their healthcare costs. Social services have budgets that are supported by the social charges (*cotisations*; like the National Insurance in the United Kingdom) paid by workers and their employers. These services are available in France for the most ventilator-dependent patients.

HOME CARE SETTING

The home equipment for ventilator-assisted individuals depends on the aetiology of the chronic respiratory failure, the degree of impairment, the upper airway function and the mode of ventilatory support. If clinically stable, a middle-aged patient requiring nocturnal NIV does not require a large amount of equipment (i.e. just a ventilator with the circuit and filters, and a mask). This type of patient does not need any humidifier device or additional oxygen in the circuit and no internal or external battery. Additional elements are needed for patients on long-term oxygen therapy or those requiring mechanical cough assistance. Ventilator-dependent individuals should always have a backup ventilator, an emergency power source and a manual resuscitation bag. The electricity supplier and the regional emergency medical assistance service should be aware of these individuals.

RHCSs: Obligations, organisation and costs

OBLIGATIONS

A RHCS must provide a 24 h service with facilities for on-call intervention at home by skilled technicians, nurses or

other qualified employees. The availability of a physician who is a part- or full-time employee of the organisation ensures superior quality of home care.

In parallel, the RHCS also works with technicians who get involved either at home to ensure optimal maintenance of the equipment as well as education and motivation of the patient and their family, or in the maintenance workshop, generally located in the headquarters of the RHCS. Such technicians provide a regular daytime service and are also on-call during the night or at weekends. The frequency of the daytime visits varies according to the patient's needs. In France, the reimbursements to the RHCS are also different, depending on the type of respiratory home care provided to the patients. Specific contracts stating a precise frequency of visits and the obligations of the RHCS may be submitted for reimbursement.

Respiratory physiotherapists also have a role in managing patients with bronchial hypersecretion and decreased cough efficacy and those patients who will benefit from pulmonary rehabilitation. The availability of on-call respiratory technicians is crucial to provide answers to patients who require information about emergency situations or technical problems, especially with ventilator-dependent patients. A RHCS also needs a well-planned administrative structure to manage the financial budget, which is important in terms of deciding future investments and purchase of equipment. Criteria, procedures and quality standards to be certified by health services or quality control commissions widely vary between different countries.

ORGANISATION

The early national public health services that historically initiated home care services have largely been replaced by the trend towards cooperation between public and private organisations. In some countries, home care is supplied entirely by private companies; in others, the public health service still has a monopoly.

In France, the Association Nationale pour les Traitements à Domicile, l'Innovation et la Recherche (ANTADIR) initiated a large public network in the beginning of the 1980s that created a federation of 33 regional associations, devoted to home respiratory care.²² At the beginning, these non-profit associations were intended to treat chronic respiratory failure patients at home by providing oxygen therapy and/or ventilatory assistance. They were funded by French Social Security to ensure delivery and maintenance of the equipment. This system largely developed alone nearly without any challenge from the private sector during the first 10 years; however, private health services became more and more interested in the business opportunities afforded by this model of care. Nowadays in France, RHCS [including treatments by continuous positive airway pressure (CPAP) for sleep apnoea syndrome] is shared between several regional associations (35%) and private national or international companies (65%). Generally, the most severe patients (i.e. those who are discharged by the public hospitals) are managed by the associative network, and patients who are less severe are managed by the private sector.

With the increasing demand, RHCS is looking to manage not only respiratory care but also the whole package for health maintenance at home (e.g. provision and installation of complex 'medical' beds, artificial feeding, home perfusion treatments, subcutaneous insulin, wheelchairs, etc.) and social worker management.

COSTS OF HOME CARE

Several studies have proven that home care is less expensive than in-hospital treatment, either in acute-care hospitals or in long-term facilities.²² NIV is effective in maintaining the clinical stability of patients with chronic respiratory failure and reducing the need for further hospitalisations. In case of slowly progressive diseases with favourable long-term prognosis, such as post-polio syndrome or thoracic deformities, the costs of the ventilatory equipment, maintenance and the possible requirement for additional oxygen constitute a major economic burden. The decision whether to purchase or rent a ventilator should be made in the light of the prognosis of the disease and economic considerations in the contract with the local dealer (accessories, maintenance, other services) and varies from one country to another. In most

European countries, a national policy regarding prescription modalities, reimbursement, assistance and medical supervision (if it exists) does not provide complete coverage, even if the costs of long-term oxygen therapy and the ventilator are usually reimbursed by the national health service or an insurance company. In France, social security covers the costs of installation, maintenance, medical and technical supervision of patients with chronic respiratory failure receiving domiciliary respiratory support through specific contracts according to the modality of the prescribed respiratory assistance. Patients are reimbursed at a 100% rate for all their specific costs related to the respiratory disease (pharmacological treatments, chest physiotherapy, etc.), but indirect costs must also be considered (Table 19.1). French social security is increasingly supported by private insurance funds through the associative network mainly regulated by ANTADIR with its public service philosophy,²² and also through private networks that have strongly increased their presence in this field during the past 10 years. When the severity of the disease increases, the cost of respiratory assistance cannot be separated from the cost of chronic care, especially in progressive neuromuscular diseases or severe COPD, leading sometimes to ventilatory dependence. Caregivers in Europe are usually family members who face progressively increasing socio-medical requirements for cooking, bathing and toileting. A home care program that includes these specific needs is obviously desirable, but funding is presently lacking in most developed countries in the world and patients must pay themselves for this part of the care.

Table 19.1 Components of home care costs

Direct costs	
Physician fees	
Formal services purchased by family	
Hospital and skilled nursing facility inpatient days	
Medication	
Equipment rental	
Oxygen	
Ambulance	
Medical supplies	
Extra-utility charges	
Major one-time purchases or remodelling	
Indirect costs	
Alterations in employment	
Lost wages resulting from caregiving	

Monitoring the patient treated by HMV (Table 19.2)

Patients on long-term mechanical ventilation require regular follow-up on a clinical basis by their GP, in collaboration with the chest physician and the CVS. The frequency of visits is greater during the first year of follow-up, or if the disease is rapidly progressive or unstable. It is more convenient for the patient to come for a daytime consultation where the

Table 19.2 Monitoring the patient treated by HMV

ITEM	M1	M3	M6	M9	M12	M18	M24
Clinical evaluation	X	X	X	X	X	X	X
Chest x-ray	X				X		X
EKG	X				X		X
Biology	X				X		X
Diurnal arterial blood gases	X	X	X	X	X	X	X
Compliance recording	X	X	X	X	X	X	X
Pulmonary function tests	X				X		X
Ventilator software analysis	X	X	X	X	X	X	X
Equipment maintenance	X	X	X	X	X	X	X

clinical status and the equipment are controlled, in collaboration with the RHCS. Moreover, it allows routine investigations (chest x-rays, electrocardiogram, arterial blood gases breathing room air or oxygen and during mechanical ventilation as needed) to be performed. However, such assessments do not provide any evaluation of patient-ventilator adaptation during the night and do not verify the correction of respiratory disturbances during sleep. Rabec et al.³ have demonstrated that about half of patients considered as correctly ventilated at home still have desaturation during night-time or other respiratory events that are not identified by daytime assessments. Remote monitoring is now a new field for clinical, technological and research developments. See also Chapters 23 and 24.

HMV IN THE NETHERLANDS

HMV has a long history in the Netherlands. It started in the 1960s as a spin-off after the poliomyelitis epidemic, as a large group of patients became depended on long-term mechanical ventilation.²³ In 1965, the first patient from Groningen was sent home with a ventilator.

Organisation of HMV in the Netherlands

While in the beginning different hospitals in our country were involved in HMV, the Dutch government decided in 2004 that only four centres, geographically spread over the country and associated with a university hospital, could initiate HMV. If patients need HMV, they have to be referred to one of these centres. To be even more precise, the postal code of the place where the patient lives determines to which centre the patient should be referred. This is the only way in which reimbursement of HMV is guaranteed. All HMV centres in the Netherlands work in more or less the same way, and the teams consist of physicians, specialised nurses and technicians. In contrast to many other HMV centres in the world, the Dutch teams work both inside and outside the hospital. This means that the centres are responsible both for the start of the HMV and for the follow-up. As more and more patients needed HMV and safety issues became more important, the government forced us in 2012 to develop a Dutch guideline. It was developed with all societies who are involved in this process, including GPs, intensive care physicians, physiatrists, neurologists and of course patients. In this guideline, a Dutch HMV centre is clearly defined: (1) it initiates HMV in at least 50 patients per year, (2) it is responsible for follow-up of at least 200 patients yearly and (3) all patients are regularly monitored according to the disease leading to CRF.

Indication for HMV

The number of patients on HMV shows linear growth over time in all patient groups (Figure 19.4). The group including patients with a neuromuscular, central or peripheral nervous system disorder is the largest group in our country.

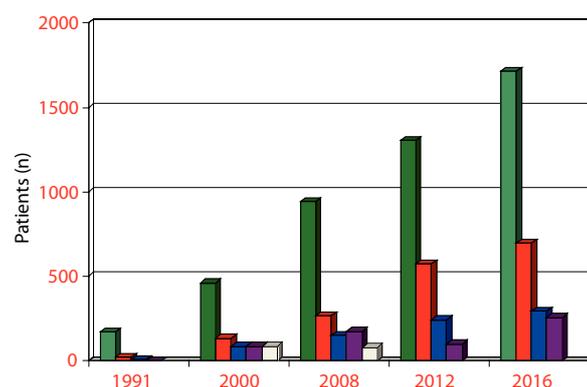


Figure 19.4 Different patient groups on HMV in the Netherlands from 1991 to 2016. Green: neuromuscular; red: thoracic cage problems; blue: lung; purple: sleep related; grey: miscellaneous.

Examples are patients with various muscular disorders, amyotrophic lateral sclerosis, spinal cord injury or diaphragm paralysis.

The second group entails patients with a thoracic cage problem, for example, congenital kyphoscoliosis. The obesity-hypoventilation syndrome belongs also to this group, as the obesity has a negative effect on the mobility of the thoracic cage. The latter diagnosis is valid if patients fulfil all the following criteria: a BMI > 30 kg/m², an arterial pCO₂ > 6.0 kPa (45 mmHg) and hypercapnia cannot be explained by a disease other than the obesity.

The third group entails patients with lung diseases, and as shown in Figure 19.5, this is a small group in the Netherlands. The reason for this is that a recent meta-analysis did not show beneficial effects of HMV in COPD patients with stable hypercapnic failure.²⁴ However, this group will show a significant growth in the future, as a recent German study showed both an improved survival and improved quality of life due to chronic HMV.²⁵

The fourth group contains patients with sleep-related breathing disorders, like obstructive sleep apnoea syndrome and central sleep apnoea syndrome. HMV might be an option in these patients if CPAP is not effective.

Referral and outpatient clinic

As mentioned previously, HMV can only be started after the patients have been referred to one of the four centres. After referral, patients will first be seen at the outpatient clinic by both a physician and specialised nurse. The task of the physician is to assess whether there is an indication for starting HMV, while the nurse will provide information about HMV and evaluates whether the social circumstances are sufficient for HMV. Spirometry, daytime arterial blood gases, nocturnal oximetry and transcutaneous capnography are the usual baseline assessments. In addition to information about chronic ventilatory support, the specialised nurse will also check the effectiveness of the patient's cough

and will teach air stacking if needed. At the end of the visit, a decision will be made whether HMV should be started or not.

Start of HMV

If the patient fulfils the criteria for HMV, he/she will be admitted to hospital. The four centres all have different settings in the hospital where HMV should be started. Some admit the patients to the ICU; some initiate HMV on the pulmonary ward. Despite the difference in settings, all wards must have specific knowledge of chronic ventilatory support and adequate monitoring, and safety must be guaranteed, being requested by the Dutch guideline. Regular nocturnal oximetry and transcutaneous capnography and readings from the ventilator give us insight into how the patient is ventilated. During this process, training of the patient and family/partner is started to teach them how to handle the mask and the machine. After the patient is adjusted to the ventilator and the settings are correct, the patient is ready to go home.

As we believe that the way we set up chronic ventilatory support is too expensive and less comfortable for the patient, we recently carried out a local study showing that initiation of HNV at home is equally effective, safe and cheaper compared to inpatient initiation.²⁶ To implement this nationally, we are currently conducting a study with all four centres in patients with a neuromuscular disorder or a thoracic cage.

Discharge and follow-up

Discharge can only take place at the time that safety issues around HMV are guaranteed. The patient and all healthcare providers get instruction on how to use the equipment and are informed about the possible alarms and the actions to be taken if problems occur. On the day of discharge, the patient is visited at home by our specialised nurse and the equipment installed. The department of HMV can be contacted 24/7 and is therefore always available in case of problems. Once a year, both oxygen saturation and carbon dioxide during the night will be checked while the patient is being ventilated, and if needed, this can be done more frequently. At least once a year, the patient will visit the outpatient clinic of the HMV centre.

The GP is the physician with primary responsibility for patients on HMV and the first to contact in case of problems. The activities and the role of the GP depend on the degree of disability of the patient and the severity of the underlying disease. In the final stages of the disease, the family, caregivers and healthcare professionals are coordinated by the GP to provide effective palliative care.

CONCLUSIONS

The provision of home ventilation is complex and involves much more than just the purchase of a machine and ancillary equipment. It is best delivered by a specialist service

looking after a large number of patients, with a well-trained, and experienced, multidisciplinary team. It should not be delivered on an occasional basis by a general pulmonology service.

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A different pathway exists in England. Home NIV setup is only performed by tertiary referral centres. Home NIV services have one tariff for each patient setup on home NIV. Therefore, they need to provide their care in the most efficient way.

The highlights of our book chapter are the following:

- There is a need for a multispecialty and holistic management of CRF patients and a comprehensive network of care to improve quality of life and outcomes.
- The displacement of the clinical and technological expertise to the patient's home should increase the feasibility of a pertinent follow-up and a minimally invasive monitoring to enhance the management of this chronic condition and to prevent acute exacerbations or decompensations.

II. *A better patient phenotyping for a better resource allocation*

G. *Original research: Step-down from non-invasive ventilation to continuous positive airway pressure: a better phenotyping (Respirology, 2019)*

We have seen that patients with OHS account for 29.5% of patients setup on home NIV ⁶⁴ and that more patients suffer from obesity ⁵⁶. As American guidelines suggest the use of CPAP as a first line treatment for patients with OHS, we need to question ourselves if all our OHS patients established on NIV should be step-downed to CPAP.

Until recently, very few data were available regarding that subject. In a small sample sized study, this approach appears not to be harmful despite some heterogeneity in patients evolution and a very short term assessment ¹⁹⁵. Another prospective observational study shown that 29% of patients failed NIV to CPAP step-down ¹⁹⁶. In response to this study, we reported the outcome of withdrawal strategy in our centre.

This argumentation has been accepted to publication in Respirology ¹⁹⁷.

Patout, M., Dantoing E., De Marchi M., Hart, N., Murphy, P. B, & Cuvelier A. (2019). Step-down from non-invasive ventilation to continuous positive airway pressure: A better phenotyping is required. *Respirology*. <http://doi.org/10.1111/resp.13746>



CORRESPONDENCE

Step-down from non-invasive ventilation to continuous positive airway pressure: A better phenotyping is required

To the Editors:

Arellano-Maric *et al.* report that patients with obesity hypoventilation syndrome (OHS) treated with non-invasive ventilation (NIV) can be safely switched to continuous positive airway pressure (CPAP) in a recent publication in *Respirology*.¹ The results of their study suggest that CPAP is preferred over NIV in a majority of patients. However, a sizeable minority of patients (12; 29%) included in their observational trial failed to step-down from NIV to CPAP.

We reviewed 182 consecutive patients with OHS treated in our home ventilation programme between 2017 and 2018 (forced expiratory volume in 1 s:forced vital capacity, FEV₁:FVC: 76 (71–84); body mass index, BMI: 41.9 (36.9–48.6) kg/m²). Patients were established on nocturnal NIV for 2.2 (0.3–6.5) years and daytime carbon dioxide partial arterial pressure (P_aCO₂) was 5.9 ± 0.9 kPa with a residual apnoeic event rate of 1.2 (0–3.4) events/h. After exclusion of 38 patients with an NIV adherence <4 h/night, 54 (38%) patients had a daytime P_aCO₂ >6 kPa despite an NIV adherence of 6.9 (5.4–8.2) h/night. Patients with persistent hypercapnia had greater impairment of quality of life than eucapnic patients (Severe Respiratory Insufficiency Questionnaire²: 58 (48–71) vs 69 (53–80); *P* = 0.009). Nineteen (10%) eucapnic patients (P_aCO₂ 5.1 (4.8–5.6) kPa) were switched from NIV to CPAP. Of the 19 patients, 8 (42%) failed step-down to CPAP: 5 relapsed with daytime hypercapnia (6.4 (6.3–6.7) kPa), 2 died within 6 months and 1 patient preferred NIV over CPAP. Our results, similar to Arellano-Maric *et al.*'s study, highlight that although a proportion of patients with OHS may be successfully treated with CPAP therapy, many patients will suffer treatment failure following step-down from NIV and therefore require careful monitoring if this is to be performed in clinical practice. Future work should focus on identifying treatable characteristics³ that predict success or failure of CPAP therapy⁴ in OHS allowing more rational decision-making.

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From the Authors:

We thank Dr Patout *et al.* for sharing their experience with the treatment of patients with obesity hypoventilation syndrome (OHS) when switching from non-invasive ventilation (NIV) to continuous positive airway pressure (CPAP) therapy. Some of the baseline characteristics of their cohort are reported, and allow a rough comparison with our cohort. Overall, both cohorts seem to be similar, although the body mass index (BMI) in our cohort tended to be higher (45 vs 41.9 kg/m²).

In our interventional trial, we were able to switch 28% of OHS patients in contrast to the 10% in Patout *et al.*'s cohort. Of note, 21% of their cohort had bad NIV therapy adherence and were not offered a switch to CPAP. Interestingly, we did not exclude bad adherent patients as we considered the switch to CPAP to potentially improve treatment adherence. No information about the NIV pressures was provided, but a significant proportion of Patout *et al.*'s cohort (38% of therapy adherent patients) remained hypercapnic precluding a CPAP switch. In our cohort, only 6% of patients were hypercapnic after a careful therapy optimization under polysomnography.

Finally, the success rate in the patients in whom a CPAP switch was intended was 58% in Patout *et al.*'s cohort and 81% in our cohort. This difference is probably related to the patient selection criteria and the use of a CPAP titration protocol under polysomnography in our trial.

Indeed, a significant proportion of OHS patients will require NIV to be adequately treated. We agree with the authors that a close monitoring is needed to avoid undertreatment following a step-down from NIV to CPAP. We also agree that the predictors of CPAP response need to be established in the future. Furthermore, patient preference between both therapies is a pivotal aspect of this long-term therapy.

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The main findings of this study are:

- A significant portion of compliant patients with OHS (38%) have residual daytime hypercapnia and therefore should not be candidate to step-down from NIV to CPAP.
- Switch down from NIV to CPAP in our cohort was associated to a very high failure rate: 42%.

Hence, despite published data, we believe that patients with OHS will remain a significant proportion of patients established on home NIV. Therefore, novel treatment approaches should be offered in this CRF population.

III. *Automated mode of ventilation: a substitute for NIV titration*

1. Volume targeted non-invasive ventilation

For patients with simple sleep disordered breathing for which CPAP is the first line treatment, automated positive airway pressure devices (APAP) have replaced the need for overnight titration in the sleep laboratory. Such management has been shown to be cost-effective ^{198,199}. In addition, as we shown in patients with COPD-OSA ¹⁶⁷, Corral *et al.* have shown in a larger trial that PSG was not useful for CPAP initiation in patients with OSA ²⁰⁰.

The usual mode of ventilation delivers a fixed inspiratory and expiratory pressure to improve alveolar ventilation. Similarly, to OSA, the level of pressure required may vary overnight. Indeed, during REM sleep, hypoventilation is worsened. Therefore, NIV manufacturers have developed volume targeted mode of NIV. In volume targeted ventilation, the level of inspiratory pressure is adjusted to achieve a pre-set volume. The volume is calculated by the ventilator using the expiratory flow and the pressure modified according to built-in algorithms. The adjustments algorithms vary between manufacturers.

Volume targeted ventilation has been assessed in several categories of CRF. In patients with ALS, it was shown that volume targeted ventilation achieved higher tidal volume than conventional pressure support ventilation ²⁰¹. This result is in line with previous work showing a better control of hypoventilation in volume controlled ventilation ²⁰². However, both studies were retrospective.

In single-centre trials about COPD patients, similar physiological outcomes were found using volume targeted ventilation or pressure support ventilation ^{203,204}.

In patients with OHS, similar outcome using volume targeted ventilation was seen in the first trial ^{188,205}. However, a sleep-focused cross-over trial suggested an altered quality of sleep using volume targeted ventilation ¹⁰⁹.

One of the main limitations of volume targeted ventilation is the fact that it does not take into account upper airway obstructive events. As they are commonly found in patients with COPD ⁶⁴ and even more in patients with OHS, their use still requires a positive expiratory airway pressure titration that can only be assessed during sleep. A second-generation volume-targeted ventilation has been developed to overcome this issue. These new ventilators have the ability to detect upper airway obstruction and to adjust the level of EPAP. When using these modes of ventilation, clinicians have to

set a range of EPAP to overcome upper airway obstruction and a range of inspiratory pressure to correct hypoventilation. These new modes of ventilation may replace overnight in-hospital titration.

Volume targeted ventilation with auto EPAP titration was shown to be safe in patients with COPD-OSA ²⁰⁶. Short-term cross-over clinical trials in heterogenous populations did not show any detrimental effect, especially on sleep quality ^{207,208}. However, we still lack data regarding the efficacy of these mode of ventilation in randomised controlled trials.

2. Evaluation of volume targeted ventilation with automated expiratory positive airway titration in patients with obesity hypoventilation syndrome

H. Original research: AVAPS-AE vs ST mode: A randomized controlled trial in patients with obesity hypoventilation syndrome (Respirology, 2020)

Given the gaps in the literature, we conducted a randomised controlled trial that aimed to compare the benefit of a volume targeted ventilation with automated expiratory positive airway titration *versus* the usual pressure support ventilation in patients with CRF secondary to OHS.

The trial was conducted across France in ten centres and has been published in *Respirology*²⁰⁹. The results of the trial were presented at the American Thoracic Society Congress held in Dallas 2019²¹⁰:

Patout, M., Gagnadoux, F., Rabec, C., Trzepizur, W., Georges, M., Perrin, C., et al. (2020). AVAPS-AE vs ST mode: A randomized controlled trial in patients with obesity hypoventilation syndrome. *Respirology*. <http://doi.org/10.1111/resp.13784>



ORIGINAL ARTICLE

AVAPS-AE versus ST mode: A randomized controlled trial in patients with obesity hypoventilation syndrome

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ABSTRACT

Background and objective: Average volume-assured pressure support—automated expiratory positive airway pressure (AVAPS-AE) combines an automated positive expiratory pressure to maintain upper airway patency to an automated pressure support with a targeted tidal volume. The aim of this study was to compare the effects of 2-month AVAPS-AE ventilation versus pressure support (ST) ventilation on objective sleep quality in stable patients with OHS. Secondary outcomes included arterial blood gases, health-related quality of life, daytime sleepiness, subjective sleep quality and compliance to NIV.

Methods: This is a prospective multicentric randomized controlled trial. Consecutive OHS patients included had daytime $P_aCO_2 > 6$ kPa, BMI ≥ 30 kg/m², clinical stability for more than 2 weeks and were naive from home NIV. PSG were analysed centrally by two independent experts. Primary endpoint was sleep quality improvement at 2 months.

Results: Among 69 trial patients, 60 patients had successful NIV setup. Baseline and follow-up PSG were available for 26 patients randomized in the ST group and 30 in the AVAPS-AE group. At baseline, P_aCO_2 was 6.94 ± 0.71 kPa in the ST group and 6.61 ± 0.71 in the AVAPS-AE group ($P = 0.032$). No significant between-group difference was observed for objective sleep quality indices. Improvement

SUMMARY AT A GLANCE

Automated expiratory positive airway pressure (EPAP) and volume-targeted non-invasive ventilation achieve similar control of sleep-disordered breathing as pressure support ventilation in patients with obesity hypoventilation syndrome. Objective sleep quality at 2 months of ventilation therapy is not altered by the use of automated EPAP and volume-targeted ventilation compared to pressure support ventilation.

in P_aCO_2 was similar between groups with a mean reduction of -0.87 kPa (95% CI: -1.12 to -0.46) in the ST group versus -0.87 kPa (95% CI: -1.14 to -0.50) in the AVAPS-AE group ($P = 0.984$). Mean NIV use was 6.2 h per night in both groups ($P = 0.93$). NIV setup duration was shorter in the AVAPS-AE group ($P = 0.012$).

Conclusion: AVAPS-AE and ST ventilation for 2 months had similar impact on sleep quality and gas exchange.

Clinical trial registration: NCT01757444 at ClinicalTrials.gov

Key words: chronic respiratory failure, non-invasive ventilation, obesity hypoventilation syndrome, polysomnography, sleep apnoea.

INTRODUCTION

Obesity hypoventilation syndrome (OHS) is one of the leading indication of home non-invasive ventilation (NIV) initiation.¹ In patients with OHS, NIV improves daytime vigilance, decreases P_aCO_2 , improves sleep quality and improves physical activity.^{2–5}

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NIV is usually delivered using a spontaneous timed (ST) pressure support mode with a fixed expiratory positive airway pressure (EPAP) and a fixed inspiratory positive airway pressure (IPAP). Adequate NIV titration is achieved when alveolar hypoventilation is corrected and when the residual apnoea-hypopnoea index (AHI) is inferior to 10/h.⁶ However, the required level of pressure varies between different sleep stages. Recently, manufacturers proposed innovative modes that are intended to facilitate NIV adjustments. These also called 'hybrid modes' use adaptive algorithms to automatically adjust one or more settings to achieve predefined targets. One of those modes, also called volume targeting pressure ventilation, combine features of pressure and volume modes providing a predetermined target volume while maintaining physiological benefits of pressure-targeted modes. In these modes, the physician determines a targeted tidal volume (V_t) and a minimal and a maximal IPAP. One of these features called AVAPS (average volume-assured pressured support; Philips Respironics, Murrysville, Pennsylvania, USA) has been shown to be effective to control CO_2 .² However, Janssens *et al.* have shown that objective and subjective sleep quality were worse using the AVAPS mode when compared to standard ST ventilation despite better transcutaneous CO_2 (TcCO_2) reduction and an unaffected index of fragmentation and percentage of restorative sleep.⁷

As most of the patients with OHS have concomitant apnoeic events, an automated EPAP (AE) mode has been added to the AVAPS. Thus, AVAPS-AE mode combines a targeted volume to an automated adjustment of EPAP level. Obstructive apnoeic events are detected using a forced oscillation technique (FOT) that dynamically determines upper airway resistance.⁸ If apnoeic events are detected, EPAP is increased to obtain upper airway patency. Thus, combining a targeted volume to an automated adjustment of EPAP may allow a better control both for alveolar hypoventilation and obstructive events. However, to date, no study has specifically evaluated the clinical benefit of AVAPS-AE mode in a population of patients with OHS.

The primary aim of this study was to compare the effects of 2-month AVAPS-AE ventilation versus ST ventilation on objective sleep quality in stable patients with OHS. Secondary outcomes included arterial blood gases, health-related quality of life, daytime sleepiness, subjective sleep quality and NIV compliance.

METHODS

We conducted a prospective single-blind multicentre ($n = 10$) randomized controlled trial (NCT01757444) in France. The trial was conducted according to national and international ethical guidelines and approved by the French North West I ethic committee (agreement number CPP 2012-017 - 2012 A00731-42). The study protocol was published prior to beginning the trial.⁹ The trial was promoted by the Antadir and funded by Philips Respironics.

Patients

Eligible patients for this trial were adults between 20 and 85 years old with newly diagnosed OHS defined

by a body mass index (BMI) $\geq 30 \text{ kg/m}^2$ and a daytime $\text{P}_a\text{CO}_2 \geq 6.0 \text{ kPa}$. Patients had to be clinically stable, that is, without clinical signs of acute respiratory failure over the last 2 weeks. Exclusion criteria were: concomitant obstructive pulmonary disease (forced expiratory volume at 1 s/forced vital capacity <0.7), neuromuscular disease, kyphoscoliosis, cardiac insufficiency, unstable psychiatric disorder that would lead to impaired understanding or compliance to study protocol, cancer under treatment and patients with more than 10% of central apnoeic events. Patients treated with benzodiazepines were excluded if benzodiazepine was introduced <1 month prior to screening. Patients who lacked capacity to provide consent were excluded.

All patients received written information on the protocol and provided a written consent for inclusion.

Randomization

After baseline polysomnography (PSG) and patient's consent, patients were randomized 1:1 in the intervention arm: AVAPS-AE group or the control group: ST group. Randomization was performed using a central computerized software. Stratification was based on the participating centre to ensure balanced arms in each centre.

NIV setup

After randomization, patients were established on NIV as inpatients. The same respirator (A40; Philips Respironics) was used in both groups. Patients were blinded to group allocation as they did not have access to device settings and as the appearance of the ventilator was identical in both groups. In the AVAPS-AE group, the targeted V_t was set at 8–10 mL/kg of ideal body weight (defined as the weight that would be associated to a BMI of 23 kg/m^2 and calculated as follows: $\text{height} \times \text{height} \times 23$) with an automatic back-up rate. In the ST group, baseline settings were a pressure support at 14 cm H_2O and initial EPAP level was set according to the initial AHI: at 5 cm H_2O if AHI $< 15/\text{h}$ and between 6 and 12 cm H_2O if AHI $\geq 15/\text{h}$. Complete details of baseline settings and titration protocol can be found in Figure S1 (Supplementary Information). In both groups, after daytime acclimatization, overnight titration was performed using overnight polygraphy and TcCO_2 tension monitoring. Further adjustments were performed according to results of the overnight study. Successful titration was defined as follow: (i) an overnight mean saturation $> 90\%$, (ii) morning P_aCO_2 decrease of 0.5 kPa, (iii) overnight stability or decrease of TcCO_2 and (iv) a residual AHI $\leq 15/\text{h}$. If satisfactory control was not achieved after the first night, patients remained from one to two additional for settings adjustments (Fig. S2 in Supplementary Information). All patients received in-hospital structured training on the use of their ventilator. On the day of discharge, the homecare service in charge of delivering NIV performed a home visit for each patient. The homecare service provider performed monthly home visit and retrieved monthly data from the ventilator built-in software.

Study follow-up

Two months following NIV setup, patients were readmitted for an overnight stay. They underwent PSG on NIV. Data from the built-in software were retrieved at follow-up assessment to assess compliance and delivered pressures.

Polysomnography

PSG was interpreted locally in each centre by a trained respiratory physician for patients' care purposes, inclusion in the trial and device's settings adjustment. A blind centralized reading was then performed by two expert readers from two participating centres (A.P. and R.T.). These expert readers were not involved in patients' care and were not aware of the treatment group. However, in order to perform their analysis, they had access to all PSG signals including the pressure signal. Agreement between PSG readers was good for all PSG results ($r > 0.7$), moderate for N3 duration ($r = 0.626$) and mild for N1 and N2 duration ($r = 0.447$ and 0.334 , respectively) (Table S1 in Supplementary Information). Hypoventilation was defined as following: oxygen saturation (SpO_2) $< 85\%$ for more than 5 min in association with $TcCO_2 > 6$ kPa. PSG scoring was performed according to the American Academy of Sleep Medicine 2012 guidelines.¹⁰ Patient-ventilator asynchrony was scored as residual respiratory event. Only patients with both baseline and follow-up PSG were included in the final analysis regarding sleep quality.

Outcome measures

All outcome measures were taken twice: at baseline prior to treatment and then after 2 months with treatment. The primary endpoint was objective polysomnographic sleep quality improvement at 2 months. Secondary endpoints included change in P_aCO_2 , compliance to NIV and quality of life questionnaire.

Sample size calculation

Previous studies evaluating AVAPS mode showed significant differences in sleep quality in a cross-over design with 9 and 10 patients.^{7,11} With alpha and beta risk of 5% and 20%, respectively, based on previously published data,⁷ 50 patients would have been required to detect a change in total sleep time, 56 would have been required to detect a change in stage 2 sleep duration and 60 patients were required to detect a change in wake after sleep onset (WASO). Based on previous data published,² 50 patients appeared sufficient to detect a 0.5-kPa improvement in P_aCO_2 with an alpha risk of 5% and a beta risk set at 20%. Therefore, we targeted to include 60 patients with 1:1 randomization.

Statistical analysis

Data are presented as mean \pm SD or median (interquartile range) as appropriate. Student's t-tests were performed when explained variables had a normal distribution as assessed by the Jarque Bera test (null hypothesis). When explained variables were not normally distributed, Wilcoxon tests were performed

(alternative hypothesis). For complementary analysis, we used mixed linear regression analysis that included the randomization group, baseline AHI, baseline P_aCO_2 and baseline BMI in the model. Agreement between PSG readers was assessed by Spearman's test and intraclass correlation coefficient. Mean value from each parameter was included in the analysis. Missing data were replaced using multivariate imputations by chained equations method. All patients were analysed in their respective randomization group. Those who did not attend the follow-up PSG were excluded from the analysis of the primary outcome. Statistical analysis was performed using R version 3.5.0 (2018-04-23; R Foundation, Vienna, Austria). All tests were two-sided and type I error rate was set at 0.05.

RESULTS

Of the 88 patients screened, 69 were randomized between April 2013 and December 2017 (Fig. 1). Of those, 60 were included in the trial following successful NIV setup. There were 29 patients randomized in the ST group and 31 in the AVAPS-AE group. Baseline and follow-up PSG were available for 26 patients in the ST group and 30 in the AVAPS-AE group. Baseline characteristics are reported in Table 1. Ten patients (17%) had a baseline $P_aO_2 < 7.3$ kPa: four in the ST group and six in the AVAPS-AE group ($P = 0.732$). Seventeen patients (28%) had a baseline AHI $< 30/h$: eight in the ST group and nine in the AVAPS-AE group ($P = 1$). Despite randomization, at baseline, patients in the AVAPS-AE group had a higher BMI than those in the ST group: 46.8 versus 42.6 kg/m^2 ($P = 0.013$). Patients in the AVAPS-AE group also had lower daytime P_aCO_2 and bicarbonate level than those in the ST group: 6.6 versus 6.9 kPa ($P = 0.034$) and 29.0 versus 30.6 mmol/L ($P < 0.001$).

Successful NIV setup was achieved in 60 patients. In a post hoc analysis, we observed that the length of stay for NIV setup was higher in the ST group when compared to the AVAPS-AE group, 4 (4; 5) days versus 3 (3; 4) ($P = 0.001$).

At 2 months, objective polysomnographic sleep quality improved significantly in both groups without between-group difference (Table 2). Indeed, N3 and rapid eye movement (REM) sleep duration increased and consecutively N1 sleep decreased which corresponds to an improvement in sleep structure. Accordingly, sleep microstructure improved with a decrease in the arousal index. Given imbalanced baseline characteristics between groups, we performed a post hoc mixed linear regression analysis. There was no significant correlation between baseline P_aCO_2 and any of the sleep quality parameters. Baseline BMI was not correlated to any of the sleep parameters except for N1 duration ($F = 0.333$, $P = 0.021$).

At follow-up, adherence to treatment was similar between both groups with a mean NIV use of 6.2 ± 1.9 h per night in the ST group and 6.2 ± 1.6 h per night in the AVAPS-AE group. Delivered pressure was similar in both groups, while respiratory rate was lower in the AVAPS-AE group than in the ST group ($P = 0.031$) (Table 3).

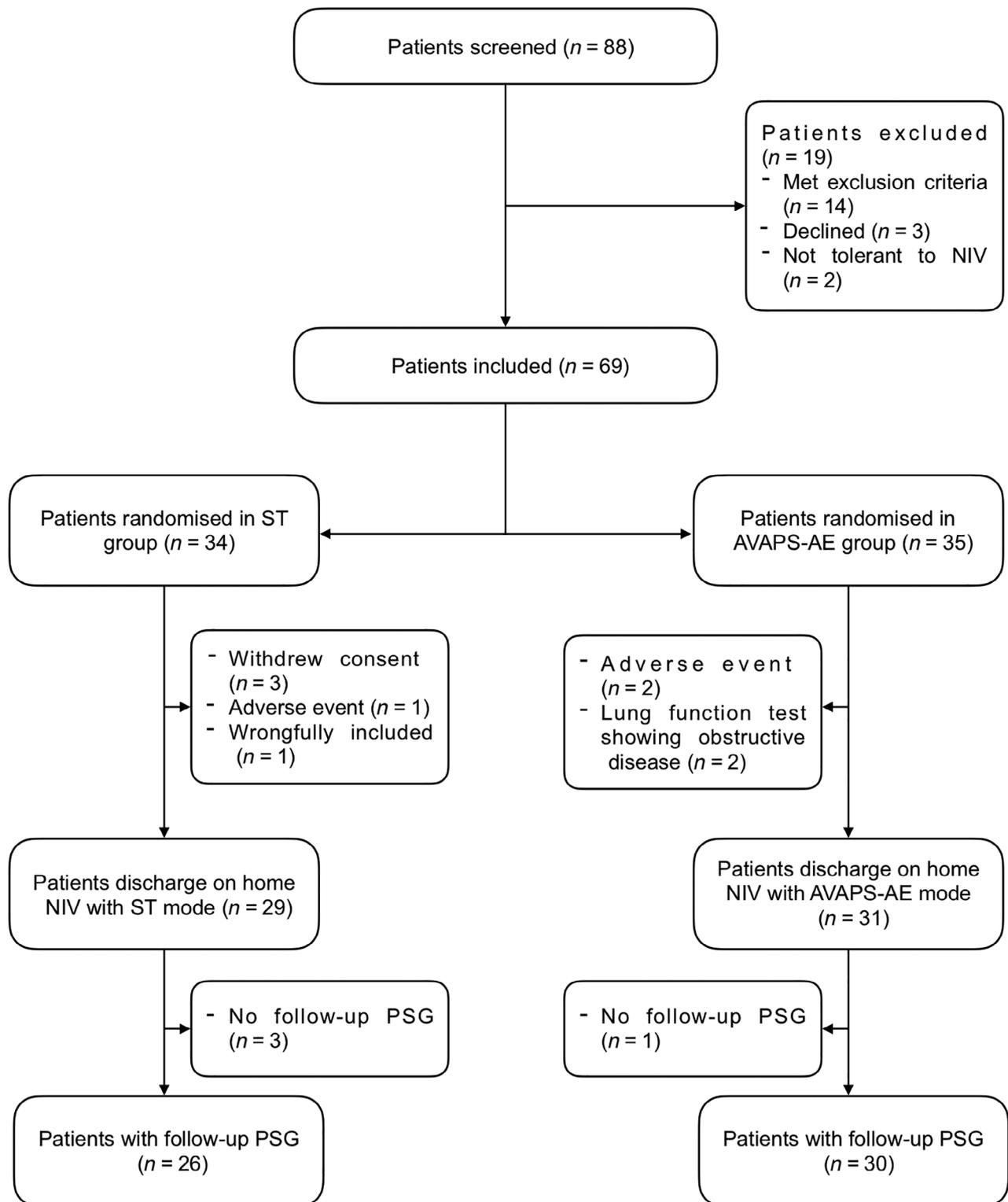


Figure 1 Study flow chart. AVAPS-AE, average volume-assured pressure support—automated expiratory positive airway pressure; NIV, non-invasive ventilation; PSG, polysomnography; ST, spontaneous timed.

At follow-up, improvement in P_aCO_2 was equivalent between both groups with a mean reduction of -0.87 kPa (95% CI: -1.14 to -0.50) in the AVAPS-AE group versus -0.87 kPa (95% CI: -1.12 to -0.46) in the

ST group ($P = 0.984$). Improvement in P_aO_2 was equivalent with a mean increase of 1.03 kPa (95% CI: $+0.37$ to $+1.7$) in the AVAPS-AE group and of $+1.37$ kPa (95% CI: $+0.58$ to $+2.1$) in the ST group ($P = 0.896$). Similarly,

Table 1 Baseline characteristics of randomized patients

	ST (<i>n</i> = 29) Mean ± SD	AVAPS- AE (<i>n</i> = 31) Mean ± SD	<i>P</i> - value
Age (years)	59.8 ± 14.4	59.8 ± 13.1	0.986
Male (%)	13 (45%)	15 (48%)	1
Body mass index (kg/m ²)	42.6 ± 7.5	46.7 ± 10.4	0.013
Dyspnoea (mMRC)	2.0 ± 1.1	2.2 ± 1.4	0.503
Lung function test			
FEV ₁ (L)	1.9 ± 0.9	2.0 ± 0.6	0.640
FEV ₁ (%)	70.2 ± 23.5	73.7 ± 17.4	0.409
FVC (L)	2.4 ± 1.0	2.5 ± 0.8	0.377
FVC (%)	71.1 ± 23.1	74.0 ± 17.3	0.277
FEV ₁ /FVC	79 ± 6	78 ± 6	0.540
Baseline arterial blood gas			
pH	7.38 ± 0.03	7.39 ± 0.04	0.494
P _a O ₂ (kPa)	8.62 ± 1.5	8.99 ± 1.5	0.406
P _a CO ₂ (kPa)	6.94 ± 0.71	6.61 ± 0.71	0.032
Bicarbonates (mmol/L)	30.6 ± 3.2	28.8 ± 1.8	<0.001

AVAPS-AE; average volume-assured pressure support—automated expiratory positive airway pressure; FEV₁, forced expiratory volume at 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council; P_aCO₂, arterial partial pressure of carbon dioxide; P_aO₂, arterial partial pressure of oxygen; ST, spontaneous timed.

Table 3 Data from ventilator built-in software at 2 months follow-up

	ST (<i>n</i> = 29) Mean ± SD	AVAPS- AE (<i>n</i> = 31) Mean ± SD	<i>P</i> - value
Mean IPAP (cm H ₂ O)	20.9 ± 4.4	21.0 ± 4.7	0.942
90% IPAP (cm H ₂ O)	21.6 ± 3.3	24.2 ± 4.5	0.134
Mean EPAP (cm H ₂ O)	9.6 ± 2.4	8.2 ± 2.1	0.141
90% EPAP (cm H ₂ O)	9.7 ± 2.4	10.8 ± 2.4	0.306
Back-up rate (/min)	16.9 ± 1.7	15.0 ± 2.9	0.031
Expired Vt (mL)	501 ± 149	616 ± 172	0.105
Expired volume/kg of ideal body weight (mL/kg)	8.0 ± 2.0	9.6 ± 2.3	0.044
Total leaks (L/min)	47 ± 10	46 ± 9	0.907

AVAPS-AE, average volume assured pressure support—automated EPAP; EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; ST, spontaneous timed; Vt, tidal volume.

there was a comparable improvement in bicarbonates with a mean reduction of -2.2 mmol/L (95% CI: -1.0 to -3.2) in the AVAPS-AE group and -2.3 mmol/L in the ST group (95% CI: -1.3 to -3.4) ($P = 0.684$) (Fig. 2).

Table 2 Results from overnight polysomnography at baseline (room air self-venting) and at 2-months follow-up (under non-invasive ventilation) (t-test)

	ST (<i>n</i> = 26)			AVAPS-AE (<i>n</i> = 30)			Between-group comparison at follow-up
	Mean ± SD			Mean ± SD			
	Baseline	Follow-up	Pre-post <i>P</i> -value	Baseline	Follow-up	Pre-post <i>P</i> -value	
AHI (/h)	50 ± 29	10 ± 10	<0.001	56 ± 33	12 ± 13	<0.001	0.347
3% ODI (/h)	61 ± 31	22 ± 16	<0.001	72 ± 43	22 ± 15	<0.001	0.817
TST < 90% (%)	64 ± 38	31 ± 32	<0.001	62 ± 35	33 ± 31	<0.001	0.600
Mean saturation (%)	85 ± 6	91 ± 3	<0.001	86 ± 4	91 ± 3	<0.001	0.982
TST (min)	320 ± 101	311 ± 115	0.381	342 ± 92	329 ± 81	0.449	0.481
Sleep latency (min)	21 ± 29	24 ± 28	0.397	18 ± 20	19 ± 27	0.773	0.704
Arousal index (/h)	44 ± 23	20 ± 12	<0.001	48 ± 30	19 ± 10	<0.001	0.909
Respiratory arousal index (/h)	8 ± 23	1 ± 1	<0.001	7 ± 7	1 ± 1	<0.001	0.365
Hypoventilation (min)	63 ± 102	5 ± 18	0.002	35 ± 63	7 ± 14	0.002	0.296
WASO (min)	104 ± 88	80 ± 53	0.468	75 ± 54	65 ± 39	0.272	0.331
Awakenings (<i>n</i>)	38 ± 24	31 ± 23	0.085	33 ± 19	29 ± 24	0.070	0.634
Sleep efficacy (%)	75 ± 17	75 ± 22	0.897	79 ± 13	81 ± 10	0.365	0.534
REM (%)	11 ± 8	16 ± 12	0.045	11 ± 8	19 ± 10	0.001	0.227
N1 (%)	29 ± 16	19 ± 11	0.024	28 ± 19	18 ± 15	0.011	0.386
N2 (%)	46 ± 11	46 ± 11	0.752	44 ± 12	44 ± 9	0.996	0.408
N3 (%)	16 ± 9	21 ± 12	0.059	18 ± 12	23 ± 12	0.039	0.525

AHI, apnoea-hypopnoea index; AVAPS-AE, average volume-assured pressure support—automated expiratory positive airway pressure; N1, N1 sleep stage; N2, N2 sleep stage; N3, N3 sleep stage; ODI, oxygen desaturation index; REM, rapid eye movement; ST, spontaneous timed; TST, total sleep time; TST 90%, TST spent with a saturation <90%; WASO, wake after sleep onset.

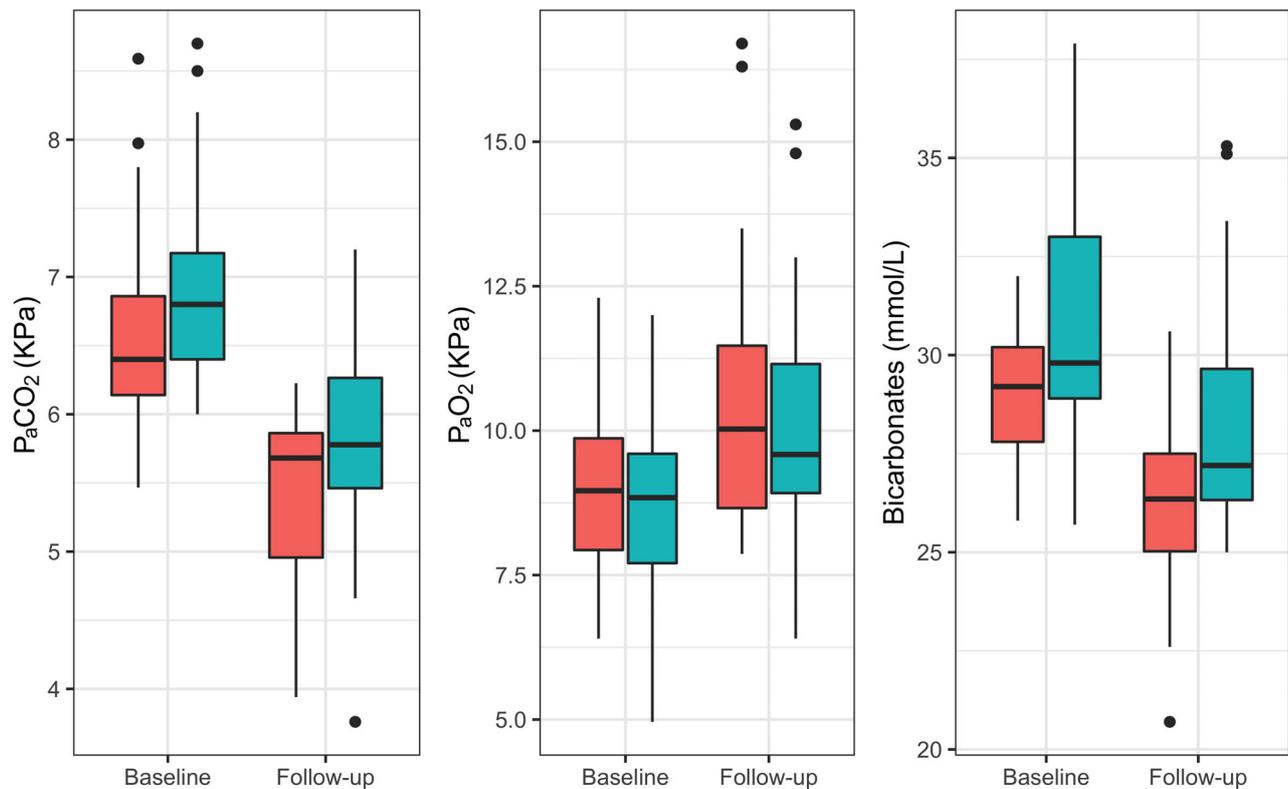


Figure 2 Change in arterial blood gas from baseline to follow-up in both groups. ■, average volume-assured pressure support—automated expiratory positive airway pressure (AVAPS-AE); ■, spontaneous timed (ST).

Table 4 Quality of life and subjective sleep quality at baseline and at 2 months follow-up (t-test)

	ST (n = 29)			AVAPS-AE (n = 31)			Between-group comparison at follow-up
	Mean ± SD			Mean ± SD			
	Baseline	Follow-up	Pre-post p-value	Baseline	Follow-up	Pre-post p-value	
SRI-RC	62 ± 22	72 ± 21	0.020	64 ± 25	76 ± 19	<0.001	0.538
SRI-PF	62 ± 27	66 ± 26	0.057	59 ± 28	66 ± 27	0.021	0.976
SRI-AS	48 ± 22	60 ± 20	<0.001	57 ± 19	70 ± 21	0.002	0.053
SRI-SR	72 ± 20	76 ± 24	0.174	74 ± 18	82 ± 17	0.021	0.794
SRI-Ax	65 ± 27	74 ± 26	0.013	70 ± 26	81 ± 18	0.008	0.391
SRI-WB	61 ± 24	71 ± 26	0.007	67 ± 21	76 ± 22	0.02	0.667
SRI-SF	68 ± 27	69 ± 27	0.665	71 ± 22	81 ± 18	0.007	0.081
SRI-total	63 ± 21	70 ± 19	0.003	65 ± 18	76 ± 15	<0.001	0.346
PSQI	9.9 ± 4.9	7.3 ± 4.7	0.091	7.8 ± 4.2	6.1 ± 4.4	0.224	0.309
ESS (/24)	7.9 ± 4.8	5.1 ± 4.2	0.032	10.4 ± 5.6	6.0 ± 4.9	<0.001	0.6
Self-assessed sleep quality (0: very poor/10: very good)	4.4 ± 2.8	6.4 ± 2.6	0.007	4.4 ± 2.8	7.3 ± 2.0	<0.001	0.175
Self-assessed tiredness (0: no tiredness/10: very tired)	5.3 ± 2.8	3.3 ± 2.9	0.003	5.3 ± 2.6	3.1 ± 2.3	<0.001	0.994

AS, attendant symptoms and sleep; AVAPS-AE, average volume-assured pressure support—automated expiratory positive airway pressure; Ax, anxiety; ESS, Epworth Sleepiness Scale; PF, physical functioning; PSQI, Pittsburgh Sleep Quality Index; RC, respiratory complaint; SF, social functioning; SR, social relationship; SRI, Severe Respiratory Insufficiency; ST, spontaneous timed; WB, psychological well-being.

At follow-up, sleepiness and quality of life improved in both groups without between-group difference (Table 4). In a post hoc subgroup analysis, the improvement in the Severe Respiratory Insufficiency (SRI) questionnaire was significantly better in the subgroup of patients who had a baseline $P_aCO_2 > 7$ kPa ($P = 0.015$). Weight remained stable in both groups: -2.3 kg in the AVAPS-AE group and -1.2 kg in the ST group ($P = 0.401$). The 6-min walking test distance did not improve significantly in both groups: $+19$ m in the AVAPS-AE group and $+5$ m in the ST group ($P = 0.355$).

DISCUSSION

In the two arms (AVAPS-AE and ST groups) of this randomized controlled trial, objective polysomnographic sleep quality, sleep-disordered breathing, arterial blood gases, health-related quality of life and sleepiness were significantly improved 2 months following NIV initiation. All improvements were similar in the two arms of the study. Compliance to treatment was similar between both groups. NIV setup duration was shorter in the AVAPS-AE group.

Our study is the first study to focus on the impact of an automated mode of ventilation on objective sleep quality using PSG in a multicentric prospective parallel design. Indeed, in patients with OHS, most of the trials that have evaluated different modes of ventilation used a cross-over design and included less than 30 patients.^{7,11–13} In these trials, sleep quality was assessed using PSG. The only randomized, parallel, controlled trial that evaluated an automated mode of ventilation against fixed pressure support in OHS patients was conducted by Murphy *et al.* In their study, subjective sleep quality was improved but not assessed using a follow-up PSG.²

Previously published data showed that the use of AVAPS mode may alter sleep quality with an increase of awakenings.⁷ Our results show that improvement in objective sleep quality was similar with AVAPS-AE and ST modes. This result is strengthened by the centralized double-blind reading. Both groups had a significant improvement in the duration of REM sleep and of their arousal index. In the AVAPS-AE group, N3 sleep was significantly increased ($P = 0.039$) but not in the ST group ($P = 0.059$). However, none of the group had a significant improvement in WASO, total sleep time or in sleep efficiency. The lack of improvement in these polysomnographic parameters is in line with results from the Pickwick trial.¹⁴

Our results show that the AVAPS-AE mode had a comparable effect in treating apnoeic events in OHS patients. The reduction in the AHI in the AVAPS-AE group was similar to the one achieved in the ST group ($P = 0.588$). This result differs from Orr *et al.* who showed, in a heterogeneous population, a better control of hypopnoeic events using an AE mode.¹² In a homogeneous population of COPD-obstructive sleep apnoea (OSA) overlap patients, Murphy *et al.* showed that an AE adjustment achieved similar control of apnoeic events.¹⁵ Our study confirms these findings in a homogeneous population of OHS patients after 2 months of NIV initiation.

In our study, patients were setup using a time- and resource-consuming protocol. Such NIV setup was

required for adequate evaluation of our primary endpoint. The in-hospital monitoring, in the ST group, may have reduced patient-ventilator asynchrony^{16,17} that may have led to a better NIV adherence.¹⁸ We acknowledge that such resources do not reflect daily clinical practice where NIV can be setup in an outpatient setting.^{19–21} Therefore, our results show that the use of the AVAPS-AE mode provides similar outcomes than a high-end inpatient NIV setup. However, in our study, patients in the AVAPS-AE group were also hospitalized. During their inpatient stay, careful mask adjustments, leak minimization as well as training on the use of NIV may have contributed to the efficacy of the AVAPS-AE mode. Therefore, a dedicated randomized controlled trial is needed to ascertain the safety and efficacy of AVAPS-AE for outpatient NIV setup.²²

Our results showed that delivered pressures were similar in both groups with trends suggesting that higher pressure support was achieved using the AVAPS-AE. Indeed, the expired V_t per kg of ideal body weight was higher in the AVAPS-AE group with a significant difference between the mean IPAP and the 90th percentile delivered pressure, a lower respiratory rate and similar percentage of triggered breaths. The level of total leaks was similar in both groups. However, the mean value of total leaks is a poor estimate of occasional high leakage which is more likely to disrupt sleep.

It has been previously hypothesized that automated mode could improve patient's tolerance to NIV.¹¹ However, in our study, sleep latency was similar between groups. Similarly, compliance and perceived comfort of NIV were comparable between groups. We therefore believe that one of the main advantages of using AVAPS-AE mode is to shorten the time required for NIV titration. As our study was not designed to show such difference, this benefit remains to be demonstrated as it was for autoadjusted continuous positive airway pressure (CPAP) in eucapnic OSA.²³

Compliance to the use of NIV was high in both groups (6.2h/night) when compared to previous randomized trials.^{2,14} Therefore, it was unlikely to see any additional benefit from the use of the AVAPS-AE mode. In future clinical trials, it may be of interest to evaluate the AVAPS-AE mode in non-compliant patients. Similarly, evaluating AVAPS-AE in insufficiently controlled patients under ST mode may provide useful tools to clinicians.

In patients with OHS, CPAP is now considered to be first-line therapy by the American Thoracic Society guidelines.²⁴ Indeed, previous randomized controlled trials failed to show a benefit of NIV over CPAP.^{14,25,26} Masa *et al.* have shown that NIV setup was more costly than CPAP.²⁷ This increased cost was mainly driven by inpatient costs required for NIV titration. However, CPAP can fail as a first-line treatment²⁸ or as a second-line treatment in patients with OHS.^{29,30} In our study, despite a mild baseline hypercapnia and despite a significant improvement of the AHI, mean time spent with an oxygen saturation $<90\%$ was high at 2 months (31% and 33% in the AVAPS-AE and ST groups, respectively). An increase in the level of positive expiratory pressure may have further improved overnight oxygenation. However, it has been previously shown that it may not

be sufficient in obese patients.³¹ Our protocol did not specify how to manage residual hypoxaemia. Therefore, we can only speculate that a more satisfactory overnight oxygenation may have been achieved by an increase of the level of pressure support of the targeted volume or with oxygen supplementation. If nocturnal hypoxemia is associated with poorer outcome,³²⁻³⁴ there is still a lack of evidence showing the benefit of restoring normal overnight oxygenation. Indeed, in patients with COPD, correction of nocturnal hypoxaemia is not associated with a better outcome.³⁵ In patients with OHS, we still lack data regarding the clinical impact of nocturnal hypoxaemia under ventilation. However, Masa *et al.* have shown that the long-term hospitalization and mortality rate were low in this population,²⁷ which had similar time spent with an oxygen saturation <90%.

In conclusion, among OHS patients with moderate hypercapnia, AVAPS-AE and ST ventilation for 2 months had similar impact on sleep quality and gas exchange. Our results suggest that AVAPS-AE might reduce the burden of NIV setup. With reassuring data regarding the impact on sleep quality, we believe that further studies should be conducted in patients not tolerant to standard mode of NIV, in those requiring a high level of pressure and in those with difficult upper airway management.

Data availability statement: The data that supports the findings of this study are available from the corresponding author upon reasonable request.

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Abbreviations: AE, automated EPAP; AHI, apnoea-hypopnoea index; AVAPS, average volume-assured pressured support; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; EPAP, expiratory positive airway pressure; FEV₁, forced expiratory volume at 1 s; FVC, forced vital capacity; IPAP, inspiratory positive airway pressure; NIV, non-invasive ventilation; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnoea; P_aCO₂, Arterial partial pressure of carbon dioxide; P_aO₂, Arterial partial pressure of oxygen; PSG, polysomnography; REM, rapid eye movement; SRI, Severe Respiratory Insufficiency; ST, spontaneous timed; TcCO₂, transcutaneous CO₂; Vt, tidal volume; WASO, wake after sleep onset.

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Figure S1 Participant flow chart.

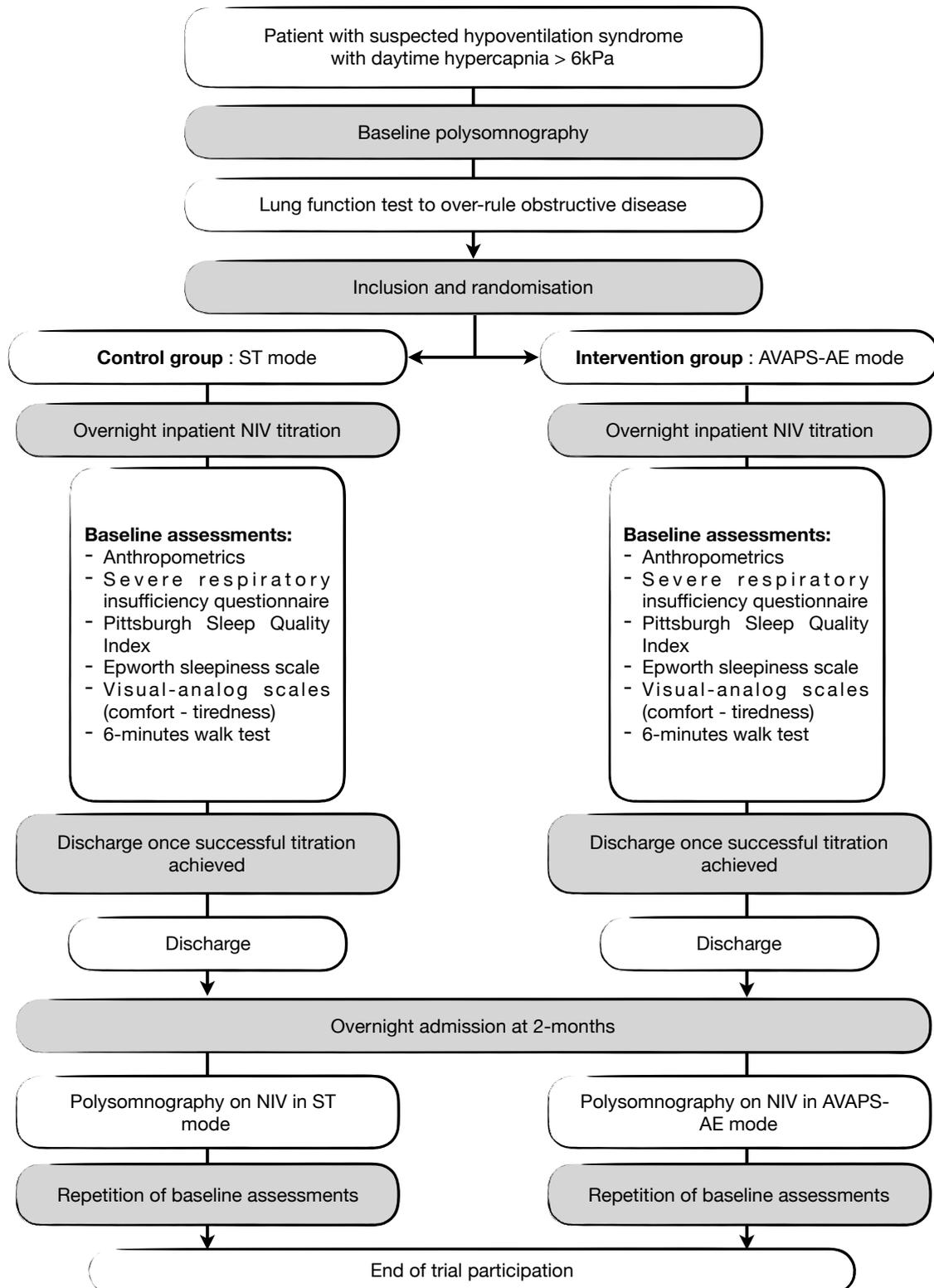
Figure S2. Titration protocol.

Table S1. Agreement in polysomnography (PSG) scoring between two independent PSG readers.

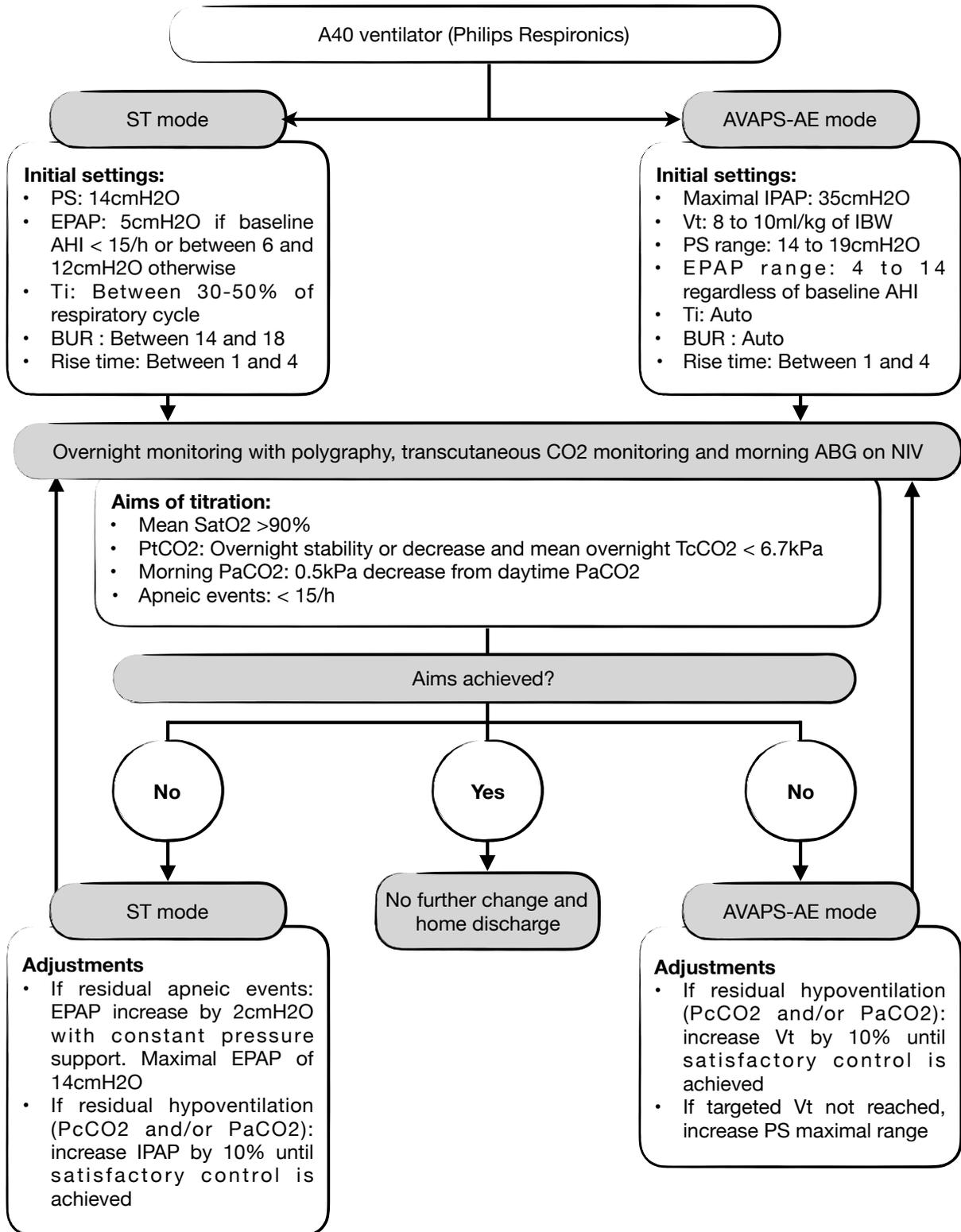
Visual Abstract Average Volume Assured Pressure Support and auto-EPAP (AVAPS-AE): Similar efficacy than ST mode in obesity hypoventilation.

Online supplement for AVAPS-AE vs ST mode: A randomised controlled trial in patients with obesity hypoventilation syndrome

Participant flow chart – eFigure 1



Titration protocol – eFigure 2



eTable 1: Agreement in polysomnography scoring between two independent PSG readers.

	Rho	p value	ICC [Lower – Upper bound]	p value
AHI (/h)	0.962	<0.001	0.97 [0.96 – 0.98]	<0.001
3% ODI (/h)	0.847	<0.001	0.99 [0.98 – 0.99]	<0.001
TTS < 90% (%)	0.976	<0.001	0.98 [0.97 – 0.98]	<0.001
Mean saturation (%)	0.969	<0.001	0.97 [0.96 – 0.98]	<0.001
TST (min)	0.898	<0.001	0.86 [0.81 – 0.90]	<0.001
Sleep latency (min)	0.817	<0.001	0.44 [0.29 – 0.58]	<0.001
Arousal Index (/h)	0.861	<0.001	0.82 [0.76 – 0.88]	<0.001
Respiratory arousal index (/h)	0.844	<0.001	0.69 [0.58 – 0.77]	<0.001
WASO (min)	0.807	<0.001	0.88 [0.83 – 0.91]	<0.001
Awakenings (n)	0.728	<0.001	0.60 [0.47 – 0.70]	<0.001
Sleep efficacy (%)	0.770	<0.001	0.82 [0.76 – 0.87]	<0.001
REM (%)	0.827	<0.001	0.33 [0.17 – 0.48]	<0.001
N1 (%)	0.447	<0.001	0.24 [0.07 – 0.40]	0.003
N2 (%)	0.334	<0.001	0.02 [-0.19 – 0.16]	0.570
N3 (%)	0.626	<0.001	0.52 [0.38 – 0.64]	<0.001

ICC: intraclass correlation, AHI: apnea-hypopnea index, ODI: oxygen desaturation index, TTS 90%:

total time spent with a saturation < 90%; TST: total sleep time, WASO: wake after sleep onset, REM:

Rapid eye movement, N1: N1 sleep stage, N2: N2 sleep stage, N3: N3 sleep stage.

The main findings of this study were:

- No difference was seen in the objective sleep quality of patients' treated with targeted volume ventilation when compared to standard pressure support ventilation
- Similar gas control exchanges were found with either mode
- Similar compliance to treatment was achieved in both mode of ventilation
- NIV setup duration was shorter in patients randomised in the targeted volume ventilation group.

Results of our clinical trial suggest that this mode of ventilation is comparable to NIV setup using standard mode in expert centres. This study was not designed to assess outpatient NIV setup, but such trial was led with the active involvement of our centre ¹⁸⁹.

These results support the idea that automated mode of NIV could facilitate NIV setup in patients with OHS. However, we suggest that greater changes in healthcare organisation may be achieve using tele-monitoring and tele-medicine.

Chapter 4: Using telemonitored data to improve the outcome

The development of electronic tools and telecommunications is the framework for the development of tele-health. Similarly to other domains, health digitalisation is changing the way healthcare is delivered ²¹¹.

Tele-medicine is an important part of tele-health and includes different approaches:

- Tele-monitoring which consists of the remote transmission of clinically relevant medical information from the patient or a medical device to the physician. Such monitoring can rely on patient's involvement or can be automated.
- Tele-consultation which consists of a remote consultation with direct interaction between the healthcare professional and the patient.
- Tele-expertise which consists of a remote medical advice between two healthcare professionals.
- Tele-assistance which consists of a remote guidance from a healthcare professional to another whilst performing an intervention.

In France, tele-medicine has been defined since 2009 (Art. 78 law 2009-879). Tele-consultation has been reimbursed since August 2018. The use of tele-monitoring is now common in patients with OSA in our country as the reimbursement by the Social Security now depends on tele-monitoring implementation and on patient's compliance to treatment. Such approach is well accepted by patients ²¹². However to date, clinical trials have failed to demonstrate a significant benefit on clinical relevant outcomes in patients with OSA ^{213,214} despite showing an economical benefit ²¹⁵.

In patients with CRF, tele-monitoring has been shown to be an efficient way to achieve home NIV initiation ^{193,194}. Data from an Italian study suggest a benefit of a tele-medicine program with a cost reduction mainly driven by an increase in the admission free survival ²¹⁶. Conversely, in line with a randomised controlled trial in COPD patients ²¹⁷, a recent English clinical trial showed that the use of telemonitoring increases costs without objective clinical benefit ²¹⁸.

1. Reliability of data obtained from NIV software

1. Data reliability

In order to develop a telemonitoring strategy in patients treated by home NIV, we must first ensure that the data provided are accurate. Data provided by NIV software include an estimation of leaks, tidal volume, percentage of triggered breaths, respiratory rate and inspiratory time. These data are derived from the flow and pressure measured by the internal pneumotachometer of the ventilator. A major criticism about these data is related to the fact that they are acquired with low acquisition frequencies and sometimes results from calculations or estimations according non-public algorithms. Indeed, such calculations are required in order to take unintentional leaks into account. Even considered as approximations a recent bench experimentation found that the data provided are accurate ²¹⁹.

In addition to these data, NIV software can now integrate physiological data such as oximetry and display them synchronised with the flow and pressure curve. Similarly, software provides to physicians' data on the number of residual apnoeic events and their type. However, the accuracy of detection of these events were not validated on the bench test as it is difficult to simulate apneic events ²¹⁹.

2. Reliability of residual events data

a) Introduction

Expert guidelines recommend monitoring data from NIV built-in software in addition to a clinical evaluation and overnight oximetry. The residual apnoea-hypopnoea index reliability has only been evaluated for Resmed® ventilators (San Diego, USA) ^{220,221} but not for Philips Respironics® ventilators (Murrysville, USA). We conducted a study that aim to assess the accuracy of Philips NIV derived AHI (AHI_{NIV}) when compared it with overnight polygraphy (AHI_{PG}).

b) Methods

We conducted a single centre prospective service evaluation. We included all the patients admitted for setup or review of their NIV using a compatible device (A30/40, Philips, Murrysville, PA, USA) and in whom the supervising physician requested overnight polygraphy on NIV. Overnight

polygraphy was undertaken by nurses trained on polygraphy setup and was performed using an Embletta (Embla, Broomfield, USA). Polygraph was setup using abdominal and thoracic respiratory inductance plethysmography straps, finger pulse oximeter and the built-in pressure transducer connected to the NIV mask. RemLogic Version 2.0 (Embla, Broomfield, CO, USA) was used to score the polygraphy recordings. Two independent readers performed the scoring of residual events using the American Academy of Sleep Medicine criteria Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. Data from the ventilator were downloaded using dedicated software: DirectView v2.3 (Philips, Murrysville, PA, USA).

Normal distribution was assessed using Shapiro-Wilk tests. Results are expressed as number and percentages, means and standard deviation (SD) when normally distributed or medians, and inter-quartile range (IQR) when not normally distributed. Inter-observer and AHI scoring agreement was assessed using Bland and Altman plots.

c) Results

Thirty-seven polygraphs were performed between March and May 2016. Twenty-three were included in analysis (Figure 4).

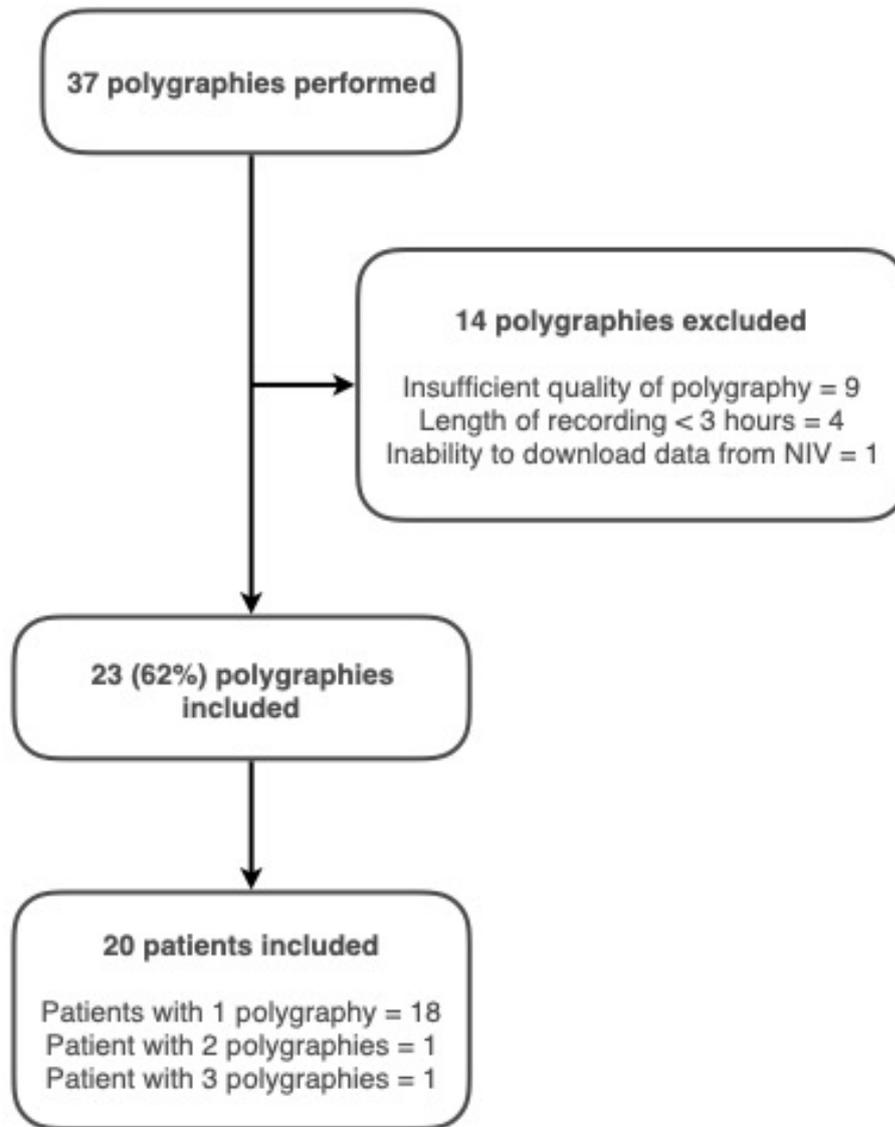


Figure 4: Study flow chart

Patient characteristics and NIV settings are summarised in table 2.

	Mean / Median / n	SD / IQ / %
Demographics		
Age (years)	65.2	14.7
Gender (male)	6	30%
BMI (kg/m ²)	42.9	8.5
FEV ₁ (L)	1.0	0.5
FVC (L)	1.5	0.5
Underlying disease		
OHS/OSA (n, %)	12	60%
COPD/OSA (n, %)	5	25%
COPD (n, %)	1	5%
OSA (n, %)	1	5%
Post-polio syndrome and OSA (n, %)	1	5%
Admission for		
Setup of NIV (n, %)	7	35
Review of NIV (n, %)	13	65
Arterial blood gas		
pH	7.4	[7.4 – 7.4]
PaCO ₂ (kPa)	6,9	1,2
PaO ₂ (kPa)	8,5	1,4
HCO ₃ ⁻ (mmol/l)	29.7	[27.7 – 30.9]
Non Invasive ventilation		
Mode		
ST (n, %)*	18	90
AVAPS-AE (n, %)*	2	10
Interface		
Full face mask (n, %)	18	90
Nasal mask (n, %)	2	10
Settings		
IPAP (cmH ₂ O)	26	[26 – 29]
EPAP (cmH ₂ O)	12	[10 – 12]
BUR (/min)	14	[14 – 16]
Ti (s)	1.2	[1.2 – 1.4]

Table 2: Population characteristics (ST: spontaneous timed / AVAPS-AE: average volume assured pressure support - auto EPAP)

The length of polygraphic recording was 400 [380 – 434] minutes. The average oxygen saturation was 89.7±3.1%. The 4% desaturation oxygen desaturation index was: 4.9 [3.6 – 6.4] per hour. The AHI_{PG} was 9.1 [6.0 – 14] per hour. The AHI_{NIV} was 4.9 [2.9 - 9.2] per hour.

Agreement between AHI_{NIV} and AHI_{PG} was low with a mean bias of - 4.4±5.7 events/h, with 95% limits of agreement: -15.6 events/h and 6.8 events/h. Agreement between the two independent scorers was high with a mean bias of - 0.1±0.7, with 95% limits of agreement: -1.4 events/h and 1.2 events/h (Figure 5).

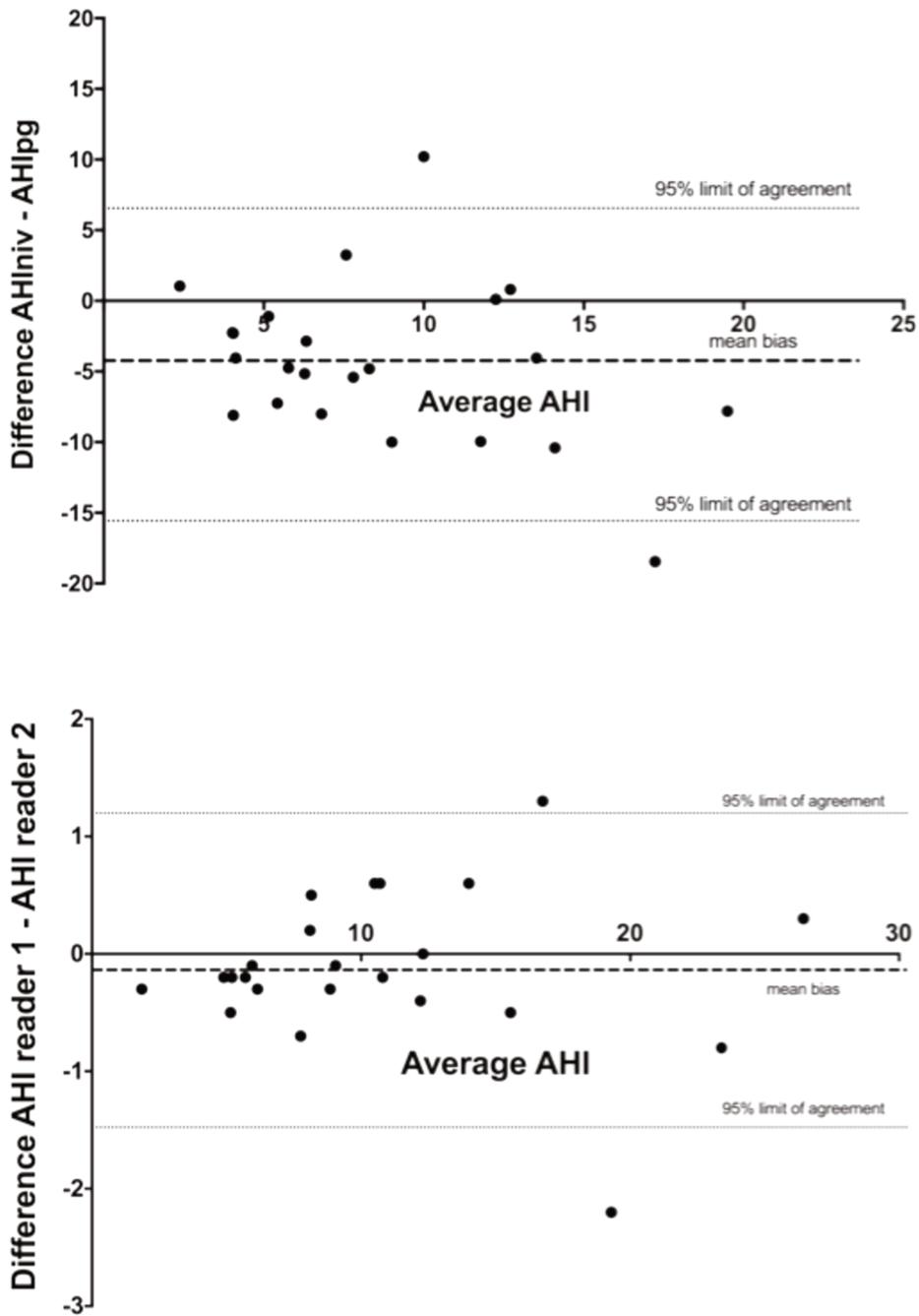


Figure 5: Agreement between AHI calculated by NIV and by manual scoring using polygraphy (A) and between the two independent polygraphy scorers (B)

Using a threshold of a residual AHI at 10/h to define satisfactory control of ventilation, the built-in software had a sensitivity of 36.4%, a specificity of 91.7%, a positive predictive value of 80% and a negative predictive value of 61%. Its Youden's index was 0.28.

d) Discussion

Our data showed that AHI derived from a NIV device may not reflect that obtained during limited respiratory polygraphy. In particular the AHI_{NIV} had poor sensitivity albeit with adequate specificity to detect clinically significant residual obstructive events. Therefore, clinicians should show care when interpreting the values with high values suggesting residual sleep disordered breathing but low values not excluding it.

Our results contrasts in previous studies ^{220,221} who showed good agreement between AHI obtained from NIV devices and polysomnography. In those studies, patients had upper airway involvement. In our study, such selection was not performed. The difference with our study can also be explained by the fact that they used different NIV devices and software to ours. The comparison of these data indicates that clinicians require independent validation of the output of derived values from medical devices to ensure accuracy and clinical utility. Other outputs obtained from NIV device software that are derived rather than directly measured are correctly identified as 'estimated' on many of the software outputs. The data from this study suggests that in a similar manner AHI should be labelled as estimated or derived to give a clear indication to the clinician that it is not interchangeable with polygraphy-acquired AHI. However, it must be acknowledged that polygraphy in this study had a significant failure rate with 13/37 recordings not providing sufficient data for analysis compared to 1/37 for the NIV device. Furthermore, polygraphies were performed during an inpatient admission. Hence, the use of NIV data are a better reflection of the domiciliary use of NIV and may better reflect patient experience (mask fitting, sleep position, etc). Therefore, this study indicates that further validation of NIV device scoring is required before it can be advocated as part of routine clinical care.

3. Perspective on the use of telemonitored data during NIV

I. Review: Technological advances in home non-invasive ventilation monitoring: Reliability of data and effect on patient outcomes (Respirology, 2019)

As data provided by NIV software are, for most of them, reliable, their use for telemonitoring is tempting. However, the last decade, NIV manufacturers have added to their ventilators remote communication abilities that are now built in. In addition, they have developed web-based interface to allow patients' remote monitoring.

Thus, telemonitoring is an available tool for patients established on NIV. In the following article, we conducted a review on the technical and clinical aspect of telemonitoring during NIV.

The review that was published in *Respirology* in 2019 ¹⁶⁸:

Borel, J.-C., Palot, A., & Patout, M. (2019). Technological advances in home non-invasive ventilation monitoring: Reliability of data and effect on patient outcomes. *Respirology*, 25, 1025. <http://doi.org/10.1111/resp.13497>



INVITED REVIEW SERIES:
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Technological advances in home non-invasive ventilation monitoring: Reliability of data and effect on patient outcomes

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ABSTRACT

Home non-invasive mechanical ventilation (NIV) has become a well-established treatment for patients with chronic hypercapnic respiratory failure. NIV monitoring has been developed to evaluate the effectiveness of mechanical ventilation on patient outcomes, with built-in systems providing data on compliance, leaks and respiratory parameters. Although these data seem intuitively useful, two main concerns have been raised in the literature: (i) are they reliable and (ii) to what extent does their use improve patient outcomes. These two concerns are currently relevant since the very recent development of telemonitoring provides the possibility of adjusting ventilator settings remotely, based on the longitudinal assessment of NIV parameters and respiratory variables provided by the system. This may influence the future management strategies of health organizations for patients under home NIV. This narrative review describes technological advances in patient monitoring using home mechanical ventilation with a main focus on data provided by built-in NIV monitoring systems. The use of these systems is discussed, including their advantages and limitations in different clinical situations, and perspectives for long-term patient monitoring are discussed.

Key words: built-in ventilator software, chronic hypoventilation, non-invasive ventilation, telemonitoring.

INTRODUCTION

Since the mid 1980s, home non-invasive mechanical ventilation (NIV) has become a well-established treatment for patients with chronic hypercapnic respiratory failure.¹ The aim of NIV is to reduce hypoventilation, alleviate symptoms and reduce healthcare utilization,

thereby improving health-related quality of life and survival.² Few data regarding the prevalence of home NIV use have been reported. More than 15 years ago, this prevalence was estimated at 6.6 per 100 000 inhabitants in Europe.¹ Since then, the number of patients using home NIV has inevitably grown, although indications and practices differ between countries.^{3–5} The ageing of populations, the increase in prevalence of extreme obesity^{6,7} and recent evidence for the benefits of NIV in patients with severe hypercapnic COPD^{8,9} have all contributed to this growth.

Along with the increased use of home NIV, methods to monitor patient outcomes have progressively developed to ensure the effectiveness of therapy, particularly during sleep (Fig. 1). Monitoring is carried out not only at treatment initiation, but also during long term follow-up. Initially, assessment of the effectiveness of NIV was limited to the control of diurnal arterial blood gases and changes in symptoms. Treatment compliance was assessed by interview and/or home visits.¹⁰ Advances in sleep medicine¹¹ have driven manufacturers to build monitoring systems into NIV devices to record data regarding compliance and leaks, as well as respiratory parameters (respiratory rate, tidal volume, minute ventilation and residual respiratory events). These technological advances are considered useful as they provide clinicians with additional information regarding the effectiveness of the ventilation and possible causes of inadequate ventilation. Moreover, recent studies have shown that changes in the values of certain parameters recorded by NIV devices may be associated with alterations in clinical status.^{12–14} However, two important concerns have been raised regarding variables recorded by NIV devices: (i) are they reliable and (ii) to what extent does their use improve patient outcomes. Recent developments in telemonitoring allow patients to be closely monitored, with the possibility of remote adjustment of ventilator settings. These developments may be a response to the increasing needs for home NIV and increasingly constrained hospital resources, and are likely to change the future management of patients under home NIV by health organizations.¹⁵ It is

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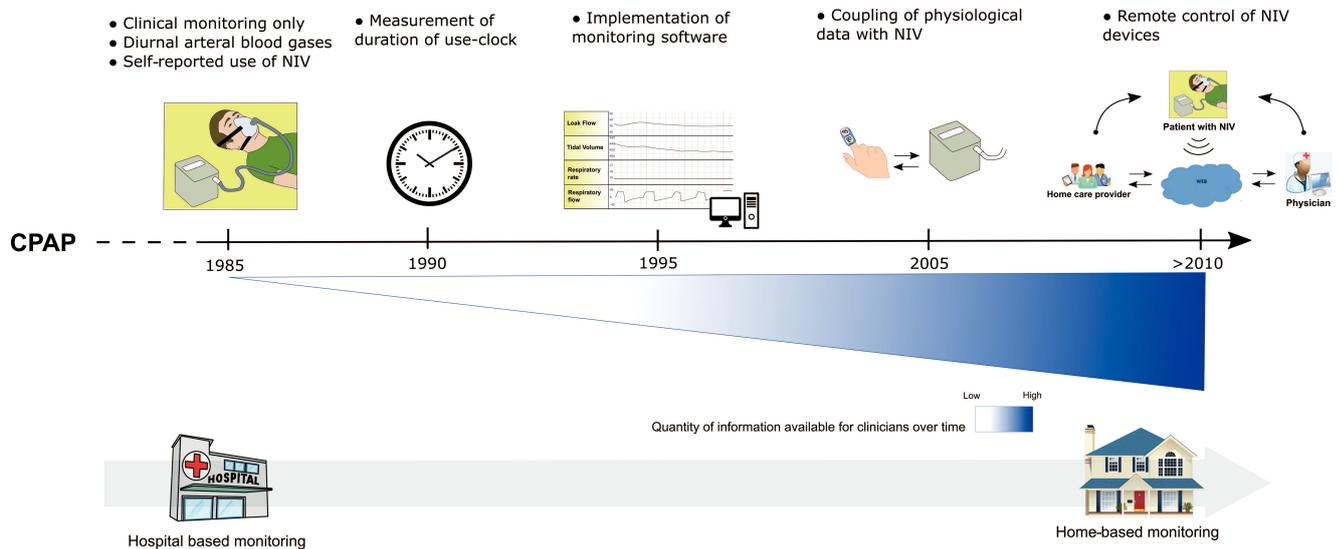


Figure 1 Timeline showing changes in the monitoring of variables for NIV. CPAP, Continuous Positive Airway Pressure; NIV, non-invasive ventilation.

therefore crucial that the data provided by NIV systems are both reliable, clinically useful, and they should lead to improvements in patient outcomes.

This narrative review describes technological advances in patient monitoring using home mechanical ventilation with a main focus on data provided by built-in NIV monitoring systems. The use of these systems is discussed, including their advantages and limitations in different clinical situations, and perspectives for long-term patient monitoring are discussed. For this narrative review, we identified references via a search carried out in PubMed from January 1995 to July 2018 that related to 'Noninvasive ventilation monitoring' in respiratory diseases. We used the search terms 'Noninvasive ventilation' or 'NIV' or 'Home Mechanical ventilation' and 'monitoring' or 'telemonitoring': *((Noninvasive ventilation) OR (NIV) OR (Home Mechanical ventilation) AND (monitoring) OR (telemonitoring)) AND ('1995/01/01'(Date - Publication): '2018/07/01'(Date - Publication)) AND English (Language)) AND respiratory(Title/Abstract))*. Studies were selected based on our expertise and perception of their relevance. We also reviewed all references cited in the studies selected. Older articles could be cited to provide background information and context. We also searched studies on different clinical registration sites using the same formula 'Noninvasive ventilation' or 'NIV' or 'Home Mechanical ventilation' and 'telemonitoring'.

NIV MONITORING SYSTEMS

NIV hardware

Home mechanical ventilators have built-in monitoring tools. The first tool developed was the ventilator timer that provides an estimate of the number of hours of daily ventilator use. In addition to ventilator use, the integrated pneumotachograph provides physicians with a summary of pressures delivered, flow, the percentage of cycles triggered by the patient, inspiratory and expiratory time, tidal volume, minute ventilation and the level of leak.

Those data are now available in almost all recent home ventilators. They are displayed on built-in screens and can be accessed directly by physicians at the bedside.

Persistent oxygen desaturation is considered as one of the major determinants of inadequate NIV adaptation and experts recommend that mean overnight oxygenation should be above 90% for 90% of the time.¹⁶ However, although it is a common practice to assess overnight oximetry values, variations in SpO₂ under NIV lack specificity and can reflect a wide variety of respiratory events.¹⁶ To simplify interpretation of SpO₂ tracings, ventilators manufactured in the mid-2000s used finger pulse oximeters to monitor oxygen saturation. Oximeters are connected to a dedicated port on the ventilator or through an external adaptor.

Data from clinical trials and cohort analyses have shown that a reduction in hypoventilation is associated with favourable outcomes.^{9,17} This has led to the integration of CO₂ monitoring in ventilators. Some manufacturers have integrated a connector to input the expired CO₂ signal; some have also integrated a transcutaneous CO₂ (PtcCO₂) monitoring signal provided by an external transcutaneous capnograph.

Patients established on NIV frequently have upper airway obstruction or may develop it whilst on NIV.¹⁸ To help clinicians diagnose residual apnoea events, manufacturers have included connectors for integrated overnight cardiorespiratory polygraphy given additional signals such as thoraco-abdominal belts.

With the development of such advanced monitoring tools, variables previously recorded in sleep laboratories can now, or will soon be, monitored at home. It is expected that this will improve the quality of home mechanical ventilation.

NIV software

The expansion of home ventilator monitoring abilities requires the parallel development of dedicated software for data recovery and analysis. The use of such software requires a licence and, in most cases, the manual

transfer of data from the ventilator to a computer using a memory card or a flash universal serial bus storage. Most ventilator software display continuous signals such as flow, pressure and leak for curve analysis and provide an automatic detection of residual apnoeic-hypopnoeic events. In addition to the data recorded by the ventilator, the software can integrate and synchronize the signals communicated by each port, for example, providing a simultaneous display of pressure and flow curves and oximetry or, capnography or cardiorespiratory polygraphy recordings. This is essential for the clinician to determine the underlying mechanisms of any occurring events.

However, each manufacturer has developed their own software, thus clinicians must adapt to the user interface of the system purchased. Moreover, the data presented by each software vary, for example, some types of software indicate the estimated unintentional leaks, whereas others indicate the estimated total leaks. The sampling frequency can also vary from one manufacturer to another which affects the display of events, such as unrewarded inspiratory efforts.

Cloud platforms

Cloud platforms are a recent development to simplify monitoring. They are automatically fed with data sent by the home ventilators (Table 1), avoiding laborious manual transfer and allowing more frequent monitoring of patients. To date, few ventilators are equipped with teletransmission systems, but this is expected to become integrated in all devices in the near future.

Data are usually transmitted to the cloud platform once a day when the ventilator is not in use. Most systems transmit a summary of pre-analysed data. This has the advantage of reducing the amount of data uploaded, although it may also result in important information being missed by the clinician. For example, occasional massive leaks that cause arousals would not show in the summary if only mean, median or percentile data regarding leaks is presented.

Another limitation of current telemonitoring systems is the fact that data are not transmitted in real time but once per day, thus close follow-up is not possible. Although rapid progress in telecommunications and decreases in costs associated with data transfer will likely soon overcome this limitation, the clinical relevance or importance of real-time telemonitoring at home remains to be demonstrated.

Telemonitoring can also be performed using trans-platform monitoring devices such as Twitoo (H2AD, St Jean Bonnefonds, France), T4P-NIV (SRETT, Boulogne-Billancourt, France) or SPIRI-NIV (Sleepinnov Technologies, Moirans, France). These systems consist of an external pneumotachograph that records use, flow and pressures delivered by the ventilator, as well as breath-by-breath data. An advantage of these systems is they can be used with all ventilator brands; however, they require an external piece of equipment on the ventilator circuit and do not include the pulse oximetry signal, or any other data that can directly be inputted in the ventilator (e.g. PtcCO₂ and abdomino-thoracic belts).

Once data have been uploaded to the cloud platform, they can be accessed by physicians using secured

access codes. Similar to NIV software and desktop platforms, the data provided by cloud platforms vary greatly in format between manufacturers. This is an important issue as it limits the development of homogenized methods of telemonitoring by clinicians. Some platforms provide alarms that automatically notify the clinician or the healthcare provider of an event. Other platforms allow a remote change of the settings of the ventilator. The functions provided by the different platforms are summarized in Table 1.

Data reliability

Data provided by ventilators are used to determine the need to optimize ventilation settings. It is therefore of great importance that they are reliable. A bench study by Contal *et al.* found that estimations of leak were reliable in most ventilators evaluated. However, the estimation of tidal volume was less accurate, with significant differences in accuracy between ventilators when significant leaks occurred.¹⁹ Regarding respiratory and back-up rates, it is not clear how the different software deal with double triggering events. However, these events are rare enough to have a limited impact on the overall reliability of respiratory rate estimation.²⁰ Reliability of respiratory rate and percentage of cycles triggered by the patient has never been studied and can be compromised by leaks or obstructive respiratory events which can mask the detection of inspiratory efforts by the patient.

It is important to screen for residual apnoea events¹⁶ and most built-in software provides residual apnoea-hypopnoea indexes (AHI). Georges *et al.* showed that the AHI provided by the RESMED ventilator is sufficiently precise to discern patients who had more than 10 events/h but that the recording of the actual number of events is not sufficiently accurate.²¹ Another study found that the AHI provided by the A40 ventilator (Philips-Respironics, Murrsville, PA, USA) was not sufficiently sensitive to detect residual sleep-disordered breathing compared to standard polygraphy.²² The reliability of AHI estimation may be limited by the fact that it is not possible to know if the patient is asleep under NIV. Manual scoring of raw data provided by built-in software of home NIV devices may be more reliable than ratings provided by the automated analyses.²³ Further studies are needed to evaluate other brands of NIV as well as other groups of patients as currently published studies mainly studied patients with obesity hypoventilation syndrome (OHS).^{21,22}

USE OF NIV DATA IN DIFFERENT CLINICAL SITUATIONS

Are NIV data useful to determine optimal NIV settings at treatment initiation?

It is not usually possible to optimize NIV device settings during a hospital stay of a few days. It commonly takes several weeks for patients to get used to the device and to become compliant, and optimization of settings can be more appropriate at this time. Data from nocturnal home monitoring by the NIV device software associated with nocturnal oximetry and capnography can thus be very useful. A randomized pilot study by Patout *et al.* found no difference in daytime

Table 1 Examples of web-access platforms for NIV telemonitoring

Web-access platforms for NIV telemonitoring	NIV or CPAP models	Specifications							
		Daily summary of NIV data (leaks, respiratory rate, etc.)	Clinical alerts can be set up	Display of overnight pressure/flow curve	Raw data download	Summary of settings	NIV setting can be changed remotely	Communication platform for the patient	Connectivity
EncoreAnywhere (Philips, Amsterdam, The Netherlands)	DreamStation BIPAP [†] and CPAP [‡] ; A30 [‡] , A40 [‡]	X	X	X (with Dreamstation only)		X	X	X (for Dreamstation CPAP only)	WiFi (Dreamstation only) and 3G
Airview (RESMED, Sydney, Australia)	Lumis-VPAP [‡] ; Aisense-S10 [†]	X	X			X	X		3G
e-Servicing Eove (EOVE, Pau, France)	EO-150 [†]	X	X	X	X	X			Wifi/Bluetooth
Everywhere (Breas, Mölnlycke, Sweden) [§]	Vivo 45 [†] , Vivo45LS [†] , Vivo50 [‡] , Vivo55 [‡] , Vivo60 [‡] , Vivo65 [‡] , Z1 [†]	X	X	X	X	X	X		Wifi/Bluetooth
Prisma CLOUD (Löwenstein Medical technology, Hamburg, Germany) [§]	Prisma-VENT30-C [‡] , Prisma-VENT40 [‡] , Prisma-VENT50 [‡] , Prisma-VENT50-C [‡] , Prisma-Smart [‡]	X				X	X		3G

[†]Built-in connectivity.

[‡]Connectivity via external plugin.

[§]Platform not yet open, available functions are subject to changes.

BIPAP, Bilevel Positive Airway Pressure; CPAP, Continuous Positive Airway Pressure; NIV, non-invasive ventilation.

PaCO₂ and adherence at 3 months in optimization of the NIV set-up for an overlap syndrome between nurse-led oximetry–capnography titration and polysomnograph measurements.²⁴ This suggests that NIV can effectively be initiated with simple tools and thus potentially at home. Hazenberg *et al.*²⁵ carried out a randomized study that showed NIV set-up at home with telemonitoring (data transmission from home ventilator, nocturnal pulse oximetry, nocturnal capnography along with telephone support) was as effective as NIV set-up in hospital. Moreover, health costs were reduced in the home set-up.

The first weeks after the initiation of NIV are crucial for long-term adherence, thus the set-up must be rapidly optimized. Early alerts to the prescribing physician with daily telemonitoring of compliance, leakage and residual AHI may allow prompt intervention and avoid rejection of the therapy by the patient as demonstrated with CPAP.²⁶

Are NIV data useful for clinical follow-up?

Nocturnal respiratory events under NIV, such as patient-ventilator asynchrony, leaks, hypoventilation, upper airway obstruction (with and without reduction of ventilatory drive) reduce both sleep quality²⁷ and NIV effectiveness, jeopardizing the treatment and the patient's prognosis.²⁸ Polysomnography under NIV is the gold-standard method for the optimization of device settings and the reduction of nocturnal respiratory events.²⁹ Vrijsen *et al.* found that residual nocturnal respiratory events under NIV were prevalent in patients with amyotrophic lateral sclerosis, justifying screening with polysomnography under NIV.³⁰ However, a single night in a sleep laboratory may be insufficient to fully correct nocturnal events. Moreover, access to in-lab may be limited by bed availability and cost. Additionally, patients generally prefer home monitoring and sleep tends to be more efficient at home.³¹ Rabec *et al.* showed that the use of data from ventilator software combined with oximetry to monitor patients reduced the majority of residual nocturnal respiratory events.³² These results suggest that set-up can be effectively optimized at home and that polysomnography under NIV can be reserved for complex cases.¹⁶ The major consequences of air leakage on both ventilation efficiency and sleep quality have been extensively described.³³ Leaks are responsible for intolerance, nocturnal awakenings, poor compliance, patient-device asynchrony and suboptimal correction of nocturnal respiratory events. Thus, telemonitoring of leaks by the home ventilator software may be very useful and would allow rapid intervention at home should adjustments be required.³⁴

Good compliance with NIV is essential to improve clinical outcomes and blood gases.^{35–37} Telemonitoring of compliance from the home ventilator is reliable and clinically useful. Intermittent use may reflect poor tolerance of the system or discomfort.³⁸ In contrast, increased NIV usage may be a marker of severity and indicates the patient should be reviewed.³⁹

Can NIV data detect changes in clinical status?

Exacerbations of respiratory disorders are a leading cause of mortality and reduce both short- and long-term quality

of life. In patients with COPD, exacerbation-related hospital admissions are a large economic burden for society.⁴⁰ Effective management strategies are needed to reduce the number of hospital admissions in patients with COPD. Most randomized trials of telemonitoring in COPD to prevent hospital admissions have found that the number of admissions was not reduced^{41–43}; however, none of these studies involved telemonitoring of data from NIV. Telemonitoring of ventilatory parameters with new generation ventilators may more effectively detect exacerbations, a contention supported by results from two studies. Borel *et al.* showed that variations in the respiratory rate and percentage of respiratory cycles triggered by the patient recorded by ventilator software were associated with the onset of an exacerbation of COPD.¹³ Blouet *et al.* also showed that the change in respiratory pattern detected using data from home ventilator software could predict admission to hospital for exacerbation.¹² Respiratory rate seems to be the most reliable parameter for the prediction of an exacerbation of COPD.^{12,13} However, these data come from pilot studies and further investigations are needed to assess whether NIV data may be useful for the monitoring of patients under NIV and for the early detection of exacerbations.

Measuring variations in daily use of NIV to detect exacerbations is less reliable as some patients tend to increase their use of NIV a few days prior to an exacerbation, while others may decrease use due to asynchrony, mucus hypersecretion or anxiety. In patients under NIV for OHS, telemonitoring with data from the device could be very useful for the early detection of cardiac decompensation. Indeed, it seems that there is an early and progressive increase in the AHI during cardiac decompensation induced by fluid accumulation.¹⁴

ACCEPTABILITY OF TECHNOLOGY AND MONITORING TOOLS FROM A SERVICE-USER PERSPECTIVE

Home telemonitoring seems to be generally well accepted by patients.⁴⁴ It may have a positive impact on their behaviour due to the sensation of security it generates, along with an increase in self-awareness of health and symptoms.⁴⁴ However, procedures that require the active participation of patients in home measurements have been shown to be associated with a progressive decline in investment and poor adherence to the monitoring system.^{45–47} Furthermore, elderly patients may feel ill at ease with new technologies.⁴⁸ In the study by Vitacca *et al.*, 32% of eligible patients with chronic respiratory failure were not included because of reduced cognitive status or insufficient family cultural requisites.⁴⁹ One advantage of telemonitoring of NIV data is that it does not require active patient involvement and thus may be more broadly utilized. Studies are warranted to assess patient engagement in telemonitoring and long-term acceptance of this procedure.

PERSPECTIVES FOR THE FUTURE OF NIV MONITORING

Results from both bench tests and clinical studies suggest that the majority of ventilatory parameters

Table 2 Ongoing clinical trials investigating telemonitoring for NIV parameters

Title	Clinical trial identifier	Sample size	Pathology	Start date	Design	Intervention	Primary outcomes and time frame	Location
Effect of the integrated telemonitoring management of NIV treatment	NCT03471091	166	COPD	2018	Multicentric RCT	Integrated telemonitoring management including uploaded daily NIV usage data	Adherence to NIV (12 months)	China
Monitoring and promoting adherence to NIV in motor neurone disease using EncoreAnywhere telemonitoring	ISRCTN17560073	40	Motor neuron diseases	2015	Monocentric RCT	Telemonitoring using 'EncoreAnywhere system' (Philips) to identify data collected daily Remote adjustment of settings on the NIV device	Adherence to NIV (3 months)	United Kingdom
Impact of a telemonitoring programme on the rate of hospitalizations for worsening of cardiorespiratory symptoms in COPD patients treated at home by long-term NIV: a randomized controlled trial	NCT02756533	140	COPD	2016	Multicentric RCT	Telemonitoring of daily parameters recorded by NIV	Number of hospitalizations for worsening of cardiorespiratory symptoms (12 months)	France
Initiation of long-term NIV in COPD RECONSIDER/	NCT02652559	72	COPD	2016	Monocentric RCT	Telemonitoring from transcutaneous PaCO ₂ , EMG measurements and data from the ventilator	Change in daytime PaCO ₂ (6 months)	The Netherlands
Pilot study evaluating feasibility and benefits of telemonitored NIV treatment on COPD patients	NCT02258191 [†]	20	COPD	2014	Monocentric RCT	Telemonitoring of daily parameters recorded by NIV via Easycare Online Platform	Blood gases and nocturnal transcutaneous carbon dioxide partial pressure (PtCO ₂) evolution	France

Source of research: <http://apps.who.int/trialsearch> search for 'non-invasive ventilation' or 'NIV' or 'home mechanical ventilation' and 'telemonitoring'. Website consulted on 1 October 2018.

[†]Recruitment completed.

EMG, electromyogram; NIV, non-invasive ventilation; PaCO₂, Arterial pressure of carbon dioxide.

recorded by software are reliable.^{19,21,23,32} However, there is minimal evidence that the use of NIV data for the management of patients under home NIV improves short- or long-term outcomes, due to the paucity of studies on this subject. Telemonitoring of NIV parameters is recent and not yet widespread.⁵⁰ To date, studies have mainly demonstrated its feasibility in different clinical situations such as initiation of NIV within the home, or to identify changes in clinical status. Most studies are single centre, with short-term follow-ups, relatively small sample sizes and driven by expert teams, which limit the representativeness of the results.^{25,34}

Several clinical trials investigating telemonitoring for NIV parameters are currently ongoing or have just been completed (Table 2). The French Health Authority (DGOS: Direction Générale de l'Offre de Soins) is funding national evaluations of telemonitoring in four different diseases: (i) diabetes, (ii) renal failure, (iii) cardiac failure and (iv) chronic respiratory failure treated by home NIV. The aim of these national studies is to improve the quality and effectiveness of care by facilitating information exchange between the professionals involved in NIV follow-up.

These studies have been designed within the regulatory frameworks of each specific disease and reflect the potential future organization of telemonitoring with regard to health professional obligations, telemonitoring system specifications, data protection and reimbursement schemes.

The framework for the monitoring of patients with chronic respiratory failure treated with NIV is as follows:

1. Telemonitoring must be prescribed and patients must give informed consent for their involvement.
2. The telemonitoring system must record at least the following parameters: daily use of NIV, respiratory rate and leaks.
3. Telemonitoring is a medical act and the physician must check for pre-determined alerts and, if necessary, determine an action plan for the patient.
4. Patients must be involved in a therapeutic education programme during the period of telemonitoring.
5. Health professionals and the telemonitoring provider receive payment for the service provided, so that the work undertaken for this clinical activity is recognized.

This experimental framework is currently applied in the French healthcare system, and we suggest each key point mentioned above should be considered when deploying telemonitoring systems in other countries. As telemonitoring alone is not likely to be sufficient to improve patient outcomes, it must be integrated with other services such as homecare, social services and access to hospital. The cost-effectiveness and cost utility of telemonitoring would be key performance indicators of such a strategy.

CONCLUSION

Over the last 20 years, the number of parameters monitored by systems built into home ventilators has grown steadily. Although these data seem intuitively useful

and, for the majority of variables, appear reliable, there is a paucity of evidence to support their effectiveness in improving outcomes in patients receiving domiciliary NIV. Telemonitoring via web platforms appears pertinent for the future management of these patients; however, although manufacturers and healthcare authorities are rushing to introduce it, it is our opinion that large-scale multicentre studies are required before-hand to assess the impact of such systems on patient outcomes.

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Abbreviations: AHI, apnoea-hypopnoea index; COPD, chronic obstructive pulmonary disease; CPAP, Continuous Positive Airway Pressure; NIV, non-invasive ventilation; OHS, obesity hypoventilation syndrome; PaCO₂, Arterial pressure of carbon dioxide; PtcCO₂, transcutaneous CO₂; SpO₂, blood oxygen saturation.

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In this review, we have seen:

- That technology to provide NIV telemonitoring is currently available.
- That studies showing a benefit from the use of such telemonitoring are sparse.

Given the increasing burden of COPD on healthcare costs ^{89,222}, patients with COPD and home ventilation are a priority target to initiate telemonitoring strategies.

II. *Improving the management of acute exacerbation*

1. Current situation

J. Original research: Efficacy of a home discharge care bundle after acute exacerbation of COPD (International Journal of COPD, 2019)

One of the goals of COPD management is to avoid hospital admission given their costs and their impact on survival ¹⁸⁷. One of the causes of hospital readmission following a severe acute exacerbation may be the lack of coordination between hospital specialists and general practitioners. Post-discharge care bundles could be a useful approach ^{223,224}.

In France, the Social Security has implemented a home discharge care bundle for patients admitted for severe exacerbation of COPD. However, this program has not been validated by a clinical randomised clinical trial.

In our centre, we reviewed the outcome of patients included in this home discharge care bundle. The results of this study were published in The International Journal of COPD ¹⁶⁹ in 2019:

Cousse, S., Gillibert, A., Salaün, M., Thiberville, L., Cuvelier, A., & Patout, M. (2019). Efficacy of a home discharge care bundle after acute exacerbation of COPD. *COPD*, 14, 289–296. <http://doi.org/10.2147/COPD.S178147>

Efficacy of a home discharge care bundle after acute exacerbation of COPD

This article was published in the following Dove Medical Press journal:
International Journal of COPD

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Purpose: Acute exacerbations of COPD (AECOPD) are frequent and associated with a poor prognosis. A home discharge care bundle, the PRADO-BPCO program, has been set up by the French National Health System in order to reduce readmission rate after hospitalization for AECOPD. This program includes early consultations by the general practitioner, a nurse, and a physiotherapist after discharge. The aim of our study was to evaluate the effect of the PRADO-BPCO program on the 28-days readmission rate of COPD patients after hospitalization for AECOPD.

Patients and methods: This was a retrospective cohort study including all patients admitted for AECOPD in our center between November 2015 and January 2017. The readmission or death rate at 28 days after hospitalization for AECOPD was compared between patients included in the PRADO-BPCO program and patients with standard care after discharge. Inclusion in the program was decided by the physician in charge of the patient.

Results: A total of 62 patients were included in the PRADO-BPCO group and 202 in the control group. At baseline, patients in the PRADO group had a more severe COPD disease and more severe exacerbations than the control group and mean inpatient stay was shorter in the PRADO group: 8.6 ± 4.3 vs 10.4 ± 7.4 days ($P=0.034$). Readmission or death rate at 28 days was similar between groups: 10 (16.1%) in the PRADO group vs 30 (14.9%) in the control group ($P=0.81$). Ninety-days readmission or death rate and overall survival were similar in the two groups.

Conclusion: In our center, despite more severe COPD and a shorter hospitalization time, the PRADO-BPCO program failed to prove a benefit on the 28 days readmission or death rate when compared with standard care.

Keywords: COPD, exacerbation, patient readmission, patient care bundles, continuity of patient care

Introduction

Acute exacerbations (AE) are frequent in patients with COPD. They occur in 16.4% of patients with COPD and more frequently in patients with very severe disease.¹ AECOPD alters quality of life² and increases mortality.³⁻⁵ Hospitalization costs for AECOPD is 678 million euros in France.⁶ Previous AECOPD is a risk factor for further admissions for AECOPD.⁷⁻¹⁰ Therefore, preventing readmission after AECOPD hospitalization is a public health priority, and most hospitals are incited to reduce 28-days readmission rates.^{11,12} Strategies to identify patients at risk have been developed^{1,13-16} and discharge care bundles have sometimes been set at a national level. A meta-analysis showed that discharge care bundle may reduce hospital readmission with a risk ratio of 0.80.¹⁸ However, none of the analyzed studies was conducted in France and with the specific French Health Care Organization. Notably, 28-days readmission rate of

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exacerbated COPD patients is low in France (7.2%),¹⁸ when compared with that in UK (20%).¹⁹

Despite this seemingly positive result, the French social welfare (Sécurité Sociale) has developed a discharge care bundle named PRADO-BPCO (Programme d'accompagnement de retour à domicile) that begun in 2015. The discharge coordinator works for the social welfare and the patient is provided with a personalized treatment plan. At discharge, patients can be referred to the social welfare to benefit from this program. If so, a discharge coordinator performs a home visit after hospital discharge and organizes a follow-up that includes outpatient appointment with the general practitioner within 7 days and with a chest physician within 2 months. During these medical appointments, smoking cessation advice is given as well as a verification of their vaccinal status regarding influenzae and *S. pneumoniae*. It also includes home weekly therapeutic education sessions provided by a nurse. During these education sessions, the nurse provides a training on the disease and the warning signs, on inhalers technique, and provides smoking cessation advice. The program also includes 30-minute sessions of home-based rehabilitation by a physiotherapist for which the exercise program is defined by the physiotherapist. In case of recurrence of AECOPD symptoms, patients are instructed to call their nurse who will then liaise with the general practitioner. The discharge care bundle does not include self-managed antibiotics or steroids. The follow-up is for 2 months after discharge but can be extended by the patient's general practitioner. Participation to PRADO is not mandatory.

The aim of this study was to assess the efficacy of PRADO discharge care bundle in patients admitted for AECOPD in our center. The primary outcome was 28-days readmission or death. The secondary outcomes were time to next severe AECOPD or death, 3-months' readmission rates, number of severe AECOPDs following discharge, and adherence to PRADO discharge care bundle.

Patients and methods

This is a retrospective monocentric cohort study including all patients admitted for AECOPD to the Rouen University Hospital department of pulmonary and intensive respiratory care, between November 2015 and January 2017.

Patients were identified using hospital electronic database. They were included if they were admitted for an AECOPD and if they had a lung function test confirming the diagnosis of COPD according to GOLD guidelines. Patients admitted for another cause than AECOPD, patients who died during inpatient stay, or who were discharged to a rehabilitation

and aftercare facility were not included. Medical history and management during inpatient stay were collected using the electronic medical record. Frequent exacerbators were defined as patients having two or more AECOPD within the last 12 months or having one severe AECOPD within the last 12 months. Severe AECOPD was defined as an AECOPD requiring hospitalization.

Data regarding follow-up and participation to the PRADO program were collected from the social welfare database. Referral to PRADO discharge bundle was decided by the senior clinician in charge of the patient. Hence, patients were allocated to the PRADO group, and were referred for the discharge care bundle, or were allocated to the control group in which they received only standard care. This study was approved by Rouen University Ethical Board (CERNI – approval E2018-65), and patients gave a written informed consent to participate. All patients' data were anonymized.

Primary outcome was defined as readmission or death within 28 days following discharge for an AECOPD. Readmission for another cause than AECOPD was not considered.

Normal distribution was assessed using Shapiro–Wilk tests. Results were expressed as number and percentages, mean and SD when normally distributed, or medians and IQR when not normally distributed. Comparisons were performed using the student's unpaired *t*-test for normally distributed continuous variable and a Mann–Whitney test for non-normally distributed continuous variable. Chi-squared test was used for categorical values. A log-binomial generalized linear model, adjusted on COPD severity (grade 3–4 vs grade 1–2) and exacerbator phenotype, was used for the multivariate analysis. The incidence rate of deaths/readmissions was estimated in a negative binomial regression. Profile-likelihood CI and likelihood ratio tests were used for statistical estimation. In order to take into account the very low number of events, a conservative exact conditional Poisson method was used to estimate the risk ratio of death at 28 days. Survival data were analyzed using the Kaplan–Meier method and Log-rank test. All tests were two-sided with type I error rate was set at 0.05. The analyses were performed using GraphPad Prism 6® for Mac OS X® (GraphPad Software, Inc., La Jolla, CA, USA), IBM SPSS® Statistics v20.0 (IBM Corporation, Armonk, NY, USA) and R (version 3.5.0, R Foundation for Statistical Computing, Vienna, Austria).

As this study was retrospective and monocentric, the sample size was not controlled. A post hoc power analysis was conducted. Assuming a 16% readmission rate in the

control group, with 62 patients in the PRADO group and 202 patients in the control group, a 5% two-sided type I error rate, the statistical power to detect a 5% absolute readmission risk reduction (31% RR reduction) would have been 18% (normal approximation power analysis). As many readmissions are not preventable and that not all preventable readmissions would be prevented by PRADO, a larger risk reduction was not considered. For a smaller 3.2% absolute readmission risk reduction (20% RR reduction), the statistical power would have been 9.4%.

Results

Six hundred twenty-six admissions of patients with COPD were identified during the inclusion period. Two-hundred ninety-four (47%) admissions were related to an AECOPD episode. Two-hundred sixty-four patients were included in the final analysis. PRADO discharge care bundle was offered to 87 (33%) patients. Among them, 25 patients declined, and 62 (23.5%) accepted to be enrolled in the PRADO discharge care bundle (Figure 1). Among the 25 patients who declined, 8 (32%) were readmitted within 28 days.

The characteristics of the study population are summarized in Table 1. Patients in the PRADO group had more severe COPD and more AECOPD prior to inclusion when compared with the control group ($P=0.02$, $P=0.008$, respectively). Inpatient management was similar between

groups except for the use of diuretics, which was higher in the control group. Inpatient stay was shorter in the PRADO group compared with controls: 8.3 ± 4.3 vs 10.4 ± 7.4 days ($P=0.034$; Table 2). In the PRADO group, the median delay to the general practitioner appointment was 4.0 (3.0–6.0) days, 3.0 (1.5–5) days to the nurse appointment, and 3.0 (1–4) days to the physiotherapist, and the mean time to the chest physician appointment was 48.1 ± 24.7 days. In the PRADO group, 53 (86%) had their general practitioner appointment within 7 days of discharge, 58 (94%) had appointment with a nurse within 7 days of discharge, 54 (87%) had a physiotherapist within 7 days of discharge, and 43 (70%) had a chest physician appointment within 2 months following discharge.

Twenty-eight days' readmission and death rate were similar between groups with 10 (16.1%) patients reaching primary end point in the PRADO group and 30 (14.9%) in the control group. Patients in the PRADO group did not have a significant lower risk for readmission (RR = 1.09 [95% CI: 0.53–2.01], $P=0.81$). During the 28 days following hospitalization discharge, two (3.2%) patients died in the PRADO group and seven (3.5%) patients died in the control group (RR = 0.93 [95% CI: 0.09–4.89], $P=1.00$). Excluding patients who died within 28 days, with or without readmission, 8 (13.3%) patients in the PRADO group and 23 (11.8%) patients in the control group had a readmission within 28 days after hospital

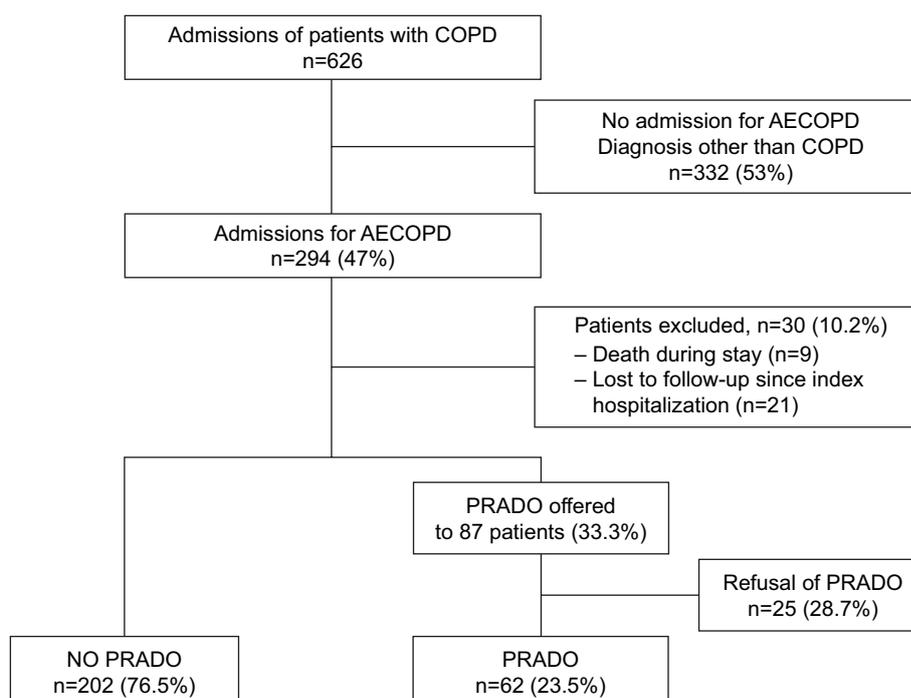


Figure 1 Study flowchart.

Abbreviations: AECOPD, acute exacerbations of COPD; PRADO, Programme d'accompagnement de retour à domicile.

Table 1 Characteristics of the patients with AECOPD

Characteristics	PRADO (n=62)		Control (n=202)		P-value
Sex ratio (M/F)	0.59	(23/39)	0.46	(64/138)	0.428
Age, years, median (IQR)	65.5 (61.4–75.3)		70.1 (63.1–77.7)		0.141
Body mass index, kg/m ² , mean ± SD	25.2±7		26.4±7.3		0.269
Diabetes, n, %	12	19.3%	40	19.8%	0.938
High blood pressure, n, %	24	38.7%	93	46.0%	0.310
Dyslipidemia, n, %	17	27.4%	61	30.2%	0.095
Chronic heart failure, n, %	20	32.2%	77	38.1%	0.402
LVEF, %, mean ± SD	59±10.4		58.3±11.8		0.750
Chronic renal failure, n, %	6	9.5%	20	9.9%	0.668
Cirrhosis, n, %	1	1.6%	4	2.0%	0.853
Depression, n, %	8	12.9%	37	18.3%	0.321
Cancer, n, %	4	6.4%	27	13.4%	0.139
Moderate-to-severe OSA, n, %	15	24.2%	37	18.3%	0.309
Excessive alcohol intake, n, %	9	14.5%	21	10.4%	0.371
Tobacco, n, %					0.839
No tobacco history	2	3.2%	10	5.0%	
Active smoker	24	38.7%	79	39.1%	
Former smoker	36	58.1%	113	55.9%	
Pack-years of smoking, mean ± SD	49.04±22.13		45.32±22.61		0.280
Baseline mMRC dyspnea grade, mean ± SD	2.36±1.25		2.50±1.64		0.668
Functional respiratory exploration					
FEV ₁ , L, mean ± SD	0.99±0.48		1.10±0.47		0.126
FEV ₁ , % of predicted value, mean ± SD	39.48±17.26		43.79±17.77		0.097
FVC, L, mean ± SD	2.20±0.84		2.19±0.81		0.946
FVC, % of predicted value, mean ± SD	67.23±20.07		67.83±21.91		0.854
TLC, L, median (IQR)	6.92 (5.62–8.42)		6.81 (5.67–8.00)		0.332
TLC, % of predicted value, median (IQR)	126 (105–148)		116 (100–134)		0.079
RV, L, mean ± SD	4.66±1.40		4.52±1.54		0.597
RV, % of predicted value, median (IQR)	225 (155–257)		188 (146–240)		0.074
KCO, %, median (IQR)	38.00 (28.00–58.50)		41.50 (31.00–64.75)		0.566
Severity of COPD (GOLD 2011), n, %					0.021
Mild	1	1.6%	7	3.5%	
Moderate	14	22.6%	55	27.2%	
Severe	22	35.5%	91	45.0%	
Very severe	24	38.7%	45	22.3%	
COPD diagnosis >5 years, n, %	29	46.8%	99	49.0%	0.758
Prior <i>Pseudomonas aeruginosa</i> isolation, n, %	9	14.5%	36	17.8%	0.545
Prior <i>Mycobacteria</i> isolation, n, %	5	8.1%	20	9.9%	0.666
Prior <i>Aspergillus fumigatus</i> isolation, n, %	11	17.7%	20	9.9%	0.093
Pulmonary rehabilitation program, n, %	8	12.9%	20	9.9%	0.502
Frequent-exacerbation phenotype	37	59.7%	86	42.6%	0.018
Number of AECOPDs within previous 12 months, n, %	1.83±1.63		1.17±1.58		0.008
Hospitalized AECOPDs within previous 12 months, n, %	1.26±1.49		0.64±1.15		0.001

Abbreviations: AECOPD, acute exacerbation of COPD; F, female; KCO, carbon monoxide transfer coefficient; LVEF, left ventricular ejection fraction; M, male; mMRC, modified British Medical Research Council dyspnea scale; OSA, obstructive sleep apnea syndrome; PRADO, Programme d'accompagnement de retour à domicile; RV, residual volume; TLC, total lung capacity.

Table 2 Characteristics of index hospitalization

Characteristics	PRADO		Non PRADO		P-value
	n=62		n=202		
Length of stay in hospital, days, mean \pm SD	8.3 \pm 4.3		10.4 \pm 7.4		0.034
ICU during stay, n, %	22	35.5%	94	46.5%	0.125
Arterial blood gas					
pH, mean \pm SD	7.38 \pm 0.08		7.37 \pm 0.09		0.554
PaO ₂ , kPa, mean \pm SD	10.4 \pm 2.6		11.2 \pm 4.7		0.208
PaCO ₂ , kPa, mean \pm SD	7.3 \pm 2.1		7.4 \pm 2.8		0.741
HCO ₃ ⁻ , mmol/L, mean \pm SD	31.3 \pm 7.3		30.3 \pm 6.9		0.313
Oxygen flow rate, L/min, median (IQR)	2 (1–3)		2.5 (0.75–4.25)		0.391
Antibiotics, n, %	47	75.8%	160	79.2%	0.569
Oral corticosteroids, n, %	25	40.3%	59	29.2%	0.100
Diuretics, n, %	11	17.7%	64	31.7%	0.033

Abbreviations: ICU, intensive care unit; PRADO, Programme d'accompagnement de retour à domicile.

discharge (RR =1.13 [95% CI: 0.50–2.29], $P=0.75$). In the multivariate analysis, inclusion in the PRADO group was neither significantly associated with 28-days readmission or death (RR adjusted [RRa] =0.99 [95% CI: 0.48–1.85], $P=0.97$) nor with the frequent exacerbator phenotype (RRa =1.09 [95% CI: 0.61–1.96], $P=0.78$), but was significantly associated with stage 3 and 4 COPD (RRa =2.89 [95% CI: 1.28–8.24], $P=0.008$).

Similar results were found at 3 months: 18 (29.0%) readmissions or deaths in the PRADO group and 55 (27.2%) in the control group (RR =1.07 [95% CI: 0.66–1.63], $P=0.78$). In the multivariate analysis, inclusion in the PRADO group (RRa =0.91 [95% CI: 0.56–1.38], $P=0.66$) was not significantly associated with 90-days, readmission or death while having a stage 3 or 4 COPD (RRa =1.63 [95% CI: 1.01–2.88], $P=0.0475$) and having a frequent exacerbator phenotype (RRa =1.66 [95% CI: 1.11–2.53], $P=0.014$) were significantly associated. At 3 months, 5 (8.1%) patients died in the PRADO group and 18 (8.9%) died in the control group (RR =0.91 [95% CI: 0.31–2.16], $P=0.83$).

The median time to readmission for AECOPD or death was not significantly different between the PRADO and the control groups: 134 (95% CI: 103–Infinity) days in the PRADO group vs 263 (95% CI: 179–363) days in the control group (HR =1.14 [95% CI: 0.74–1.76], $P=0.55$; Figure 2). Median overall survival time was not met. Overall survival was not significantly different between the PRADO and the control groups (HR =0.66 [95% CI: 0.29–1.48], $P=0.31$, Figure 3). Adjustment on stage 3/4 and on exacerbator phenotype had little effect (Hazard Ratio adjusted (HRa) =0.61 [95% CI: 0.27–1.37], $P=0.23$). The annualized number of deaths/

exacerbations was not significantly different in the two groups: 1.52 (95% CI: 1.12–2.05) readmission or death/person/year in the PRADO group vs 1.18 (95% CI: 0.99–1.41) in the control group ($P=0.16$). The median follow-up times for the overall survival in the PRADO and control groups were 228 ($Q1=101$, $Q3=362$) and 226 ($Q1=58$, $Q3=359$), respectively.

Discussion

In this retrospective cohort study, the PRADO discharge care bundle did not significantly improve 28-days readmission rate and mortality. However, patients in the PRADO group had a more severe COPD with more frequent exacerbations than those in the control group. Adjustment on these confounding had a minor effect on results.

This is the first study to assess the feasibility of a home discharge care bundle in France for the follow-up of patients hospitalized for AECOPD. Lack of access to community support following an AECOPD is a risk factor for new AECOPD.^{20,21} Our results show that the French health care organization can provide rapid access to community support. Indeed, on average, all patients in the PRADO group were referred to the general practitioner, the nurse, and the physiotherapist within 7 days after discharge.

Our study did not show a significant improvement in early (28-days) and late (90-days) readmission or mortality rate in the PRADO group when compared with controls. This could be explained by a lack of power as the post hoc power analysis shows. Furthermore, patients in the PRADO group also had a significantly higher number of severe AECOPDs prior to inclusion. Considering the retrospective design of this study, and as inclusion to the PRADO discharge care

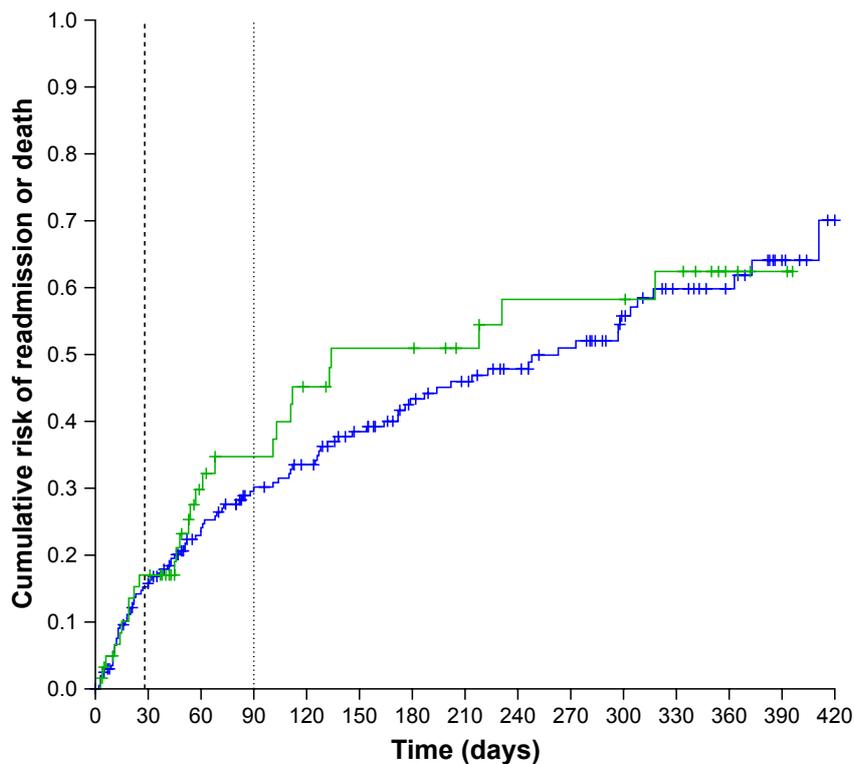


Figure 2 Cumulative risk of readmission or death in the PRADO group (green line) and in the control group (blue line) (black dashed line: 28 days – black dot line: 90 days; Log-rank: 0.37, P: 0.55).

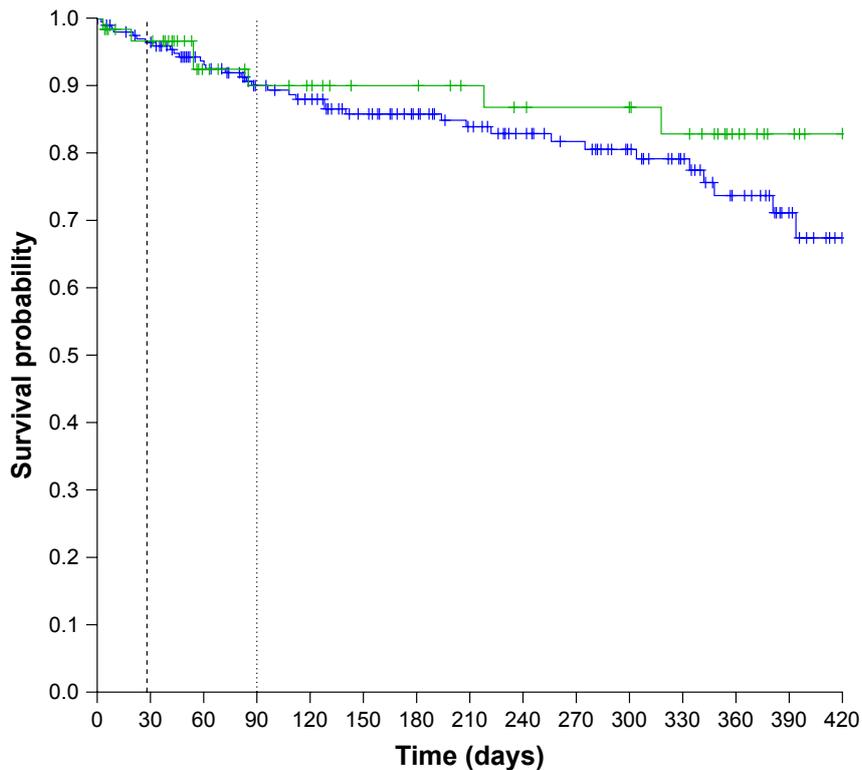


Figure 3 Probability of survival in the PRADO group (green line) and in the control group (blue line) (black dashed line: 28 days – black dot line: 90 days; Log-rank: 1.04, P: 0.31).

bundle was left to physician's judgment, we hypothesize that physicians were more likely to offer such care bundle to the most severe patients.

As this was a retrospective study, we were not able to perform a detailed phenotyping of patients during AECOPD. In contrast with stable COPD,²³ AECOPD phenotypes are not well characterized.²⁴ As patients with COPD often have comorbidities;^{25–27} such phenotyping could be useful to identify patients more likely to benefit from a home discharge care bundle. Indeed, in our population, patients in the control group were more likely to receive diuretics when compared with the PRADO group, emphasizing a different clinical presentation. Several prognostic factors for readmission have been developed,^{13,15,18} as well as noninvasive physiological assessment.^{16,28} These tools need to be evaluated to identify patients at high risk for readmission, who are more likely to benefit from a home discharge care bundle.

This study shows that patients in the PRADO group had a shorter length of stay than the control group despite being more severe. This shorter stay may have been achieved because hospital physicians were confident with the organized outpatient's follow-up. This result is important because it could contribute to the cost-effectiveness of discharge care bundle programs and such evaluation should be integrated in the future. Indeed, the trials included in the meta-analysis¹⁷ had variable interventions with variable costs. Length of stay was shorter in the PRADO group but remains higher than the average one in UK²² and Canada.²⁹ It is similar to the usual French inpatient stay duration for AECOPD, 9.9 days,⁶ illustrating another French paradox, as this longer inpatient stay could explain a lower readmission rate.¹⁸

Given health care organization in France, all patients included in the program had full access to the care. The PRADO program shows that the health care system provides rapid access to general practitioners as well as health care provided in the week following discharge. This access to care can explain why our discharge care bundle does not include self-managed antibiotic or steroids.

This study has several limitations given its retrospective design. The PRADO group is not comparable to the control group with respect to the phenotype and COPD severity of patients. This is due to a selection bias as physicians were more likely to refer patients with severe COPD to the PRADO program. However, even after adjustments for the confounding factor, we did not find any significant difference between groups. Another limitation is that patients were recruited from the initiation of the PRADO program. In 2015, this program

was new and relied on community physicians, nurses, and physiotherapists who may not have been fully aware of the program. Hence, community services may not have taken full advantage from the help of the social welfare discharge coordinator. This may have led to under-emphasize the efficacy of the program.

Conclusion

In our center, a home discharge care bundle failed to prove its efficacy on 28-days readmission and mortality after hospitalization for AECOPD. Considering longer inpatient stay for AECOPD in France compared with other countries, future randomized controlled trials evaluating the care bundle program should focus on early discharge and cost-effectiveness.

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Author contributions

SC: conception, acquisition, analysis, interpretation, drafting the work; MS, LT: interpretation and revising critically; AC: conception, interpretation, revising critically; MP: conception, acquisition, analysis, drafting the work, revising critically. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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The main findings of this study ¹⁶⁹ were:

- The rate of readmission and/or death in our COPD population was 60% at one year.
- A home discharge care bundle does not improve re-admission rate although it has been offered in a more severe group of patients.

Results from our study confirmed the need for the improvement in the home care of COPD patients as highlighted by the high readmission rate. Hence, a telemonitoring strategy in this population is justified.

2. Detecting severe acute exacerbations using NIV telemonitored data

K. Original research: Prediction of severe acute exacerbations using changes in breathing pattern of COPD patients on home non-invasive ventilation (International Journal of COPD, 2018)

Patients established on long-term home NIV with COPD have a poor prognosis ⁶⁴. NIV devices collect physiological signal such as breathing rate ¹⁸³ that is relevant during acute exacerbation. As these data can be telemonitored, the use of NIV data may be a useful tool to detect AECOPD and avoid hospital admission.

Previously, Borel *et al.* have shown that change in NIV respiratory rate could detect the onset of AECOPD and occurred prior to change in the EXACT score ²²⁵. The EXACT score is a self-administered questionnaire validated for the detection of AECOPD ^{226,227}. Results of this study have been implemented in the monitoring algorithm designed by the French Respiratory Society.

As no other data support these preliminary data, we decided to conduct an observational study to assess which change in the breathing pattern could be useful to detect severe exacerbation of COPD.

The study was published in The International Journal of COPD in 2018 ¹⁷⁰:

Blouet, S., Sutter, J., Fresnel, E., Kerfourn, A., Cuvelier, A., & Patout, M. (2018). Prediction of severe acute exacerbation using changes in breathing pattern of COPD patients on home noninvasive ventilation. *COPD*, 13, 2577–2586. <http://doi.org/10.2147/COPD.S170242>

Prediction of severe acute exacerbation using changes in breathing pattern of COPD patients on home noninvasive ventilation

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Introduction: Acute exacerbation of COPD (AECOPD) is associated with poor outcome. Noninvasive ventilation (NIV) is recommended to treat end-stage COPD. We hypothesized that changing breathing pattern of COPD patients on NIV could identify patients with severe AECOPD prior to admission.

Methods: This is a prospective monocentric study including all patients with COPD treated with long-term home NIV. Patients were divided in two groups: a stable group in which patients were admitted for the usual respiratory review and an exacerbation group in which patients were admitted for inpatient care of severe AECOPD. Data from the ventilator were downloaded and analyzed over the course of the 10 days that preceded the admission.

Results: A total of 62 patients were included: 41 (67%) in the stable group and 21 (33%) in the exacerbation group. Respiratory rate was higher in the exacerbation group than in the stable group over the 10 days preceding inclusion (18.2 ± 0.5 vs 16.3 ± 0.5 breaths/min, respectively) ($P=0.034$). For 2 consecutive days, a respiratory rate outside the interquartile limit of the respiratory rate calculated over the 4 preceding days was associated with an increased risk of severe AECOPD of 2.8 (95% CI: 1.4–5.5) ($P<0.001$). This assessment had the sensitivity, specificity, positive predictive, and negative predictive values of 57.1, 80.5, 60.0, and 78.6% respectively. Over the 10 days' period, a standard deviation (SD) of the daily use of NIV >1.0845 was associated with an increased risk of severe AECOPD of 4.0 (95% CI: 1.5–10.5) ($P=0.001$). This assessment had the sensitivity, specificity, positive predictive, and negative predictive values of 81.0, 63.4, 53.1, and 86.7%, respectively.

Conclusion: Data from NIV can identify a change in breathing patterns that predicts severe AECOPD.

Keywords: noninvasive ventilation, acute exacerbation of COPD, breathing pattern

Introduction

Acute exacerbations of COPD (AECOPD) are associated with a higher mortality and have a negative impact on the quality of life.^{1,2} AECOPD-related hospitalizations have an important economic burden for the health care system. Their cost has been estimated to 3,090USD per patient per year and is the leading driver of overall costs (56.7%).³ AECOPD-related hospitalizations are more frequent in patients with end-stage COPD.⁴

Patients with end-stage COPD benefit from the use of home noninvasive ventilation (NIV).^{5,6} Murphy et al⁵ have shown that NIV increases admission-free survival for AECOPD. In France and across Europe, COPD is one of the most common indications for home NIV.⁷

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Modern ventilators have a built-in software that records the usage of NIV and respiratory parameters such as respiratory rate, expired tidal volume, spontaneous inspirations, leaks, and residual apneic events.^{8,9} These data are reliable for the home monitoring of NIV.^{9–11} Their use is recommended by expert consensus.¹¹ Borel et al¹² have shown that data from built-in software could predict the onset of an AECOPD. They have shown that change in respiratory rate and in the percentage of triggered breaths was associated with the onset of AECOPD.¹² Such identification may trigger early therapy and alleviate the need of hospitalization.¹³ Ventilators are now equipped with tele-transmission features that may authorize tele-monitoring of these patients with advanced chronic respiratory failure. The European Respiratory Society advocates for more research in that field for COPD patients.¹³

Tele-monitoring is a promising tool for the management of COPD patients.¹⁴ However, we still have a lack of positive results from randomized controlled trials.^{15–17} In Chatwin et al,¹⁵ the negative results may be explained by day-to-day normal variability of respiratory pattern in COPD patients. Therefore, some normal changes may have triggered a non-required response from the tele-monitoring team.^{15–17}

Our hypothesis was that changes in breathing pattern recorded by the NIV built-in software would occur in patients prior to admission for AECOPD.

Our primary endpoint was to investigate the association between the change in respiratory rate and severe AECOPD. Our secondary endpoints were to assess if changes in daily compliance to NIV, leaks, tidal volume, residual respiratory events, or overnight breaks from NIV use had a predictive value for detecting severe AECOPD.

Methods

We conducted a prospective observational monocentric case-control study approved by the local ethics committee for non-interventional research (Comité d’Ethique de la Recherche non-interventionnelle du CHU de Rouen) (E2016-79) and registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03018470). In accordance with French regulation, no written consent was required. Hence, only oral informed consent was obtained.

We included all patients admitted to Rouen University Hospital respiratory ward with a confirmed diagnosis of COPD and established on long-term NIV for >4 months regardless of the reason of their admission. Based on their reason of admission, we divided the patients into the following three groups: 1) stable group that included patients with stable COPD admitted for planned outpatient respiratory review and not presenting any feature for AECOPD,

2) severe AECOPD group that included patients hospitalized for AECOPD, and 3) moderate AECOPD group that included patients admitted for planned outpatient respiratory review but had clinical features of moderate AECOPD that did not require admission.

For each patient, we retrieved their medical records and reported their comorbidities and the results of their sleep polygraphy before NIV initiation, last echocardiogram, and last lung function test. For the stable group, we used the results of the outpatient stay during which they were included in the trial. For patients with severe AECOPD, arterial blood gas and NIV settings were retrieved from their last outpatient assessment during which they had clinical stability. For patients with severe AECOPD, we collected results from admission blood samples, bacteriological sample, chest X-ray, length of stay, and outcome. Onset of exacerbation was determined using a standardized structured clinical questionnaire.

For each patient, we retrieved the memory card of their NIV devices and made a copy to a secured computer. Patients who had a mean compliance of <4 h/night were secondarily excluded.

After discharge, we performed an analysis of the data copied from the NIV memory card. For each patient, a dedicated Windows®-based software, ResScan v5.6.0 (Resmed, Moissy-Cramaye, France) or DirectView v2.4.1 (Philips Respironics, Carquefou, France), was used to analyze data from the NIV. We collected the data for each of the 10 days preceding the admission. Collected data were as follows: respiratory rate (breaths/min), daily compliance (h/day), expired tidal volume (mL), unintentional leaks (L), residual respiratory events (events/h), and overnight interruption of NIV use (interruption/night).

We assessed four different methods to evaluate a change in breathing pattern. Method A was derived from Borel’s method:¹² quartiles of each parameter were calculated over a 5-day moving window, if the value on the following day was below the first quartile or above the third quartile, it was identified as an abnormal value that had to be confirmed on 2 consecutive days. Method B was adapted from method A but included only a 4-day moving window. For method C, we performed the following analysis: standard deviation (SD) was calculated for each 2 consecutive days, if the SD varied for >5% the following day, the value was identified as abnormal and had to be confirmed for 2 consecutive days. For method D, we calculated the SD over the 10 days period.

Normal distribution was assessed using the Shapiro–Wilk test. Results are expressed as number and percentages, mean and SD when normally distributed or medians, and

interquartile range (IQR) when not normally distributed. Comparisons were performed using the unpaired *t*-test for normally distributed continuous variables and a Mann–Whitney test for non-normally distributed continuous variables. Receiver-operator characteristic (ROC) analyses were used to identify predictors of admission for AECOPD. All tests were two-sided with type I error rate set at 0.05. The analyses were performed using GraphPad Prism 6 for Mac OS X (GraphPad Software, Inc., La Jolla, CA, USA) and IBM SPSS Statistics v20.0 (IBM Corporation, Armonk, NY, USA).

Results

A total of 103 patients were included in the cohort, and 62 (60%) patients were included in the final analysis (Figure 1). Reasons for exclusions are shown in Figure 1. Patients' baseline characteristics are summarized in Table 1. All patients were ventilated using a spontaneous timed mode except three patients in the stable group who were ventilated using a volume-targeted pressure-assured mode ($P=0.519$). Patients admitted for AECOPD were similar to those admitted for their routine assessment apart from: the

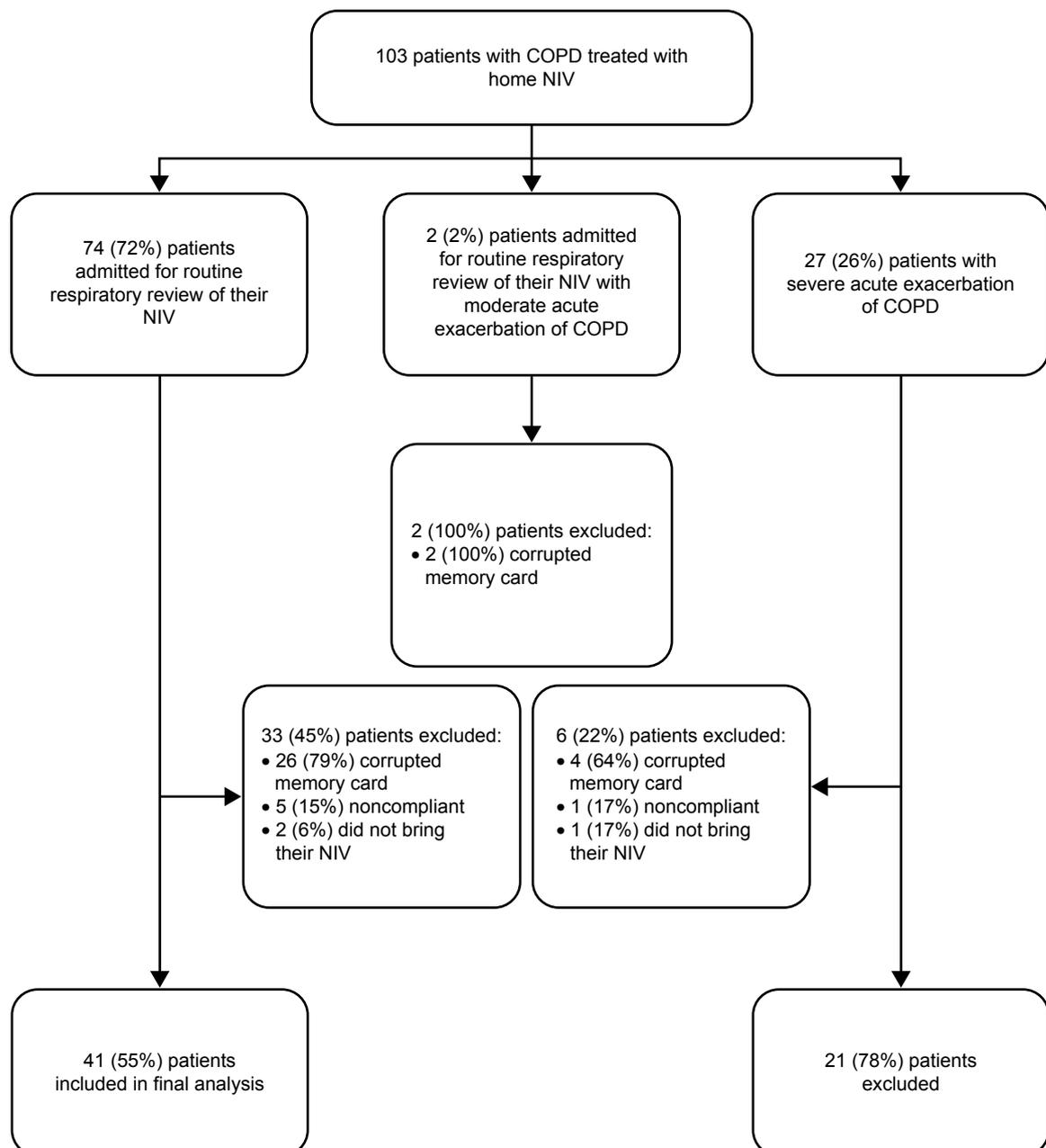


Figure 1 Study flow chart.

Abbreviation: NIV, noninvasive ventilation.

Table 1 Population characteristics (data reported as mean or median with SD or interquartile range where appropriate)

	Patients with severe AECOPD (n=21)	Stable patients (n=21)	P-value
Age (years)	69.8±1.7	66.5±1.4	0.174
Gender (male), n (%)	16 (76)	22 (54)	0.147
Comorbidities			
Hypertension, n (%)	16 (76)	27 (66)	0.586
Atrial fibrillation, n (%)	7 (33)	5 (12)	0.098
Ischemic heart disease, n (%)	3 (14)	6 (15)	0.731
Stroke, n (%)	1 (5)	9 (22)	0.731
Diabetes, n (%)	3 (14)	6 (15)	0.731
Sleep apnea syndrome, n (%)	8 (38)	14 (34)	0.976
LVEF (%) in stable state (n=43)	61.0±2.7	62.0±2.0	0.776
PAPs (mmHg) in stable state (n=39)	43.0±2.7	35.0±2.0	0.019
COPD			
Smoking history (pack-years)	40 (25–70)	40 (25–58)	0.891
Active smoker (yes), n (%)	4 (19)	9 (22)	0.949
Number of moderate AECOPD within the last 12 months	1 (0–2)	1 (0–1)	0.076
Number of severe AECOPD within the last 12 months	1 (0–2)	1 (0–1)	0.020
Days since last severe AECOPD	259 (81–895)	447 (87–969)	0.653
mMRC: from 0 to 4	3 (2–4)	3 (2–4)	0.863
COPD assessment test at admission	22 (16–23)	19 (07–23)	0.353
Lung function test at stable state			
FEV ₁ (L) (n=58)	0.71 (0.36–1.01)	0.82 (0.49–1.14)	0.293
FEV ₁ (% predicted)	29.6±3.0	37.1±3.2	0.131
FVC (L) (n=58)	1.77±0.18	1.83±0.12	0.822
FVC (% predicted)	57.7±5.5	62.5±4.8	0.538
FEV ₁ /FVC	41.1±4.0	49.4±2.6	0.078
TLC (L)	7.27 (6.8–7.9)	6.88 (6.0–7.6)	0.276
TLC (% predicted)	128 (101–143)	123 (106–148)	0.681
6-Min walking test in stable state (distance in meters) (n=43)	166 (120–368)	261 (180–337)	0.118
ABG in spontaneous breathing in stable state (n=62)			
pH	7.38 (7.37–7.41)	7.39 (7.36–7.42)	0.648
PaCO ₂ (kPa)	7.2±0.21	6.9±0.19	0.281
PaO ₂ (kPa)	9.9±0.37	10.1±0.32	0.717
Bicarbonates (mmol/L)	31.22±0.78	29.78±0.65	0.1824
ABG after 1 h on NIV in stable state (n=59)			
pH	7.40±0.01	7.42±0.01	0.072
PaCO ₂ (kPa)	6.9±0.25	6.1±0.17	0.007
PaO ₂ (kPa)	11.1±0.49	11.3±0.38	0.776
Bicarbonates (mmol/L)	30.9 (28.0–33.2)	28.1 (25.2–30.4)	0.016
NIV settings			
Positive inspiratory pressure (cmH ₂ O)	21 (19–25)	21 (19–25)	0.664
Positive expiratory pressure (cmH ₂ O)	7 (6–8)	6 (6–9)	0.670
Backup rate (1/min)	14 (12–14)	12 (12–14)	0.384

Abbreviations: ABG, Arterial Blood Gas; AECOPD, acute exacerbation of COPD; NIV, noninvasive ventilation; SD, standard deviation.

number of admission in the year preceding inclusion: one (0–2) in the severe AECOPD vs one (0–1) in the stable group ($P=0.021$), control of hypoventilation in stable state assessed by daytime PaCO₂ and bicarbonates following 1 h on NIV: 6.91±0.49 kPa and 30.9 (28.0–33.2) mmol/L in the severe AECOPD vs 6.06±0.17 kPa and 28.2 (25.3–30.5) mmol/L in the stable group ($P=0.006$ and 0.016, respectively) and for the level systolic pulmonary arterial pressure for those who had an echocardiography (n=39): 43±3 mmHg in the severe AECOPD vs 35±2 mmHg in the stable group ($P=0.019$).

Patients admitted for AECOPD had a median onset of their symptoms 2 (IQR; 1–3) days prior to admission. Vital signs, results from admission arterial blood gas, and venous blood samples are reported in Table 2. Patients admitted for AECOPD remained acidotic for a median period of 1 (IQR; 1–4) days. Their length of stay was 9 (IQR; 5–12) days. None of them required invasive ventilation or died.

Data from built-in software are reported in Table 3 and are represented over time in Figure 2. Patients with severe AECOPD had a significantly higher respiratory rate than

Table 2 Vital observations, arterial blood gas, and venous sample at admission for patients with severe AECOPD (n=21)

	Mean or median with SD or interquartile range
Observations	
Systolic blood pressure (mmHg)	141.9±5.0
Diastolic blood pressure (mmHg)	78.7±3.5
Heart rate (bpm)	93.1±3.9
Temperature (°C)	37.1±0.1
Respiratory rate (breaths/min)	23.5±1.1
Dyspnea (mMRC: from 0 to 4)	4 (3–4)
Arterial blood gas at admission	
pH	7.34±0.02
PaCO ₂ (kPa)	9.5±0.52
PaO ₂ (kPa)	8.8 (7.8–10.8)
Bicarbonates (mmol/L)	37.1±1.4
Venous blood samples	
White cell counts (g/L)	9.4 (8.1–13.8)
Neutrophils (g/L)	7.5±0.61
Eosinophils (g/L)	0.08 (0.02–0.21)
C-reactive protein (mg/L)	25 (7.5–86.5)

Abbreviations: AECOPD, acute exacerbation of COPD; SD, standard deviation.

stable patients over the 10 days preceding inclusion (18.2±0.5 vs 16.3±0.5 breaths/min, respectively) ($P=0.034$). Using linear regression, the only significant change over time was the respiratory rate in patients with severe AECOPD ($y=-0.2168 \times X + 19.55$, $P=0.049$). SD over 10 days was significantly higher for patients with severe AECOPD for respiratory rate and daily compliance when compared with the stable group (2.1 [0.8–2.6] vs 0.7 [0.4–1.2] breaths/min and 1.5 [1.0–2.4] vs 0.9 [0.7–1.3] h/day) ($P=0.003$ vs 0.021, respectively).

Usefulness of data from built-in software to predict admission for severe AECOPD according to prespecified analysis methods are reported in Table 4 and Figure 3. Respiratory rate was the parameter that gave the more consistent results regardless of the analysis method. Variability in the daily use of NIV assessed by methods C and D was the best predictor for severe AECOPD.

Discussion

We have shown that change in the breathing pattern analyzed with data provided by NIV built-in software could predict admission for AECOPD. An increased variability in respiratory rate prior to admission was consistently able to predict admission for AECOPD regardless of the method used whereas an increased variability in daily use was the strongest predictor.

Our results confirmed that respiratory rate was a good predictor to detect AECOPD. Borel et al also identified a change in the percentage of trigger breaths as a predictor for AECOPD. Such difference can be explained by the design of our respective study.¹² In Borel's study, data from NIV were collected during a long period of stable state which was used for the calculation of the quartiles. In our study, we performed all of our estimations using the data from the 10 days preceding admission. We chose this 10-day window based on the hypothesis that given the frailty of the study population, they were unlikely to exacerbate for more than 10 days prior to admission and based on technical limitations on the built-in software of ventilators used in our population. This difference could also be explained by the fact that we aimed to identify severe AECOPD whereas Borel et al¹² aimed to identify all exacerbations regardless of their severity.

Our results also differ from Borel's regarding the criteria that we identified as predictors of severe AECOPD. In his study, a change in the percentage of triggered breaths was associated with an increased risk of AECOPD. In our study, despite having a similar set back-up rate, patients with AECOPD trended to have a lower percentage of triggered breaths. This result has to be interpreted cautiously given the number of patients and the large interquartile of percentage of triggered breaths in this group (39%–90%). We hypothesize this trend to be explained by patient ventilator asynchrony that may be more frequent in exacerbating patients. In our cohort, variation in the daily use of NIV was able to predict

Table 3 Comparison of mean and SD values over the 10 days prior to admission in the stable group and in the group with severe AECOPD

	Mean or median values over 10 days			SD over 10 days		
	Patients with severe AECOPD (n=21)	Stable patients (n=41)	P-value	Patients with severe AECOPD (n=21)	Stable patients (n=41)	P-value
Respiratory rate (breaths/min)	18.2±0.8	16.3±0.5	0.034	2.1 (0.8–2.6)	0.7 (0.4–1.2)	0.003
Daily use (h/day)	8.4±0.5	8.0±0.4	0.568	1.5 (1.0–2.4)	0.9 (0.7–1.3)	0.021
Overnight breaks/night	0.6 (0.0–1.0)	0.6 (0.1–1.7)	0.627	0.7 (0–1.2)	0.5 (0.3–0.9)	0.938
Leaks (L)	5.5 (0.1–30.6)	6.2 (0–13.5)	0.583	0.8 (0.0–8.3)	2.0 (0.0–5.8)	0.902
Tidal volume (mL)	559 (435–727)	546 (463–716)	0.839	48 (31–99)	38.1 (27–101)	0.533
Percentage of triggered breath	63 (34–90)	73.8 (21–85)	0.776	10.4±1.6	7.4±0.8	0.057
Residual respiratory events	0.4 (0.2–9.3)	0.8 (0.3–2.7)	0.772	0.5 (0.3–4.7)	0.5 (0.2–1.5)	0.807

Abbreviations: AECOPD, acute exacerbation of COPD; SD, standard deviation.

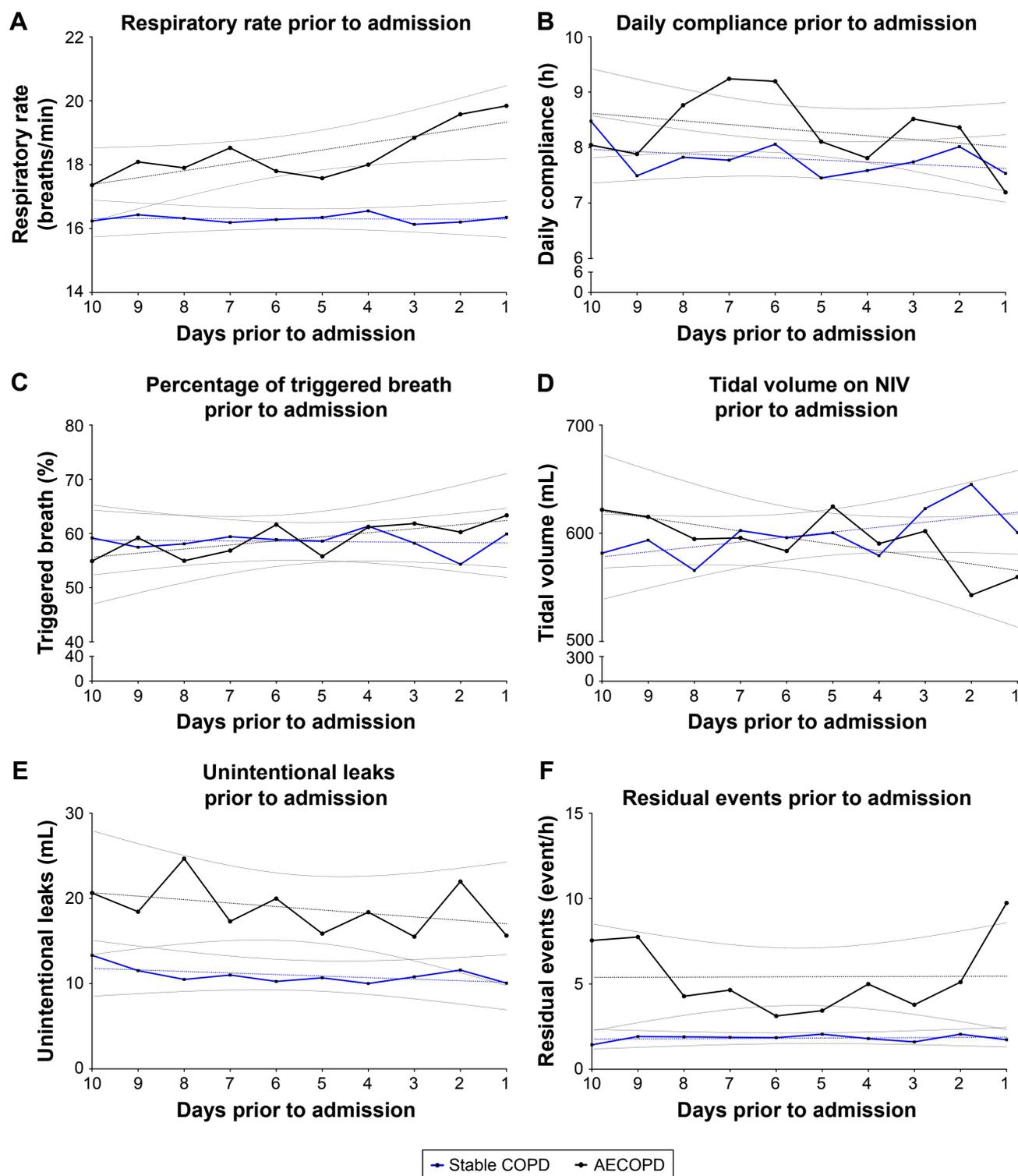


Figure 2 Change in the 10 days preceding admission (A) change in respiratory rate, (B) change in daily compliance, (C) change in triggered breath, (D) change in tidal volume on NIV, (E) change in unintentional leaks, (F) change in residual events (mean value per day for each parameter).

Abbreviations: AECOPD, acute exacerbation of COPD; NIV, noninvasive ventilation.

outcome unlike in Borel's study where daily use was only trending toward statistical significance. Daily use of NIV was only able to predict AECOPD by measuring daily variability assessed by the SD over 10 days or every 2 days but for at least 6 consecutive days. Such variability can be

explained by the fact that some patients would use their NIV more during an AECOPD and that some others would not be able to tolerate it longer due to phlegm or cough. In our cohort, we have also shown that a change in residual apneic events detected by the built-in software could predict severe

Table 4 Performance of parameters recorded by ventilator to predict severe AECOPD

	Area under the curve (95% CI)	P-value	Cutoff value	Sensitivity	Specificity	PPV	NPV	Relative risk (95% CI)	P-value
Respiratory rate									
Method A	0.675 (0.518–0.833)	0.025	2 days	57.1	87.8	70.6	0.8	3.3 (1.8–6.8)	<0.001
Method B	0.694 (0.550–0.838)	0.013	2 days	57.1	80.5	60.0	78.6	2.8 (1.4–5.5)	0.004
Method C	0.67 (0.523–0.816)	0.03	3 days	57.1	61.0	42.3	73.5	1.6 (0.8–3.3)	0.191
Method D	0.689 (0.538–0.840)	0.015	SD: 1.53	61.9	75.6	56.5	79.5	2.8 (1.3–5.6)	0.006
Daily use									
Method A	0.537 (0.392–0.682)	0.634							
Method B	0.605 (0.468–0.742)	0.178							
Method C	0.729 (0.59–0.867)	0.003	6 days	61.9	80.5	61.9	80.5	3.2 (1.6–6.4)	0.002
Method D	0.703 (0.565–0.841)	0.009	SD: 1.085	81.0	63.4	53.1	86.7	4.0 (1.5–10.5)	0.001
Percentage of triggered breath									
Method A	0.578 (0.419–0.737)	0.319							
Method B	0.629 (0.490–0.768)	0.099							
Method C	0.51 (0.361–0.66)	0.894							
Method D	0.58 (0.423–0.736)	0.308							
Tidal volume									
Method A	0.537 (0.392–0.682)	0.634							
Method B	0.663 (0.514–0.812)	0.037	2 days	66.7	56.1	43.8	76.7	1.9 (0.9–4.0)	0.112
Method C	0.646 (0.496–0.796)	0.062							
Method D	0.525 (0.380–0.670)	0.749							
Leaks									
Method A	0.505 (0.350–0.66)	0.953							
Method B	0.549 (0.400–0.699)	0.527							
Method C	0.551 (0.396–0.707)	0.513							
Method D	0.523 (0.368–0.679)	0.766							
Residual events									
Method A	0.671 (0.525–0.817)	0.029	3 days	47.6	82.9	58.8	75.6	2.4 (1.3–4.6)	0.016
Method B	0.623 (0.469–0.777)	0.115							
Method C	0.524 (0.374–0.675)	0.755							
Method D	0.531 (0.366–0.696)	0.693							
Overnight breaks									
Method A	0.574 (0.422–0.726)	0.345							
Method B	0.614 (0.466–0.763)	0.143							
Method C	0.517 (0.362–0.671)	0.829							
Method D	0.492 (0.337–0.648)	0.923							

Abbreviations: AECOPD, acute exacerbation of COPD; NPV, negative predictive value; PPV, positive predictive value; SD, standard deviation.

AECOPD that could be explained by the fact that 38% of our cohort of patients who had a severe AECOPD had concomitant obstructive sleep apnea. Rostral fluid distribution is known to increase apneic events. In patient with AECOPD, we hypothesize that acute hypoxemia induced an increase in the right ventricular pressure that leads to fluid retention. Indeed, our patients with severe AECOPD had stable higher pulmonary arterial pressure. As a result of their fluid retention and rostral redistribution, the number of apneic events may increase.

We had a significant number of patients for whom data from built-in software could not be retrieved. This can be explained by the fact that some of the memory cards were defective or missing. For others, data were not usable because of an incomplete copy of the data contained in the memory card in the computer used for the trial. As the first analyses

of the memory card were carried out 1 month after initiation of the study, we were not able to retrieve the complete data set secondarily for those with missing data. Finally, some patients did not attend to the hospital with their NIV or had insufficient use of their NIV prior to the admission.

We focused on identifying severe AECOPD in a population with severe chronic respiratory insufficiency. Identification of such an event is crucial as it could help trigger earlier treatment and avoid admission. In our cohort, patients stayed 9 (IQR; 5–12) days. Therefore, despite not using a questionnaire-based assessment of AECOPD¹⁸ as Borel et al,¹² we are confident that our patients had severe AECOPD.

New ventilators now have built-in transmission unit that allows tele-monitoring, and this has been shown to be feasible in NIV patients.¹⁹ Therefore, our results could be used for remote early identification of severe AECOPD that

may avoid hospitalization. Given the costs of hospitalization, such strategy would be likely to be cost-effective. One of the advantages of such an approach would be the fact that patients would not have to participate actively to their monitoring. This may prevent withdrawal from the tele-monitoring.^{20,21} However, to be generalized, the methods used to detect AECOPD in our study would need to be based on automatic algorithm in order to alert health care provider. This would require interoperable platforms between manufacturers' software or homogeneity of the ventilators used in each

center's cohort of patients. Given the low sensitivity of the detection methods that we used, we suggest that changes in breathing pattern should trigger an alarm to the health care provider who would then make telephone contact with the patient to further evaluate symptoms suggesting the onset of an AECOPD. Such strategy would need clinical validation and economical validation.

Our study provides new data on the ability to predict admission for AECOPD. However, the sensitivity of all the methods used remains low. Two main reasons are likely to

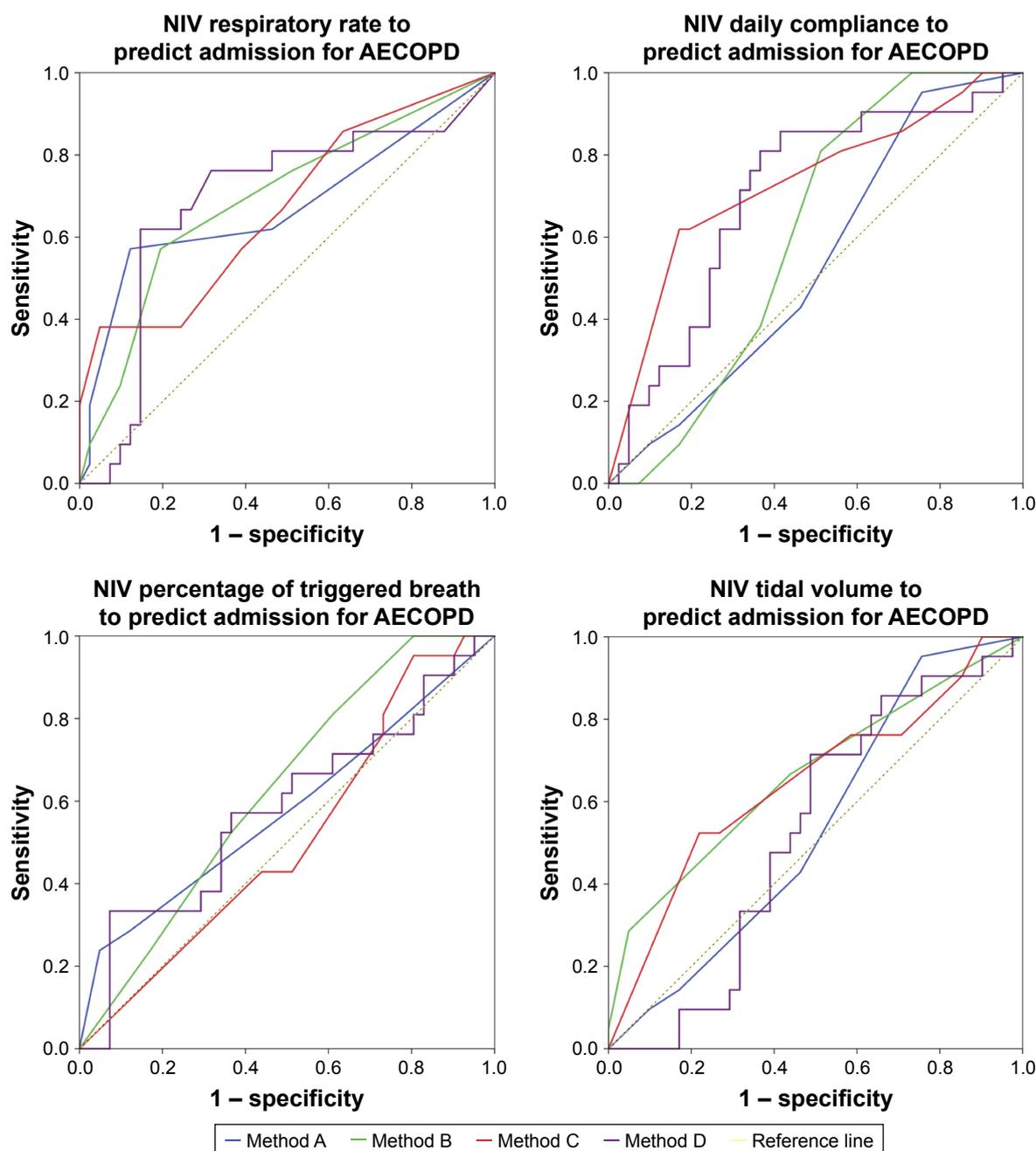


Figure 3 (Continued)

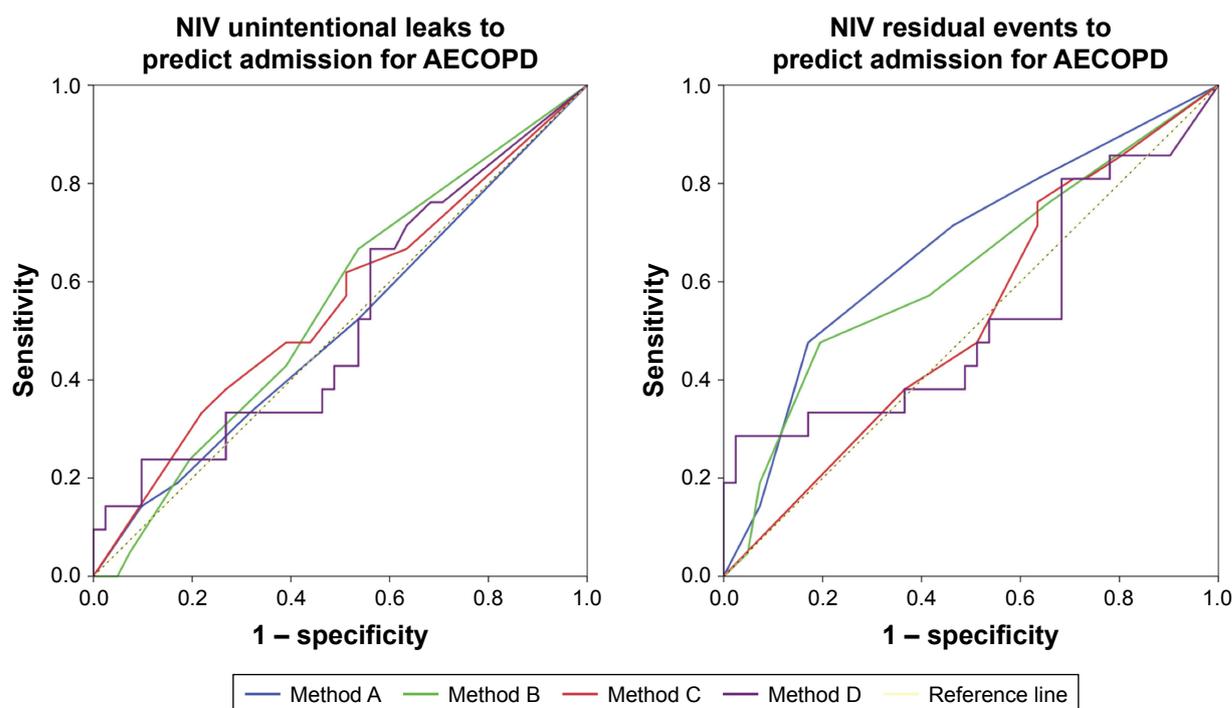


Figure 3 Receiving operator curves for the prediction of admission for AECOPD for each ventilator parameter according to methods A, B, C, and D.

explain this limit. First, the onset of an AECOPD is variable. This is highlighted by the IQR (1–3) of symptoms' onset in our patients admitted for AECOPD. Hence, if the detection method requires 2 days outside the normal values, it may not detect the change before the patient's admission. In contrast, using a detection method that assesses day-to-day variability may produce too many false positives. Second, very little is known about the normal variability of breathing pattern of patients on NIV. In this study, we only assessed individual variability over a 10-day period, but Borel et al¹² assessed normality over a more prolonged period as data were collected from inclusion to the onset of an AECOPD. Moreover, as NIV was mainly used by our patients while asleep, we think that variability in respiratory rate was minimal. However, we advocate for larger dataset to be collected in line with the recommendations of the European Respiratory Society that highlight the needs of research in the field of tele-monitoring.¹³

Conclusion

We have shown that data from NIV can identify a change in breathing patterns that predicts severe AECOPD. The clinical impact of the identification of such change remains to be evaluated.

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Disclosure

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The main findings of this study were:

- Data issued from NIV software can be used to telemonitor patients with the aim of detecting the onset of severe AECOPD.
- Exacerbation detection using telemonitored data has a poor sensitivity
- The use of telemonitoring to detect AECOPD may generate a significant number of false alarms.

Results from our study confirmed Borel's results ²²⁵. Our results also highlight that the clinical applicability of exacerbation detection is a practical challenge. Indeed, if we decide to monitor life-threatening events, we need to ensure patients that we will provide them with active management in case of an alert. To date, healthcare organisations do not provide such guarantee. This may explain why, chest physicians are reluctant to initiate home telemonitoring of home NIV patients despite funding availability (Art. 54 law 2017-1836). However, telemonitored data could be used for other purposes than exacerbation detection, as we discuss further.

III. Clinical relevance of telemonitored data to date

1. Introduction

We have seen that the implementation of exacerbation detection could be challenging. However, the use of telemonitored data could be a useful in order to improve the care quality delivered to patients.

Delivering quality of care to NIV patients is a complex process. Markers to assess the quality of ventilation are not consensual but includes:

- Efficacy of the NIV to improve gas exchange evaluated by ABG and/or overnight monitoring
- Compliance to NIV
- Breathing comfort under NIV
- Improvement in sleep quality under NIV
- Improvement in health-related quality of life
- Reduction in the number of exacerbations

Data from NIV built-in software may be a useful approach to improve sleep quality as it may help to capture events that deteriorate sleep quality or NIV efficacy. Currently, NIV data and the patient are reviewed simultaneously and always analysed with patients' feedback. However, with telemonitored data, physicians do not have this patients' feedback. Thus, it is unclear of the value that should trigger an action.

To explore this question, we conducted a simulation-based study in order to assess the impact that would have the use of telemonitored data in the long-term management of patients. The results of this collaborative work were presented at the European Respiratory Society Congress in Madrid 2019 (Oral communication).

2. Methods

We build a retrospective database that included 3-months daily NIV data of patients established on long-term NIV in Rouen university hospital. Data included in the database were: daily

compliance, leaks (median or mean and 95th or 90th percentile), tidal volume (median or mean and 95th or 90th percentile), respiratory rate (median or mean), residual apneic events, percentage of triggered breaths. Data were entered in the database by Dr. K. El Hussein and Dr. E. Dantoing. We also retrieved medical history, results from ABG's performed as part of the patient's routine care and of health-related quality of life questionnaires performed as part of the patients' routine care.

We then asked to NIV experts across France and Europe to provide us with what they would consider to be a useful algorithm to manage telemonitored data. The experts that agreed to provide an algorithm were: Profs. Cuvelier, Gagnadoux, Gonzalez, Muir, Trzepizur & Winck, Drs. Borel, Murphy, Patout, Prigent, Rabec. Mr. Dupuis a physiotherapist with an interest in NIV and an employee from ASTEN (Isneauville, France) provided an algorithm too.

Experts were informed of the data available and asked to provide a management pathway when an alert was triggered. The action that could trigger these data were: a technician phone call (11€), a home visit (100€), an overnight oximetry (74€) or an overnight capnography (95€). Costs were calculated from data provided by the home healthcare provider ASTEN.

Experts algorithm were then coded into an informatic code by Drs. Kerfourn and Fresnel (KerNel BioMedical, Bois-Guillaume, France) (Figure 6). Each expert algorithm was then run on the database.

```

8 | class Expert1(Algorithm):
9 |
10 |     used_variables = [
11 |         vt.Observance,
12 |         vt.Leaks
13 |     ]
14 |
15 |     def analysisGlobal(self):
16 |
17 |         obs7 = self.select('observance', range(7))
18 |
19 |         if obs7.mean < 4.0:
20 |             return self.onLeaks().addVariables(vt.Observance)
21 |
22 |         return Events.No()
23 |
24 |     def onLeaks(self):
25 |
26 |         ts = 50.0
27 |         l7 = self.select('leak.med', range(7))
28 |         if self.patient.machine == Machine.RESMED:
29 |             ts = 40.0
30 |             l7 = self.select('leak.95', range(7))
31 |
32 |         if l7.mean > ts:
33 |             return Events.VisitMask().addVariables(vt.Leaks)
34 |
35 |
36 |         return Events.CallPatient()

```

Figure 6: Coded version of a monitoring algorithm

3. Results

Ninety-one patients were included in the trial. Their age was 68 [59 – 67] years and 55 (60%) were male. Underlying respiratory diseases were obesity hypoventilation syndrome (n:25), COPD (n:23), COPD-OSA (n:23), neuromuscular disease (n:13) or chest-wall disease (n:7). Patients were established on NIV for 1.9 [0.8 – 5.4] years. Their PaCO₂ during self-ventilation was 5.8 [5.5 – 6.6]kPa and after one hour of NIV: 5.4 [4,6 – 6,1]kPa. Their compliance was satisfactory with a median use of 8.8 [6.6 – 10.0]hours/day. Their quality of life (assessed by the French translation of the Severe Respiratory Insufficiency questionnaire ²²⁸) was 56 [38 – 66]/100.

All experts included compliance telemonitoring. Ten (91%) included leaks, 7 (64%) respiratory rate, 6 (55%) the number of residual events, 1 (9%) the percentage of triggered breaths and none the tidal volume. Consequently, the ratio of patients for which an intervention would have been triggered by expert pathway varied from 0.2 to 1 (p<0.001) (Figure 7).

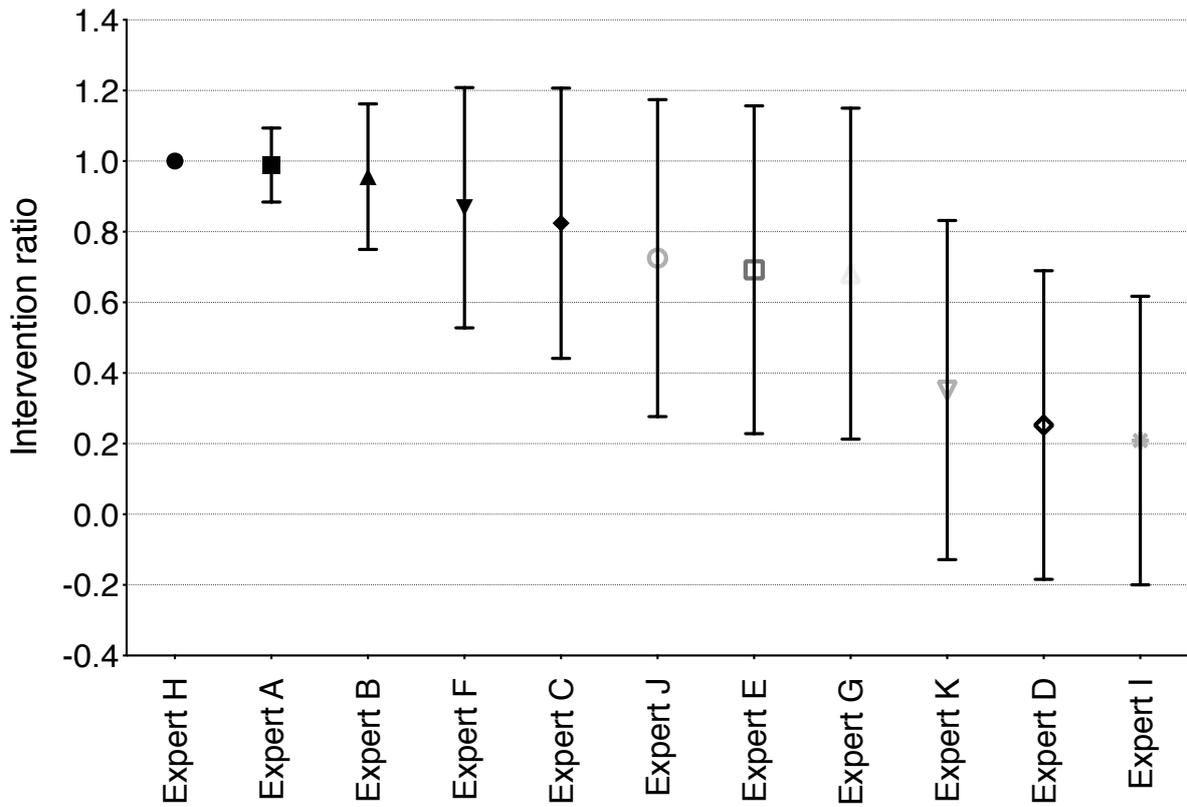


Figure 7: Intervention ratio per expert ($p < 0.001$)

In those for whom an intervention was triggered, the intervention happened from 4 to 27 days following telemonitoring initiation ($p < 0.001$). Direct costs associated to pathways varied from 216 to 3677euros for the all cohort over the 90 days period (Figure 8)

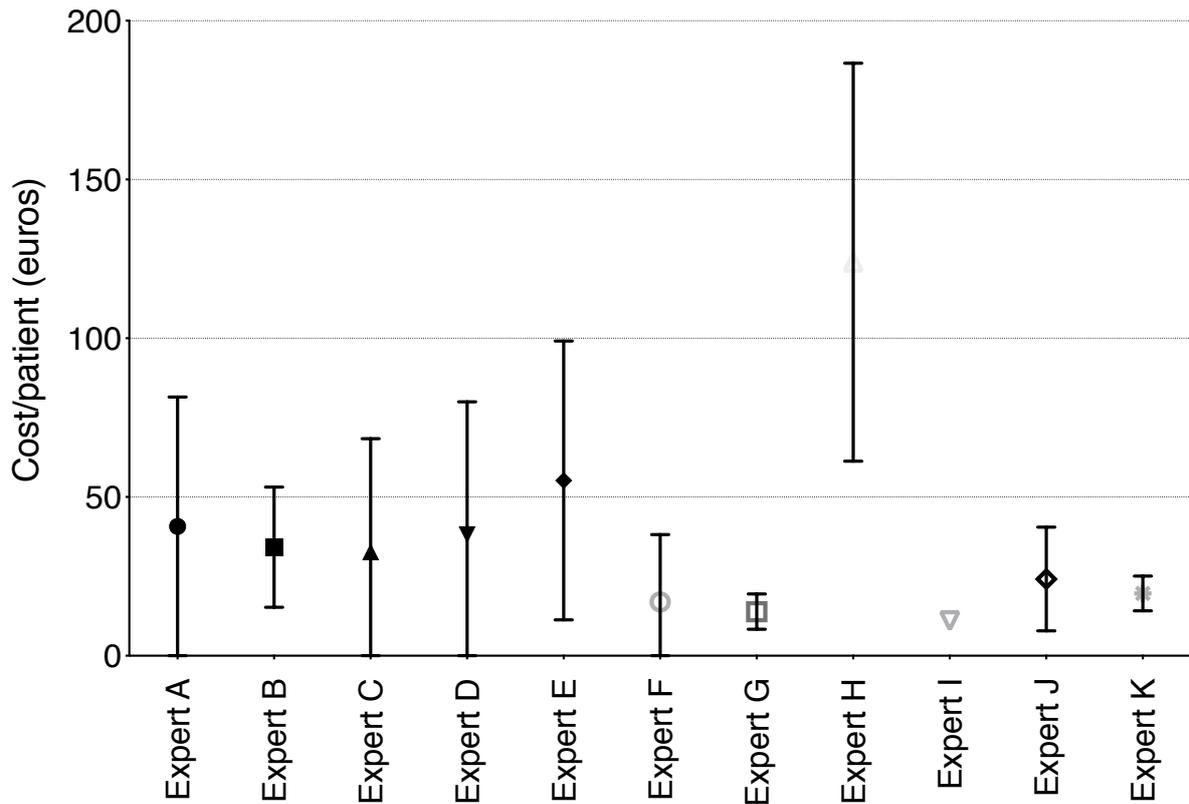


Figure 8: Costs/patient induced by each expert algorithm

4. Discussion

With this simulation study, we have shown that the use of telemonitored data induced costs in a population of stable patients setup on long term NIV with satisfactory control of their hypoventilation. The differences in the monitoring algorithm highlight the lack of data regarding the clinical relevance of NIV data without any patient feedback. Hence, the development of clinically relevant telemonitoring strategy requires more observational data and targeted large-scale trials using a multicentric approach. Our centre is actively engaged in the onset of such network of expert centres.

Chapter 5: Novel use of already established treatments for the management of chronic respiratory failure

As the benefit of telemonitoring remains to be proven in patients with CRF, we will detail in the following chapter how treatments already in place can be utilised in new ways or in novel subgroups of patients.

1. Extending the use of high-flow oxygen therapy to the home setting

1. Current use of high-flow oxygen therapy

High-flow oxygen therapy (HFO) is a new way to administrate oxygen therapy to patient. HFO devices generate a flow up to 60L/min of heated and humidified air enriched with oxygen. The inspired fraction of oxygen (F_{iO_2}) varies from 21 to 100% through a blender linked to an active humidifier. As the devices generate flows that are superior to patients' peak inspiratory flows, they can provide a F_{iO_2} up to 100% without requiring invasive ventilation. Following results from randomised controlled trials²²⁹⁻²³¹, the use of HFO has become, over the last decade, common practice in patients admitted in intensive care units for type I acute respiratory failure.

Physiological studies have shown that HFO improves airway humidification²³², airway clearance^{233,234}, increases functional residual capacity²³⁵, washes dead-space²³⁶, reduces P_aCO_2 ²³⁷, reduces work of breathing²³⁸ and improves breathlessness²³⁸. These physiological benefits are mainly attributable to the fact that HFO warms and humidifies the air delivered at a high flow to patients. All these physiological benefits are relevant in patients with CRF and especially in COPD.

Several clinical trials have assessed the potential benefit of home HFO. Rea *et al.* showed that the use of HFO lengthened time to first exacerbation but the population study was heterogeneous as also included bronchiectatic patients²³⁹. Nagata *et al.* have showed that HFO reduced daytime hypercapnia and was well tolerated with only mild side effects (night sweats (4%), nasal discharge (4%), insomnia and skin rash (1%))²⁴⁰. Overnight data suggest that HFO has no deleterious impact on overnight ventilation²⁴¹. Storgaard *et al.* showed a reduction of the number of acute exacerbations in a population of stable COPD patients. However, in that study, acute exacerbations were self-reported by the patient who was not blinded to the treatment that he received. Moreover, compliance to HFO

was low. Finally, this study evaluated stable COPD which may have led to select a population with a low risk of acute exacerbation ²⁴². A recent meta-analysis about nasal HFO in stable COPD patients confirmed no benefit in exacerbation rates but an improvement in quality of life and on daytime P_aCO₂ ²⁴³.

2. Rouen University Hospital experience in the use of high-flow oxygen therapy at home

L. Original research: Characteristics and outcome of patients set up on high-flow oxygen therapy at home (Therapeutic Advances in Respiratory Disease, 2019)

All the data available regarding the use of HFO in the home settings were from a prospective trial that did not include patients with end-stage disease. In our centre, we manage end-stage CRF. As part of the clinical care of patients, we have been using HFO in the home settings for more than ten years.

To provide some insight on the feasibility of home HFO use in the daily practice, we conducted a retrospective study that reviewed all the patients set on HFO following an acute respiratory failure and that were discharge from the respiratory intensive care unit with such a device.

The study was published in Therapeutic Advances in Respiratory diseases in 2019 ¹⁷¹:

Dolidon, S., Dupuis, J., Molano Valencia, L.-C., Salaün, M., Thiberville, L., Muir, J. F., et al. (2019). Characteristics and outcome of patients set up on high-flow oxygen therapy at home. *Therapeutic Advances in Respiratory Disease*, 13, 1753466619879794. <http://doi.org/10.1177/1753466619879794>

Characteristics and outcome of patients set up on high-flow oxygen therapy at home

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Abstract

Background: High-flow oxygen therapy (HFOT) is increasingly used for acute respiratory failure. Few data support its use at home for the treatment of chronic respiratory failure. Our aim was to report the pattern of the use of long-term HFOT in our center and the outcome of patients setup on long-term HFOT.

Methods: A retrospective monocentric study including all patients setup on long-term HFOT between January 2011 and April 2018 in Rouen University Hospital was carried out. Patients were divided into two groups, patients with hypoxemic respiratory failure treated with nasal HFOT (nHFOT) and tracheotomized patients treated with tracheal HFOT (tHFOT).

Results: A total of 71 patients were established on long-term HFOT. Out of these 43 (61%) were included in the nHFOT group and 28 (39%) were included in the tHFOT group. In the nHFOT group, underlying respiratory diseases were interstitial lung disease ($n=15$, 35%), pulmonary hypertension ($n=12$, 28%), lung cancer ($n=9$, 21%), and chronic airway disease ($n=7$, 16%). In the tHFOT group, the number of admissions for exacerbation decreased by -0.78 per year (-2 to 0) ($p=0.045$). In total, 51 (72%) patients were discharged to their homes and 20 (28%) went to a post-acute re-enablement facility. Median survival following HFOT was 7.5 months. Survival was significantly lower in the nHFOT group with a median survival of 3.6 months whereas median survival was not reached in the tHFOT group ($p<0.001$). Monthly costs associated with home delivery of HFOT were €476 (296–533) with significant differences in costs between the nHFOT group of €520 (408–628) and costs in the tHFOT group of €296 (261–475) ($p<0.001$).

Conclusions: The use of long-term HFOT allows very severe patients to be discharged at a reasonable cost from acute care facilities.

The reviews of this paper are available via the supplementary material section.

Keywords: chronic respiratory failure, high-flow oxygen therapy, home care services, oxygen therapy, palliative care

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Introduction

Long-term oxygen therapy (LTOT) is the main treatment for severe hypoxemic chronic respiratory failure. It has been demonstrated that LTOT improves survival in chronic obstructive pulmonary disease (COPD) patients.^{1,2} Its use has been extended to other etiologies of chronic respiratory failure, associated or not with home mechanical ventilation. At home, LTOT is delivered using continuous or pulse flow through an oxygen concentrator or a liquid oxygen reservoir.^{3–5}

High-flow oxygen therapy (HFOT) is a recent approach that aims to optimize oxygen delivery using specific devices. These devices can generate up to 60 l/min of heated and humidified air enriched with oxygen. The inspired fraction of oxygen (FiO_2) varies from 21–100% through a blender linked to an active humidifier. HFOT is now widely used in intensive care units for the management of acute hypoxemic respiratory failure because it reduces intubation rates.⁶

To date, trials supporting the use of HFOT at home only included patients with obstructive

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lung disease.^{7,8} Their results suggested a benefit that needs to be confirmed by larger randomized controlled trials (RCTs). However, for some patients, low flow LTOT is not sufficient to allow a safe return to their homes. In these cases, HFOT could be an interesting option. In addition to a better oxygenation, HFOT decreases the work of breathing.^{9–11} and improves dyspnea.¹² Therefore, in our center, it has been used for patients with end-stage hypoxemic respiratory disease as part of palliative management and in order to allow discharge to home.

In our center, HFOT has also been proposed for tracheostomized patients that are frequently admitted for low respiratory tract infections and that have secretion management issues. For these patients, HFOT was offered because it improves ciliary clearance,¹³ reduces the number of tracheal aspiration,¹⁴ generates a positive expiratory pressure,¹⁵ increases end-expiratory lung volumes,¹⁶ and reduces the number of exacerbations in patients with bronchiectatic diseases.¹⁷

The primary aim of our study was to describe the pattern of use of long-term HFOT in our center. The secondary aims were to describe the outcome of patients initiated on home HFOT and the costs associated with home delivery of HFOT.

Methods

We conducted a retrospective single-center study that included all patients initiated on HFOT between January 2011 and April 2018 at Rouen University Hospital. The study was approved by the Rouen University Hospital ethical committee for retrospective studies (E2018-61). Given the retrospective design of the study and the use of data already available in the patient's medical records, the need for consent was waived by the ethics committee.

In order to identify patients established on HFOT following an acute respiratory failure, we retrieved all HFOT prescriptions made to the main local home care provider (ADIR assistance, Asten, Isneauville, France). We then identified patients that had their follow up in our center. We performed a medical review of all electronic medical records and included all patients that had HFOT prescribed at home or in a post-acute re-enablement unit. We excluded patients for whom HFOT was prescribed but who died before discharge and

those who did not have any follow up in our hospital. For patients included in the study, we collected the following data using electronic medical records: gender, age, height, weight, underlying respiratory disease, smoking history, smoking status at HFOT setup, and treatments. We retrieved the last available lung function tests and echocardiography before HFOT initiation. We collected results of arterial blood gas prior to initiation of HFOT and arterial blood gas on HFOT at discharge. Previous admissions were collected from electronic medical admission registers, as well as those that followed HFOT initiation. HFOT discharge settings were established by the medical team in charge of the patient. HFOT was chosen in order to ensure sufficient oxygenation and adapted to the patient's tolerance. There was no specific protocol to determine home settings. For all following admissions, we reviewed the discharge summary to ascertain that admission was related to acute exacerbation. Acute exacerbation was defined by a worsening of respiratory symptoms associated with a change or increase in sputum color or production, and fever, abnormal chest X-Ray, or both. For all patients, all causes of acute dyspnea were overruled by the in charge physician. For patients where survival or follow up was shorter than 1 year, the number of exacerbations at 1 year follow up was calculated as follows, (number of admission during follow up/number of days of follow up) × 365. Survival data were obtained from the home care provider.

Patients were divided into two groups: patients with HFOT delivered through a nasal cannula (nHFOT) and patients with HFOT delivered through a tracheostomy cannula or a tracheal mask positioned in front of a tracheostomy cannula (tHFOT). In the nHFOT group, HFOT was initiated for oxygenation purposes. A subgroup survival analysis was performed according to the underlying pulmonary disease, interstitial lung disease, pulmonary hypertension, lung cancer, and chronic airway disease (including COPD, COPD associated with pulmonary hypertension and diffuse bronchiectasis). Only one patient had a rapidly progressive neuromuscular disease and was included in the cancer subgroup. In the tHFOT group, HFOT was initiated for humidification purposes. In this group, we assessed the number of hospitalizations related to a chest infection in the year prior to the admission and in the year following HFOT initiation. Survival was assessed in September 2018. Health costs were assessed from the home healthcare provider's

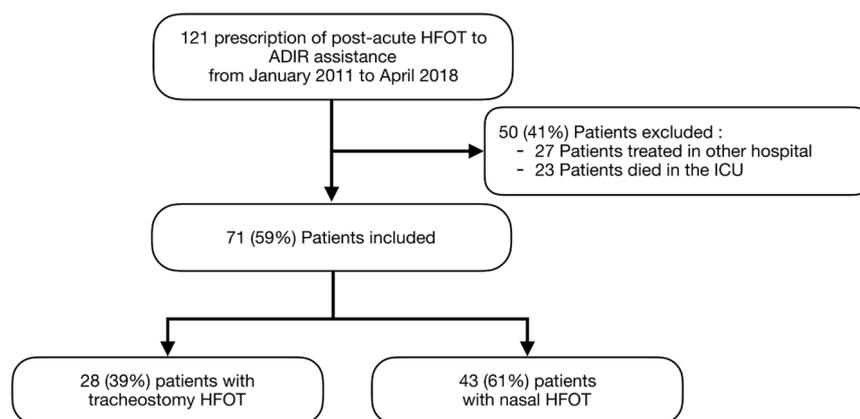


Figure 1. Flow chart for inclusion.

point of view because there is no reimbursement scheme for HFOT in France. The home health-care provider does not charge patients for HFOT delivery. HFOT costs were evaluated using the daily amortization costs, a monthly rate for consumables, and home visits performed by technicians. Oxygen costs were calculated according to the French National LTOT tariff. We were not able to include data regarding electricity costs.

Continuous data are presented as mean and standard deviation when normally distributed or median and interquartile when nonnormally distributed. Categorical data are presented as frequency counts and percentages. Comparisons were performed using the Kruskal–Wallis test, chi-squared test, and the Mann–Whitney test, as appropriate. Survival data were analyzed using the Kaplan–Meier method and log-rank test. For all tests, the significance level was set at 0.05. Analyses were performed using Prism v6.0(h) (GraphPad Software, La Jolla, CA).

Results

We retrieved 121 HFOT consecutive prescriptions. Out of those, 71 (59%) were included in our study (Figure 1). In total 43 (61%) patients were included in the nHFOT group. The underlying respiratory diseases were interstitial lung disease ($n=15$, 35%), pulmonary hypertension ($n=12$, 26%), lung cancer ($n=9$, 21%), and chronic airway disease ($n=7$, 19%). A total of 28 patients were included in the tHFOT group. The reasons for tracheostomy were neuromuscular disease ($n=12$, 40%), chest-wall

disease ($n=8$, 30%), cancer ($n=4$, 15%), and chronic airway disease ($n=4$, 15%). Patients characteristics at the initiation of HFOT are summarized in Table 1. Since 2011, the number of prescriptions of home HFOT increased annually by 96%. The HFOT devices were Airvo® (Fisher & Paykel®, Auckland, New Zealand) for 19 (27%) patients and Airvo2® (Fisher & Paykel®) for 52 (73%) patients. Patients characteristics and HFOT settings at discharge are summarized in Table 1. Arterial blood gas prior to and after home HFOT initiation are reported in Table 2. When considering only patients who had a baseline $\text{PaCO}_2 > 6$ kPa, PaCO_2 decreased significantly on HFOT with a median reduction of -0.51 kPa (-1.44 – 0.1) ($p=0.034$). Similarly, HFOT did not improve PaO_2 significantly: 0.00 kPa (-0.60 – 1.56) ($p=0.397$) in the overall population. In a subgroup analysis of patients that required oxygen supplementation on their HFOT, PaO_2 improvement on HFOT was: $+0.43$ kPa (-0.48 – 1.81) ($p=0.782$).

In the tHFOT group, the number of exacerbations decreased significantly, -0.79 per year (-2 – 0) ($p=0.045$) following HFOT initiation.

In the overall population, median survival under HFOT was 7.5 months. Survival was significantly lower in the nHFOT group with a median survival of 3.6 months after HFOT initiation when median survival was not reached in the tHFOT group ($p<0.001$) (Figure 2). Subgroup analysis in the nHFOT group showed that median survival was 1 month for lung cancer patients, 2.7 months for patients with interstitial lung

Table 1. Patient's characteristics at baseline, according to the study group.

	Total population (n = 71)	Nasal HFOT (n = 43)	Tracheostomy HFOT (n = 28)
Patients characteristics			
Age (year)	67 (55.5–73.5)	70.1 ± 14.4	55.0 ± 15.1
Gender (male) (n [%])	52 (73.1)	36 (83.7)	17 (60.7)
BMI (kg/m ²) (n = 71)	24 (21.6–27.2)	25.4 ± 4.8	24.2 ± 5.9
Tobacco (pack-years) (n = 71)	28 (0–40)	30.8 ± 29.7	22.0 ± 23.6
Previously established on home mechanical ventilation (n, [%])	29 (40.8)	12 (28%)	19 (68%)
Lung function tests			
FEV ₁ (l) (n = 42)	2 (0.8–2.3)	1.9 ± 0.8	1.2 ± 0.7
FEV ₁ (%) (n = 46)	52 (73.1)	68.8 ± 27.6	35.0 ± 20.1
FVC (l) (n = 43)	2 (1.2–3.0)	2.3 ± 1.1	1.9 ± 1.0
FVC (%) (n = 46)	65 (47.5–82.6)	76.0 ± 23.0	45.2 ± 26.6
FEV ₁ /FCV (n = 43)	75 (60.6–80.0)	69.9 ± 17.6	65.8 ± 20.8
TLC (l) (n = 38)	5 (4.2–6.8)	5.6 ± 1.9	5.1 ± 2.1
TLC (%) (n = 40)	89 (74.8–109.3)	91.0 ± 25.1	91.5 ± 38.0
KCO (%) (n = 24)	58 (39.0–71)	54.2 (30.4–73.03)	67.4 (50.5–100.3)
Echocardiography			
TRV (m/s) (n = 28)	3 (2.8–3.8)	3.6 ± 0.6	2.2 ± 1.3
PASP (mmHg) (n = 25)	62 (46.0–77.0)	59.7 ± 18.63	41.4 ± 13.99
LVEF (%) (n = 24)	55 (47.8–60.0)	56.1 ± 10.8	52.1 ± 9.3
Arterial blood gas on HFOT during inpatient stay			
pH (n = 44)	7.44 (7.42–7.48)	7.45 ± 0.05	7.46 ± 0.04
PaCO ₂ (kPa) (n = 44)	5.56 (4.90–6.50)	5.78 ± 1.41	6.11 ± 1.40
PaO ₂ (kPa) (n = 44)	9.60 (8.80–10.60)	9.30 ± 1.31	11.23 ± 5.00
Bicarbonate (mmol/l) (n = 44)	29.6 (25.9–34.9)	29.96 ± 6.66	32.17 ± 7.36
HFOT settings			
Air flow (l/min) (n = 51)	25 (15–40)	24.7 ± 11.2	32.4 ± 12
FiO ₂ (n = 57)	41 (29–63)	62.9 ± 19.7	28.5 ± 9.9
O ₂ flow (l/min) (n = 63)	6 (3–15)	12.9 ± 7.6	2.3 ± 2.7
BMI, body mass index; FEV ₁ , forced expiratory volume in 1 second; FVC, forced vital capacity; HFOT, high-flow oxygen therapy; LVEF, left ventricular ejection fraction; TLC, total lung capacity; KCO, transfer coefficient of the lung for carbon monoxide; TRV, tricuspid regurgitation peak velocity; PASP, pulmonary artery systolic pressure.			

Table 2. Patients arterial blood gas prior to and following home HFOT therapy initiation.

	Prior to HFOT initiation	Arterial blood gas on discharge home HFOT settings	<i>p</i> value
Administered FiO ₂	26 (21–48)	26 (21–39)	0.563
pH	7.44 (7.40–7.49)	7.44 (7.42–7.48)	0.657
PaCO ₂ (kPa)	5.6 (4.4–6.6)	5.4 (4.9–6.6)	0.739
PaO ₂ (kPa)	9.6 (7.8–10.9)	9.7 (8.9–10.7)	0.397
Bicarbonates (mmol/l)	28.3 (23.8–34.4)	29.4 (24.7–34.6)	0.392
Saturation (%)	95 (90–97)	95 (93–96)	0.214

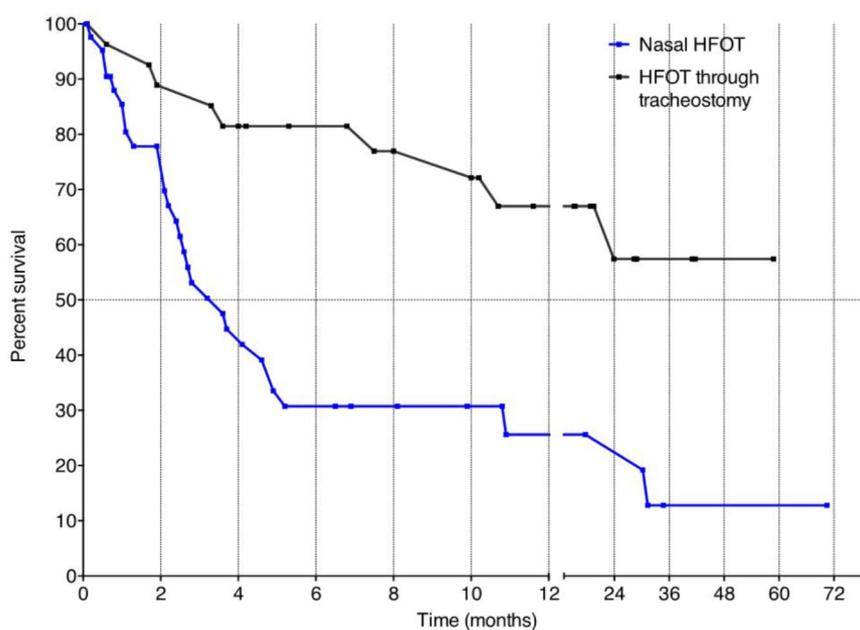
HFOT, high-flow oxygen therapy; FiO₂, fraction of inspired oxygen.

disease patients, and 30.2 months for patients with pulmonary hypertension.

After HFOT initiation, 51 (72%) patients returned home and 20 (28%) were admitted to a post-acute re-enablement unit and then a long-term care facility. For the 51 patients discharged to their homes, 31 (61%) were in the nHFOT group and 20 (39%) in the tHFOT group. For the 51 patients discharged to their homes, 28 (55%) required a liquid oxygen installation, 15 required (30%) oxygen concentrators and 7 (15%) did not require any oxygen. For those who required liquid oxygen, the median number of

liquid oxygen tanks installed was 4 (3–4). The median FiO₂ was 63% (47–76) in the nHFOT group and 23% (21–30) in the tHFOT group ($p < 0.001$). The length of stay at home was 29.3 weeks (11.6–73.3) in the overall population with the difference between groups, 15.7 weeks (0.3–35.1) in the nHFOT group and 65.9 weeks (30.7–122) in the tHFOT group ($p < 0.001$).

The cost of HFOT setup without any oxygen supplementation was estimated at €231 for the first month of use. In the overall population, including costs associated with oxygen delivery, the total cost of HFOT setup was €2455 (1337–4995) with

**Figure 2.** Probability of survival in months according to the use of HFOT through the nose or the tracheostomy ($p < 0.001$, log-rank).

significant differences between groups, €1712 (1174–3177) in the nHFOT group and €4005 (2291–9931) in the tHFOT group ($p=0.009$). Monthly costs for HFOT were €476 (296–533) in the overall population with significant differences between groups, €520 (408–628) in the nHFOT group and €296 (261–475) in the tHFOT group ($p<0.001$). HFOT contributed to $59 \pm 25\%$ of the total cost for the home care provider in the overall population with significant differences between groups, $48 \pm 20\%$ in the nHFOT group and $75 \pm 22\%$ in the tHFOT group ($p<0.001$).

In total, four patients were discontinued from nHFOT and one patient with interstitial lung disease did not tolerate HFOT because of warmth. Overall, three patients improved after the acute episode, one with lung cancer who had been established on HFOT following complete lung atelectasis that resolved after PD-L1 immunotherapy with complete oxygen weaning and two with pulmonary hypertension who improved sufficiently to be switched to standard LTOT.

Discussion

Our study reports the largest cohort of patients treated with HFOT at home or in a post-acute re-enablement facility. In patients with end-stage respiratory failure and high oxygen requirements, survival was poor but HFOT allowed patients to return home. In tracheostomized patients admitted for lower respiratory tract infections, the use of HFOT may have lowered exacerbation rate after HFOT initiation.

In our cohort, HFOT was used to treat end-stage hypoxemic respiratory failure in severe patients. Given the retrospective design of our study, we were not able to assess the quality of life of these patients. However, as part of our clinical practice, we only offered discharge with home HFOT for patients who wanted to return home. All but one patient tolerated HFOT well enough to use it at home. In the nHFOT group patients that were discharged to their homes ($n=31$) the median FiO_2 was 63%. This highlights the severity of their respiratory diseases and they would not have been able to be discharged on low flow LTOT. With a median length of stay at home of 15.7 weeks, we believe that HFOT allowed these 31 patients to spend a meaningful length of time at home. This result needs to be supported by prospective trials focused on patient-centered outcomes.

To the best of our knowledge, our cohort is the first to report the use of such a high FiO_2 in the home settings. The technical and organizational challenges need to be overcome to achieve such levels of oxygenation in the home setting. Usually, LTOT is provided through a concentrator or a tank to store liquid oxygen. In our cohort, patients had a median number of four liquid oxygen tanks. Each tank requires 1m^2 of room space to be stored safely in the patient's homes. As patients with chronic respiratory failure often have limited income, such devices may not be installed in every household. As HFOT devices are not provided with a built-in battery, electrical back-up also needs to be installed in patient's houses.

In our cohort, HFOT associated total cost was €1712 per patient in the nHFOT group. Our study was not designed to assess cost-effectiveness. However, the individual cost appears to be significantly lower than the cost that would have been associated to an inpatient stay until the patients died. For patients with tHFOT, monthly costs were lower given the lower oxygen requirements. In the tHFOT group, the total cost per patient was higher given the longer period of use of HFOT. In patients with nHFOT, the costs are driven by oxygen delivery costs. Costs of HFOT without any oxygen delivery are acceptable at €261 per month.

Our study was not designed to assess the efficacy of HFOT in an exacerbation. The pre and post-analysis suggested a reduction in the number of admissions for low respiratory tract infection following initiation of tHFOT. Therefore, the cost of HFOT may be counterbalanced by a lower readmission rate. The reality of the reduction of exacerbation, as well as the cost-effectiveness of such an approach, needs to be assessed more thoroughly. This reduction in the number of admissions has been achieved with a higher delivered airflow than the one reported in most clinical trials.^{16,18,19} Given the design of our study, we were not able to assess any correlation between the level of flow and the number of exacerbations.

Patients included in our cohort were all characterized by severe pulmonary disease or respiratory muscle weakness. Therefore, our patients were more severe than those included in RCTs evaluating the benefit of home HFOT. Of interest, the subgroup of patients with hypercapnia at baseline had a similar PaCO_2 improvement on HFOT to that seen in published trials.^{7,20} In our hypercapnic

subgroup, PaCO₂ improved by 0.51 kPa. This improvement corresponds to the cutoff usually used to assess the clinical effectiveness of noninvasive ventilation.^{21,22} However, appropriately titrated noninvasive ventilation achieved a larger decrease in PaCO₂ level in COPD patients.^{23,24}

Our study has limitations given its retrospective design and the heterogeneity of our cohort that included patients with severe respiratory disease of variable etiology and patients with muscular weakness. However, it provides real-life data on the management and the outcome associated with the use of HFOT outside a hospital. Unfortunately, the heating temperature of the HFOT was not recorded. Given its retrospective design, we were not able to do any sample size calculation. Our findings provide preliminary data on the use of HFOT at home that will be useful to perform sample size calculations in future prospective trials.

Our use of HFOT depicts two distinct clinical situations, patients with severe hypoxemia and tracheostomized patients. In the first group, we would suggest assessing the benefit of HFOT on symptoms and quality of life. In the first group, the main challenge is to provide at home quantity of oxygen and requires expert home healthcare providers. In the second group, we included patients with recurrent admissions for severe exacerbation and with secretion management issues. We would, therefore, suggest targeting readmission rates in further studies. In that group, the technical challenges are limited.

Conclusion

HFOT is a feasible technology at home and in post-acute re-enablement facilities for patients with end-stage hypoxemic lung disease and for tracheostomized patients with severe exacerbations. Associated costs with its use are reasonable. However, further prospective clinical trials are required to assess the efficacy and the cost-efficiency of such management as well as its effect on health-related quality of life.

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Conflict of interest statement

Dr Dolidon reports non-financial support from Asten and LVL outside the submitted work.

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Supplemental material

The reviews of this paper are available via the supplementary material section.

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The main findings of this study were:

- The use of HFO is feasible in very severe patients in the home setting at a reasonable cost.
- HFO is an interesting tool for the management of patients with type I end-stage CRF.
- The use of HFO may be of interest in tracheostomised patients with frequent exacerbations

Based on our local experience, we have initiated a multicentre randomised controlled trial that will aim to demonstrate the benefit of home HFO in patients with COPD admitted for severe exacerbation and meeting the criteria of LTOT. The project will involve 16 French centres. An application to the *Programme Hospitalier de Recherche Clinique* (clinical research hospital program) went through the first round of application (PHRC 19-0194).

II. Expanding the use of continuous positive airway pressure

Tracheobronchomalacia (TBM) or excessive dynamic airway collapse (EDAC) is an abnormal narrowing of the central airway. In TBM, the narrowing is due to a weakening of the trachea or bronchial anterior cartilage. TBM can be idiopathic (Mounier-Kuhn Syndrome), acquired (relapsing polychondritis) or iatrogenic (post-intubation or post-surgery) or traumatic. In EDAC, the narrowing is primarily caused by a collapse of the posterior muscular wall. EDAC is seen in patients with chronic respiratory diseases such as COPD and asthma but can be found in all disease that cause intrinsic positive end-expiratory pressure such as obesity.

TBM/EDAC symptoms are not specific and include cough and dyspnoea. In patients with chronic respiratory diseases, the lack of specific symptoms leads to under-recognition of EDAC but is present in up to 20% of COPD patients ^{244,245}. However, patients with TBM/EDAC are more likely to have prolonged hoarse or syncopal cough. Cough is often triggered by exercise or laughs.

The diagnosis of TBM/EDAC relies on dynamic flexible bronchoscopy ²⁴⁶. Non-invasive techniques such as dynamic CT can also be used ²⁴⁷ but remains limited to an evaluation at rest that does not reflect what occurs during exertion.

The management of TBM/EDAC includes management of the underlying respiratory diseases. Although inhaled steroids may favour TBM/EDAC ²⁴⁸, there is no data supporting their withdrawal in TBM/EDAC patients. Local treatment of the TBM/EDAC can be offered. Local sclerosis using Yttrium Aluminium Pevroskyte laser applied on the posterior wall of the trachea can provide some improvement ²⁴⁹. However, its use has not yet been validated in clinical trials. The use of silicon stents provides an improvement in quality of life ^{250,251} but is associated to the onset of stent-related complications such as granuloma and lower respiratory tract infections ²⁵². Surgical tracheobronchoplasty is a treatment option with good efficacy ²⁵³. However, its use is limited to selected patients with few comorbidities even if a robotic approach has been shown to be safe ²⁵⁴.

CPAP has been developed in the early 80's to treat OSA. Smaller CPAP devices that are now part of the usual care since OSA is frequent in the active population. Some patients sometimes need to travel long distances as part of their job, the use of CPAP during long-distance flights has emerged. To facilitate the use of CPAP during these flights and as not all airlines agree the use of aircraft power supply ²⁵⁵, manufacturers have issued lightweight CPAP devices with portable batteries that can also be utilised in outdoor situations with limited electric supply ²⁵⁶. CPAP is normally used to treat upper

airway obstruction. However, they have the ability to provide a pneumatic stenting of large airways such as the trachea and the main bronchi.

1. Proof of concept

M. Original research: Trial of Portable Continuous Positive Airway Pressure for the Management of Tracheobronchomalacia (American Journal of Respiratory and Critical Care Medicine, 2016)

As patients with TBM/EDAC are more symptomatic during exertion, stenting of their airways is particularly relevant during exercise. NIV improves walking distance in severe COPD ¹¹² but NIV ventilators are heavy and synchronisation with the ventilator during exercise can be challenging.

CPAP devices provide a positive pressure that can assure a pneumatic stent of the main airways. With the availability of portable CPAP that weights 500g and batteries that may last more than 8 hours, we decided to off this treatment option to one of our patients with COPD requiring LTOT and with EDAC. The level of positive airway pressure was titrated clinically. The results of this first experience have been published ¹⁷²:

Patout, M., Mylott, L., Kent, R., Arbane, G., Murphy, P. B., & Hart, N. (2016). Trial of Portable Continuous Positive Airway Pressure for the Management of Tracheobronchomalacia. *American Journal of Respiratory and Critical Care Medicine*, 193(10), e57–e57. <http://doi.org/10.1164/rccm.201511-2243IM>

Trial of Portable Continuous Positive Airway Pressure for the Management of Tracheobronchomalacia

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Figure 1. Patient mobilizing for 6-minute-walk test while using portable continuous positive airway pressure device and nasal pillows interface.

Tracheobronchomalacia frequently presents with dyspnea and exercise limitation (1). The dynamic collapse can be improved by either stenting of the airways (2) or positive airway pressure (3, 4). The former has been associated with short- and long-term complications, and the latter is limited by requiring a fixed power source and thus not being able to be used during exercise to respond to the increase in dynamic compression that occurs. We present a novel description of the use of a lightweight, portable battery-powered positive airway device (Z1 CPAP; Breas, Stratford-upon-Avon, UK) with nasal pillows interface (Swift; Resmed, Abingdon, UK) to augment exercise performance in tracheobronchomalacia.

A 62-year-old man with chronic obstructive pulmonary disease–obstructive sleep apnea overlap syndrome was referred for worsening dyspnea with recent endoscopic diagnosis of tracheobronchomalacia. As he reported severe exertional dyspnea, a trial of portable continuous positive airway pressure (CPAP) was performed (Figure 1). To evaluate CPAP efficacy, we performed three 6-minute-walk tests (6-MWTs). The patient achieved a walking distance of 60 m on the first 6-MWT performed during self-ventilation. The patient achieved a walking distance of 100 m on the second 6-MWT performed with a portable CPAP at a set pressure of 4 cm H₂O (see Video 1 in the online supplement). The patient achieved a walking distance of 100 m on the third 6-MWT performed with a portable CPAP at a set pressure of 10 cm H₂O but terminated the test at 4 minutes because of severe expiratory dyspnea. The improvement in walking distance (40 m) achieved by use of portable CPAP at a pressure of 4 cm H₂O is

comparable to the one achieved in patients with chronic obstructive pulmonary disease on bi-level ventilation (5). Yet, in this patient, use of higher pressure led to dynamic distension of the airways. Portable CPAP could be a safe therapeutic option for patients with dyspnea and exercise limitation with tracheobronchomalacia but has to be validated by further studies assessing both clinical response and optimal pressure settings. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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The main finding of this study was the fact that a portable CPAP could instantaneously improve the walking distance of a patient with EDAC in a range that is usually clinically significant in COPD patients ²⁵⁷. This result offers new insights to increase physical activity and rehabilitation in patients with TBM/EDAC and open the way to future clinical trials in this field.

2. Proof of concept

a) Introduction

As we have seen a significant clinical benefit and assessed the feasibility of such treatment, we decided to conduct a clinical trial. The clinical trial was made possible by a grant from B&D Electromedical that covered the salary of the author of this thesis. B&D Electromedical also provided the portable CPAP: Z1 with its built-in battery. B&D Electromedical was not involved in the design of the study and did not review its results. The study was sponsored by Guy's & St-Thomas' Hospital.

The aim of the study was to assess the benefit of a portable ventilator generating positive end-expiratory pressure on exercise tolerance in patients with TBM/EDAC.

b) Methods

The study was approved by London City & East NHS Research Ethics Committee (reference: 16/LO/0028) and was registered on ClinicalTrials.gov (NCT02763631).

Patients with exertional dyspnoea and diagnosed with TBM/EDAC by the mean of bronchoscopy or inspiratory/expiratory CT were included in our study. Exclusion criteria were: pregnancy, inability to perform a 6-minute walking test (6MWT), significant physical or psychiatric comorbidity that would prevent compliance with trial protocol, previous surgery for TBM/EDAC, current intra-tracheal stent, uncontrolled underlying disease that required initiation of home NIV in the last 3 months or uncontrolled pain joint, and age < 18 or > 80.

After written consent, patients were included in the trial. The first phase of the study was a run-in cross-over phase. Patients were randomised to have their 6MWT performed with the CPAP or with a sham-CPAP. Those who improved by more than 30m were then included in the prospective randomised controlled trial. Patients were allocated randomly 1:1 to go home with the portable CPAP or without other treatment. Follow-up was performed at 4 weeks. Randomisation was stratified according to the underlying disease causing TBM/EDAC (obstructive airway disease / relapsing polychondritis / idiopathic) and to the use of LTOT (yes / no).

During the run-in phase and before the 6MWT with CPAP, patients underwent physiological tests that included NRD measurements as described in chapter 2, spirometry performed accordingly to international guidelines, forced oscillation technique and fat-free mass index.

After inclusion in the randomised controlled trial, patients were given an activity monitor validated in COPD patients: SenseWear Armband (Bodymedia Inc., Pittsburgh, USA) ²⁵⁸. Patients were instructed to use their portable CPAP during exercise and for recovery. The level of EPAP was determined following NRD measurements and patient's tolerance. We choose the level of EPAP that achieve the best reduction of the EMG_{para} and that was tolerated by the patient. EPAP was evaluated at 5, 7, 10 and 12cmH₂O. A nasal interface was used. The nasal interface was chosen in order to maximise comfort and were: nasal swift, N10 or P10 masks (Resmed, San Diego, USA) or dreamwear nasal mask (Philips, Respironics, Murrysville, USA) (Figure 9). A bag was provided to patients in order to carry the portable CPAP.



Figure 9: Healthy subject wearing the portable CPAP with a nasal mask

No available data to power the trial according to the primary outcome were available. A previous study in 20 COPD patients showed an improvement in 6-MWT distance by 39m with a standard deviation of 60m while on bi-level non-invasive ventilation. Power calculation using these

results to calculate the sample size for the run-in phase with a type I risk set at 0.05 and a type II risk set at 0.2. Twenty participants will be sufficient for the run-in phase. For the main primary outcome, power calculation was based on home actigraphy monitoring in COPD. We hypothesise an improvement of 2000 steps/day with a standard deviation of 1200. Therefore, 14 patients would be sufficient with a type I risk set at 0.05 and a type II risk set at 0.2.

Normal distribution of the data was checked with the Shapiro-Wilk test. Data were expressed as mean (\pm standard deviation) for normally distributed variables, while median (interquartile range with 25th-75th percentile) were used for non-normally distributed data. Comparisons were made using t-test, paired t-test, Wilcoxon signed rank test, Fisher Exact, one way and two-way repeated measures ANOVA, and McNemar's test. Holm-Sidak and Dunn's post hoc correction methods were used where appropriate. A p-value < 0.05 was considered significant. Statistical analysis was performed using SigmaPlot V13.0 statistical software (Systat Software Inc, CA, United States).

c) Results:

Twenty-one patients were recruited, and 19 patients completed all study procedures. The anthropometric, respiratory function and quality of life data are shown in Table 3. Responders defined as those who improved their 6 MWT by at least 30m with CPAP.

	All n:19	Responders N:12	Non-responders N:7	p value
Underlying disease (RP/OAD/I)	6/10/3	4/6/2	2/4/1	0.956
Gender (M/F)	8/11	4/8	4/3	0.377
Age (year)	60 \pm 13	58 \pm 13	64 \pm 13	0.369
Height (m)	1.66 \pm 0.08	1.66 \pm 0.09	1.67 \pm 0.08	0.718
BMI (kg/m ²)	34.5 \pm 6.5	35.1 \pm 7.3	33.5 \pm 5.1	0.623
Tabacco (pack-years)	6.0 (0.0, 39.0)	3.0 (0.0, 45.8)	20.0 (0.0, 35.0)	0.823
Fat free mass (kg/m ²)	12.8 \pm 1.6	12.7 \pm 1.8	13.0 \pm 1.3	0.701
Epworth sleepiness scale	9.9 \pm 4.8	10.9 \pm 4.7	8.1 \pm 4.7	0.230
St-George Questionnaire (/100)	77 (66 - 82)	78 (76 - 83)	66 (53 - 82)	0.069
Severe Respiratory Insufficiency (/100)	46.3 \pm 14.8	42.8 \pm 11.5	52.4 \pm 18.5	0.180
FEV1 (%pred)	55 \pm 19	51 \pm 16	63 \pm 21	0.168
FVC (%pred)	69 \pm 20	63 \pm 13	78 \pm 26	0.118
FEV1/FVC (%)	67 \pm 18	67 \pm 21	65 \pm 15	0.988
SNIP (cmH ₂ O)	-80.4 \pm 27.5	-76.4 \pm 27.4	-87.1 \pm 28.5	0.428
PImax, (cmH ₂ O)	-48.7 \pm 24.1	-43.2 \pm 24.1	-58.1 \pm 23.0	0.204
PEmax (cmH ₂ O)	71.2 \pm 31.6	57.5 \pm 29.8	94.6 \pm 18.9	0.009

Table 3: baseline characteristics of patients included in the trial.

During the run-in 6MWT, the walked distance was: 252±125m self-venting, 264±120 with sham-CPAP and 296±111 with CPAP ($p<0.001$) (Figure 10). Dyspnoea at the end of 6MWT was: 5.8±2.8/10 self-venting, 4.8±2.9 with sham CPAP and 3.9±3.0 with CPAP ($p:0.011$).

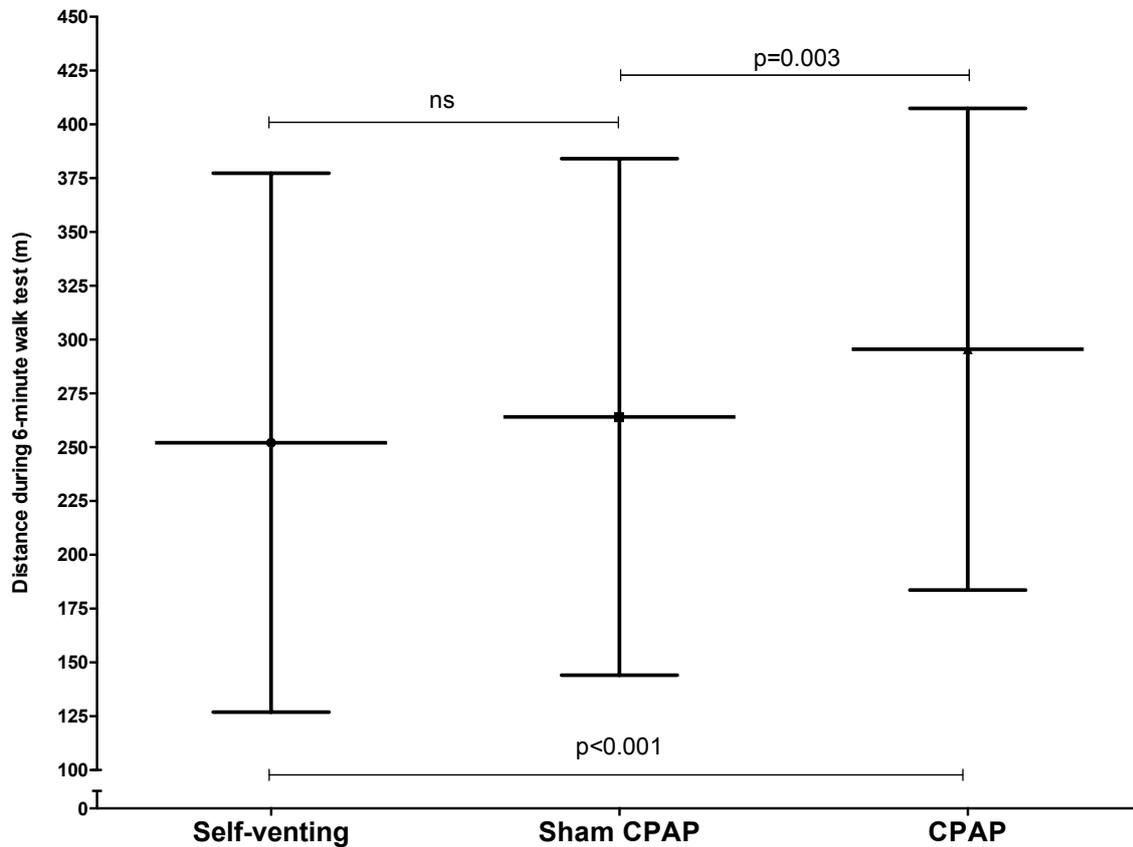


Figure 10: Distance during 6-minute walk-test self-venting, sham CPAP and CPAP

NRD assessment shown that patient who improved by more than 30m with CPAP had a greater offload on CPAP than those who did not (Table 4).

	Responders N:12	Non-responders N:7	p value
EMG _{para} self-venting (μV)	6.67 (5.69, 9.27)	6.381 (5.01, 11.2)	0.899
EMG _{para} on CPAP (μV)	5.49±2.17	5.79±1.77	0.761
Delta EMG _{para} (CPAP-Self-venting) (μV)	-1.57 (-2.94, -1.15)	-1.98 (-6.33, 1.78)	0.833
EMG _{para%max} self-venting (%)	21.74±11.32	15.35±8.09	0.210
EMG _{para%max} on CPAP (%)	15.20±7.30	11.89±6.89	0.345
Delta EMG _{para%max} (CPAP-Self-venting) (%)	-6.54±5.54	-3.46±7.61	0.322
NRDI self-venting (AU)	394.1 (268.3, 593.1)	274.1 (160.4, 328.2)	0.163
NRDI on CPAP (AU)	236.5±135.8	196.1±82.4	0.488
Delta NRDI (CPAP-Self-venting) (AU)	-166.6±109.6	-53.1±92.1	0.034

Table 4: NRD evaluation of included patients self-venting and on CPAP

Out of the 12 patients that responded to CPAP, 11 completed the clinical trial. One withdrew for personal reasons. In patients randomised in the CPAP group, reported use of the CPAP was 1.0 [0.5 - 3.2]hours/day. Activity data were only available in 5 patients per group. There was no statistically significant difference between both groups (Table 5).

	CPAP (n:5)	Control (n:5)	p
Total Energy Expenditure (kCal)	11344 [9454 to 13105]	10504 [10104 to 11497]	0.641
Average metabolic equivalent of task (MET)	1.3 [1.2 to 1.5]	1.1 [1.0 to 1.1]	0.185
Active Energy Expenditure (kCal)	1563 [1291 to 3656]	461 [313 to 807]	0.602
Physical Activity Duration (min)	66 [42 to 130]	21 [14 to 36]	0.080
Number of Steps (/day)	4658 [4596 to 4904]	4430 [2549 to 5632]	0.105

Table 5: Level of activity according to treatment group

At follow-up, there was no significant difference in the self-venting 6MWD distance between groups $+22\pm 66$ in the CPAP group and $+19\pm 25$ in the control group ($p:0.917$) neither in quality of life assessed by the SRI : $+3.7\pm 6.4$ and -3.1 ± 9.6 ($p:0.213$). There was a significant weight gain in the CPAP group: 3.2 ± 0.7 vs. 0.0 ± 1.1 in the control group ($p:0.001$). An improvement in $EMG_{para\%max}$ self-venting was seen in the CPAP group and not in the control group: -6.6 ± 7.6 vs. $+3.6\pm 7.1$ ($p:0.047$).

d) Discussion

In this pilot trial, we have seen in a larger cohort that CPAP could improve the distance achieved during a 6MWT in patients with TBM/EDAC. We failed to achieve any significant results in the randomised controlled trial, but this is not surprising taking into account the number of patients that completed the trial.

We identified in this study that some patients may not respond to CPAP. This can be explained by the way we recruited our patients. One of the inclusion criteria was the presence of exertional dyspnoea. Interpretation of such symptoms is variable and may be also explained by other conditions. For an example, we did not ask our patients to have completed pulmonary rehabilitation before being referred. Neither, did we perform cardio-pulmonary exercise testing to confirm the fact that exercise capacity was limited by respiratory mechanics. The use of NRD assessment may be a useful tool to identify patient that are likely to respond to the treatment. On the other hand, CPAP may also have been beneficial in those that did not improved their 6MWT distance. Indeed, CPAP could improve cough and other respiratory symptoms in these patients. However, our study was not designed for that purpose.

The number of patients included in the prospective randomised clinical trial is low. Therefore, we cannot conclude on a substantial benefit of the use of CPAP in this population. However, patients'

feedback was excellent, and patients asked to keep their CPAP device following participation in the trial. Our data will be useful to power larger scale studies in patients with TBM/EDAC.

3. Rouen University Hospital experience in providing portable continuous positive airway pressure in patients with tracheobronchomalacia

a) Introduction

Following this first clinical trial, we have managed several patients with TBM/EDAC and with CPAP treatment. We have presented the results of our clinical experience at the European Respiratory Society congress in Madrid 2019. The aim of this study was to assess if we achieved similar results in an unselected population of patients with TBM/EDAC.

b) Methods

We conducted a retrospective study that included all patients referred in our centre for suspicion of TBM/EDAC between 01/2017 and 02/2019 that underwent bronchoscopy that confirmed EDAC.

Data were collected from the electronic medical file.

c) Results:

Out of the 30 patients referred, 27 had EDAC. Patients had a mean age of 65 ± 11 with a BMI of $28 \pm 6 \text{ kg/m}^2$. TBM/EDAC was idiopathic in 4 patients and secondary to COPD (n:10), obesity (n:8), asthma (n:4) and lung transplantation (n:1).

At rest, mMRC dyspnea scale was 3.2 ± 1.0 . Health-related quality of life assessed by the severe respiratory insufficiency questionnaire was low: 46 ± 17 .

Daytime arterial blood gases results were: pH: 7.42 ± 0.06 , PaCO₂: $5.4 \pm 1.4 \text{ kPa}$, PaO₂: $11.0 \pm 4.0 \text{ kPa}$. Lung function tests results were: FEV₁: $1.5 \pm 0.7 \text{ L}$ ($63 \pm 34\%$), FVC: $2.3 \pm 0.7 \text{ L}$ ($77 \pm 27\%$), FEV₁/FVC: $69 \pm 23\%$.

Bronchoscopy was performed in all patients. The tracheal lumen reduction was evaluated at $36 \pm 23\%$ at rest. Level of positive expiratory pressure required to counterbalance expiratory collapse was $13 \pm 4 \text{ cmH}_2\text{O}$.

Distance achieved on the 6MWT during self-ventilation was 280m [158 – 346] (52±27%). With CPAP, distance improved significantly: +32m [8 – 53] (p:0.003). Dyspnea (Borg scale) at the end of 6MWT did not improve significantly: -1.5 [-2 – 3] (p:0.405) (Figure 11).

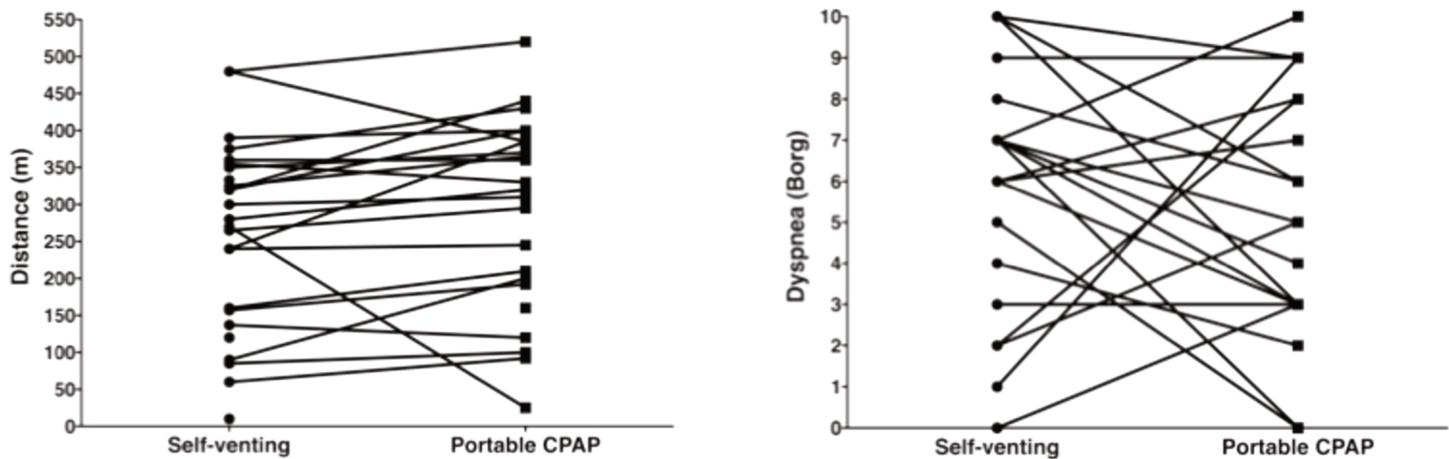


Figure 11: Distance during 6-minute walk-test and dyspnoea self-venting or with CPAP

d) Discussion

Our results confirm the data from our pilot clinical trial. Aside from the improvement in the 6MWT distance, we have also seen significant improvement in cough in patients.

Interestingly, some patients reported being more breathless with the CPAP and some walked a shorter distance. This may be explained by the level of EPAP used in those patients but also by the fact that some patients had difficulties exerting with their mouth closed. For those, the use of a nasal mask induced significant leaks that some patients found to unpleasant. Although less convenient for walking, we have issued the portable CPAP with full-face mask to some patients.

A subgroup of patients had a worsening of their breathlessness. This may explain why we did not find a significant improvement in breathlessness. As these patients were not included in any research trial, we did not perform parasternal electromyography. This tool may have been useful to have a better adjustment of the level of EPAP.

4. Conclusion

We have identified a novel and non-invasive approach for the treatment of patients with TBM/EDAC. Our results need to be confirmed by a larger study. Our results and our clinical experience suggest additional benefit in addition to enhancing exercise capacity.

For patients eligible for surgery, this approach could be a useful screening tool to ensure that patients will benefit from the surgery. For patients not eligible for surgery, our approach provides a low-cost and non-invasive treatment to give patients' symptom relief.

Chapter 6: Synthesis & development perspective

In this thesis, we demonstrated that the outcome of CRF patients treated by home NIV remains poor. Therefore, new methods like parasternal EMG could be a useful tool for risk stratification and to assess NIV efficacy in these patients. We then identified strategies for a better healthcare resource allocation including 1) a better phenotyping of patients in order to select the ventilatory support 2) an automated mode of ventilation especially in obesity hypoventilation syndrome. Afterward, we have reviewed all the data available today regarding telemonitoring and highlighted that the technological advances still need to demonstrate their clinical benefits. Finally, we have described how already established treatments may be useful in specific subgroups of patient like domiciliary high-flow oxygen therapy and with the use of portable CPAP devices in patients with TBM/EDAC.

Based on these results, we think that further improvement in the management of CRF patients could be achieved:

- By a better risk assessment in order to avoid acute type II respiratory failure and to setup NIV in stable patients. In that respect, the use of parasternal EMG could be particularly useful.
- By a better phenotyping of our patients in order to provide a tailored approach to the treatment. In that respect, the use of parasternal EMG could help identify patients with increased respiratory load.
- By a larger use of automated modes of ventilation. However, their use in other group than OHS patients still requires dedicated randomised controlled trial.
- By the use of large-scale dataset and artificial intelligence that could allow physicians to identify signal that could lead to an improvement in care.
- By providing a higher level of evidence for the use of high-flow oxygen therapy in the home setting. For that purpose, we have initiated a randomised controlled trial that will include COPD patients with CRF admitted for a severe AECOPD.
- By a better identification of TBM/EDAC in patients with chronic respiratory disease with, for instance, portable CPAP.

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