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LETTER

Adaptive non-invasive ventilation treatment for sleep apnea

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Abstract

The purpose of this study was to investigate the effectiveness of two non-invasive mechanical ventilation (NIV) modalities to treat sleep apnea: (1) Average Volume Assured Pressure Support (AVAPS) NIV, and (2) Pressure Support (PS) NIV with Continuously Calculated Average Required Ventilation (CCARV). Two detailed (previously developed and tested) simulation models were used to assess the effectiveness of the NIV modalities. One simulated subjects without chronic obstructive pulmonary disease (COPD), and the other simulated patients with COPD. Sleep apnea was simulated in each model (COPD and Non-COPD), and the ability of each NIV modality to normalize breathing was measured. In both NIV modalities, a low level continuous positive airway pressure was used and a backup respiratory rate was added to the algorithm in order to minimize the respiratory work rate. Both modalities could help normalize breathing in response to an episode of sleep apnea within about 5 min (during which time blood gases were within safe limits). AVAPS NIV and PS NIV with CCARV have potential value to be used for treatment of sleep apnea. Clinical evaluations are needed to fully assess the effectiveness of these NIV modalities.

1 | INTRODUCTION

Non-invasive mechanical ventilation (NIV) has been used to treat respiratory disorders such as periodic breathing, chronic obstructive pulmonary disease (COPD), and sleep apnea for many years [1–5]. Sleep apnea is characterized by recurrent episodes of partial breathing or complete apnea. It can be caused by the obstruction of the upper airways during sleep which is referred to as obstructive sleep apnea (OSA). Sleep apnea can also occur due to cessation of the respiratory drive from the medulla, which is referred to as central sleep apnea (CSA). It can also be caused by a combination of OSA and CSA, in which case it is referred to as complex sleep apnea [6]. This respiratory disorder causes hypoxemia, hypercapnia, frequent awakenings, daytime fatigue, and sleepiness. It can adversely affect many of the organs of the body, which can become life-threatening, and can lead to memory loss [7, 8].

Continuous Positive Airway Pressure (CPAP) and Bilevel Positive Airway Pressure (BiPAP) treatments have been used to mitigate the untoward effects of sleep apnea for many years [9]. An NIV method called Adaptive Servo-Ventilation was proposed for treatment of periodic breathing (Cheyne-Stokes Breathing [CSB]) in the early 2000s [10, 11]. In this modality, a variable positive pressure may be applied at the top of a fixed expiratory positive airway pressure (EPAP) to control tidal volume and normalize breathing during sleep. In further studies of this new modality, automatic titration of EPAP and pressure support (PS) were added to the algorithm as well as a back-up respiratory rate [12–16]. In 2015, Adaptive Servo-Ventilation was used to treat heart failure (HF) patients with CSB [17]. However, that study concluded that the modality was associated with higher mortality in HF patients. In a more recent (and broader) study, Adaptive Servo-Ventilation was found to address the needs of a much wider population than HF patients with CSB and further studies of the mode in a more general population of patients with sleep apnea were recommended [18].

The purpose of this study was to investigate the effectiveness of two NIV modalities for sleep apnea: (1) Average Volume Assured Pressure Support NIV (AVAPS NIV), which is an advanced newer modality for treatment of sleep apnea, and (2) PS NIV with Continuously Calculated Average Required Ventilation (PS NIV-CCARV) which is an advanced NIV modality proposed in this study. In both modalities, a constant EPAP is

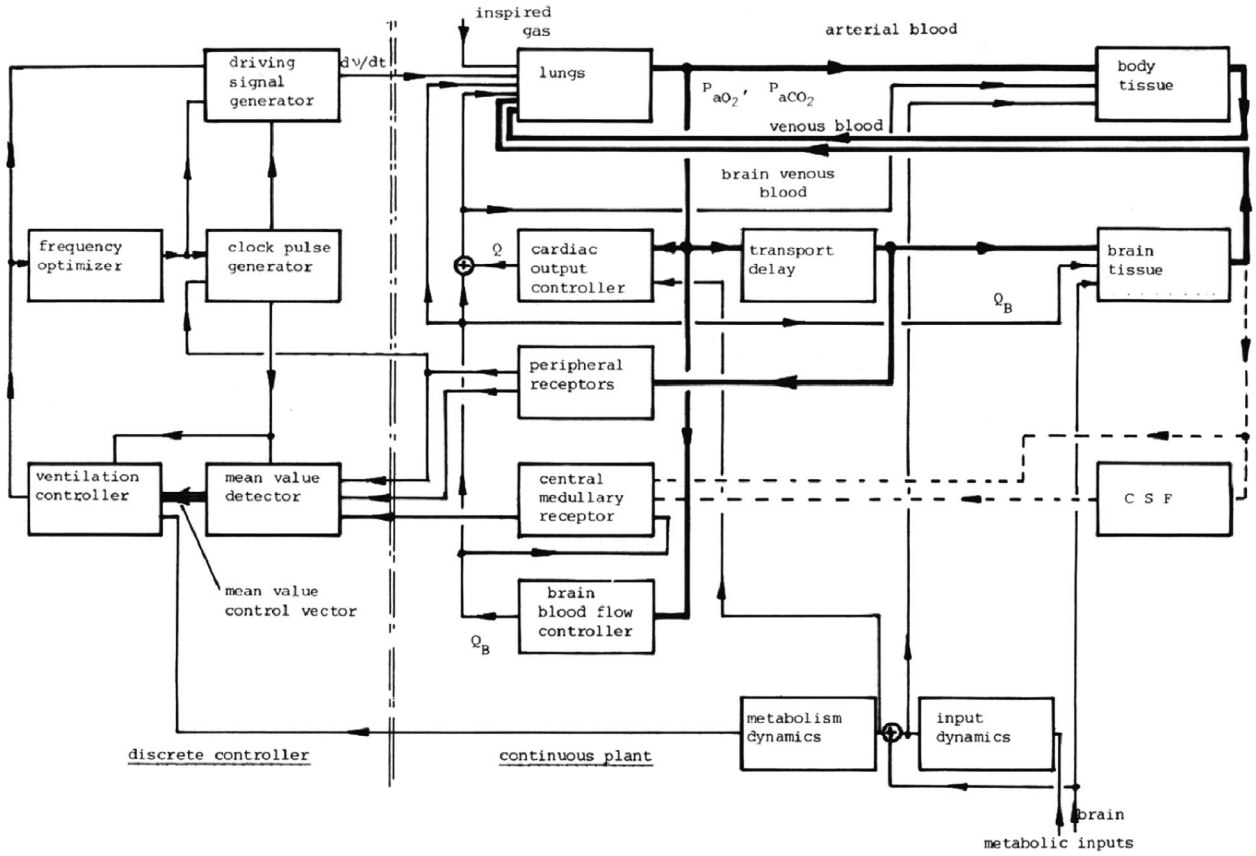

FIGURE 1 A block diagram of the simulation model used for non-COPD patients in the study [19]. ■■■ CO_2 and O_2 main blood circulation.——— central medullary CO_2 effects. COPD, chronic obstructive pulmonary disease.

used and a back-up respiratory rate to minimize the respiratory work rate is added to the algorithm. A constant EPAP is used to improve gas exchange in the lungs during sleep and an optimal back-up respiratory rate would mimic natural breathing.

2 | METHODS

A previously developed, detailed model of the human respiratory system [19, 20] was used in these simulation experiments. For the simulation of COPD patients, another previously developed model that was particularly designed for COPD patients was used in the study [21]. Figure 1 shows a block diagram of the model used for non-COPD patients.

As can be seen in Figure 1, the simulation model for non-COPD patients consists of a continuous plant and a discrete controller. The plant consists of compartments for lungs, body tissue, brain tissue, and cerebrospinal fluid (CSF). It also includes peripheral and central respiratory receptors, separate dynamic controllers for the cardiac output and cerebral blood flow, and a metabolism dynamics compartment that simulates the effects of muscular exercise. The discrete controller receives inputs from the peripheral and central respiratory receptors, updated lung mechanics from the lung compartment, and data from the metabolism dynamics compartment. Based on these input data, the discrete controller determines the amount of required ventilation and an optimum respiratory rate to minimize the respiratory work output. It makes these determinations for every breath and sends its updated respiratory drive signal to the plant at the end of expiration for each breath. The mathematical descriptions of this model and its equations are long, have been previously described [19, 20], and, in the interest of brevity, are not given here.

The simulation model used for COPD patients is also a detailed model [21] of the respiratory system that was previously developed to be used for patients afflicted with COPD. This model is a modified version of the general model shown in Figure 1. Compared with the model in Figure 1, this model incorporates the effects of increase in the respiratory dead space, the rises in the respiratory resistance, COPD-specific alveolar-arterial oxygen difference, and the changes in the ventilation/perfusion ratio in the lungs of COPD patients. The model also uses a ventilation controller that embodies the effects of a chronic shift in the acid base balance in the blood and CSF of COPD patients. This model was previously validated for COPD patients [22]. The mathematical descriptions and equations of that model are provided elsewhere [21]. Those descriptions are long and not provided here for brevity.

Two different NIV modalities were tested in the simulation experiments. In the first modality, the AVAPS NIV, a target average alveolar ventilation was calculated based on the subject's ideal body weight according to the following equations:

$$\text{VALV (rest)} = 0.06524 \times \text{Weight} \tag{1}$$

where 'Weight' is the subject's ideal body weight and VALV is the target alveolar ventilation per minute in litres, with VALV(rest) representing that value at rest. For a subject with an ideal body weight of 70.5 kg, VALV(rest) was calculated to be 4.6 L/min. The respiratory dead space (V_D) can be calculated as [19]

$$V_D = 0.1698 \times (\text{VALV}/60) + 0.1587 \tag{2}$$

Therefore, if weight is 70.5 kg, and VALV = VALV(rest) = 4.6 L/min, V_D can be calculated from Equation (2) as

$$\text{VD} = 0.1717 \text{ L}$$

With a breathing rate, F, the average minute volume (AMV) can be calculated as

$$\text{AMV} = \text{VALV} + F \times V_D \tag{3}$$

Therefore, if VALV is 4.6 L/min, $V_D = 0.1717$ L, and $F = 15$ breaths/min:

$$\text{AMV} = 4.6 + 15 \times 0.1717 = 7.175 \text{ L/min}$$

The average tidal volume (ATV) can then be calculated as

$$\text{ATV} = \text{AMV}/F \tag{4}$$

Therefore, if AMV = 7.175 L/min and $F = 15$ breaths/min

$$\text{ATV} = \text{AMV}/F = 7.175/15 = 0.478 \text{ L}$$

The required inspiratory pressure (Pinsp) exceeding an EPAP (e.g. 4 cm H_2O) will then be

$$\text{Total Pinsp} = \text{EPAP} + \text{ATV}/C \tag{5}$$

where C is the subject's respiratory dynamic compliance in L/cmH_2O.

In the second NIV modality (PS NIV-CCARV) that was evaluated by the simulation in this study, the alveolar ventilation was calculated for every breath by using the following equations [23]:

$$P_{aCO2} = P_{etCO2} + \text{K1} \tag{6}$$

where P_{aCO2} represents the subject's arterial partial pressure of carbon dioxide (CO_2), P_{etCO2} is the end-tidal pressure of CO_2 measured non-invasively (if end-tidal CO_2 monitoring is used), and K1 is the average difference between P_{aCO2} and P_{etCO2} in mm Hg. And

$$P_{aO2} = \frac{-\ln\left[1 - \sqrt{S_{aO2}}\right]}{0.046} \tag{7}$$

where P_{aO2} is the subject's arterial partial pressure of oxygen in mm Hg, and S_{aO2} is the arterial oxygen saturation measured by using pulse oximetry. Then

$$\text{VAC} = 0.405 \times P_{aCO2} - 14.878 \text{ if } P_{aCO2} \geq 33 \text{ mm Hg and VAC} = 0, \text{ if } P_{aCO2} < 33 \text{ mm Hg} \tag{8}$$

where P_{aCO2} is determined non-invasively and VAC is the effect of CO_2 on alveolar ventilation. And

$$\text{VAO} = 4.72 \times 10^{-9}(104 - P_{aO2})^{4.9} \text{ for } P_{aO2} < 104 \text{ mm Hg and VAO} = 0 \text{ for } P_{aO2} \geq 104 \text{ mm Hg} \tag{9}$$

where VAO is the effect of blood oxygen level on alveolar ventilation. Then

$$\text{VALV} = (\text{VAC} + \text{VAO}) \times \text{VALV (rest)} \tag{10}$$

where VALV(rest) is the required alveolar ventilation at rest and that can be found by using the subject's ideal body weight (Weight) from Equation (1). If in this process, VALV is found to be negative or zero, and then its value would be replaced by a positive minimum value. At this point, the following equation is used to calculate the optimum respiratory frequency to minimize the respiratory work rate

$$\mathbf{f} = \frac{-\alpha V_D + \sqrt{\left[\alpha^2 V_D^2 + 4.\alpha.\beta.\pi^2.V_D.\text{VALV}^{\bullet}\right]}}{2.\pi^2.\beta.V_D} \tag{11}$$

where f is the backup respiratory rate (BURR) in breath/seconds which is equal to F/60, to minimize the respiratory work rate, α is respiratory system elastance in cmH_2O)/L (reciprocal of compliance, C), β is the airway resistance in the lungs in cmH_2O)/L/s, VALV$^{\bullet}$ is alveolar ventilation in L/s, and V_D is the dead space volume in litres [24]. In the simulation experiments of non-COPD patients, α was 10 cmH_2O)/L, and β was 7 cmH_2O)/L/s.

From here, Equations (2) to (5) can be used to determine the required ATV and the inspiratory pressure in accordance with Equations (2) to (5) and by using the optimum frequency of breathing found from Equation (11). In both modalities under investigation, an EPAP of 4 cm H_2O was used and a BURR to minimize the respiratory work rate was defined according to Equation (11).

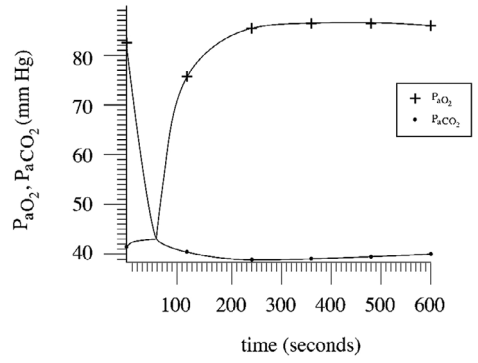

FIGURE 2 Sample simulation results of a patient with sleep apnea treated by NIV with the average volume assured pressure support. NIV, non-invasive mechanical ventilation.

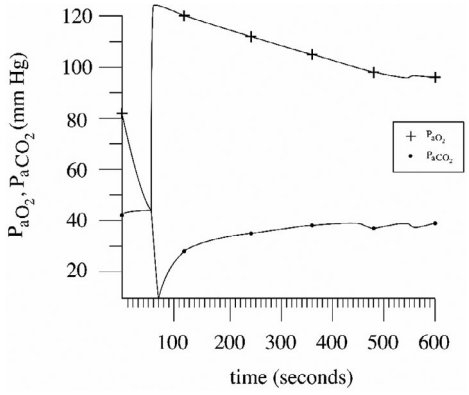

FIGURE 3 Sample simulation results of a patient with sleep apnea treated by pressure support NIV with continuously calculated average required ventilation.

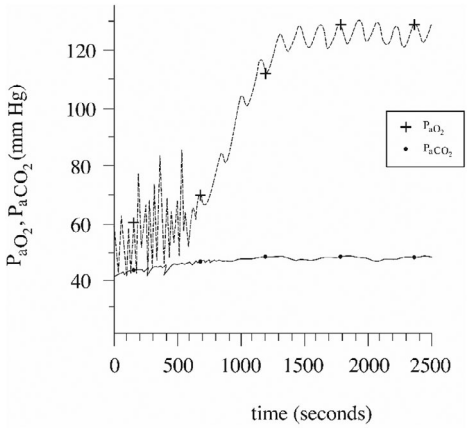

FIGURE 4 Sample simulation results for a COPD patient with sleep apnea treated by NIV with CPAP and supplemental oxygen. COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; NIV, non-invasive mechanical ventilation.

The COPD tests included the use of supplemental oxygen as well as CPAP during sleep to mitigate the effects of COPD and sleep apnea. In the simulation experiments of COPD patients, α was 34 cmH_2O/lit, β was 12 cmH_2O/lit/s, and the dead space from Equation 2, was increased by 20% above normal.

3 | RESULTS AND DISCUSSION

Figure 2 shows the results from a simulated non-COPD patient who experienced an initial period of 60 s of sleep apnea. The apneic episode was followed by activation of AVAPS NIV as described in the previous section. The pressure support non-invasive ventilator assisted the simulated patient's breathing to achieve a target alveolar ventilation of 4.6 L/min (corresponding to an average target minute ventilation of 7.175 L) and an average target tidal volume of 0.478 L. This patient had an ideal body weight of 70.5 kg. An EPAP of 4 cm H_2O was applied. As seen in Figure 2, P_{aO2} reached to about 44 mm Hg corresponding to an S_{aO2} of 74% and P_{aCO2} rose to 44 mm Hg at the end of the initial apneic period of 60 s. With the intervention of NIV, P_{aO2} rose to about 87 mm Hg (S_{aO2} of 96.4%), and P_{aCO2} stabilized to around 39 to 40 mm Hg in about 200 s after the apneic period.

Figure 3 shows the results of blood gases for a simulated non-COPD patient who experienced an initial period of 60 s of apnea. The patient had an ideal body weight of 70.5 kg. At the end of apnea, PS NIV-CCARV was activated with the alveolar ventilation calculated for every breath by using Equations (6) to (10) and based on non-invasive measurements of P_{etCO2} and S_{aO2}. An EPAP of 4 cmH_2O was applied. As seen in Figure 3, P_{aO2} went down to about 45 mm Hg corresponding to an S_{aO2} of 76%, and P_{aCO2} rose to about 45 mm Hg at the end of the apneic period. With the activation of pressure support NIV, P_{aO2} initially rose to about 120 mm Hg (corresponding to an S_{aO2} of 99.2%), and P_{aCO2} went down to about 12 mm Hg momentarily; after which P_{aCO2} stabilized around 39 mm Hg, and P_{aO2} settled around 96 mm Hg (S_{aO2} of 97.6%) in about 300 s after the apneic period.

Table 1 shows the steady-state results of selected variables of the model after an initial apneic period of 60 s. Normalization of breathing and blood gases can be seen from the results shown in this table by using the NIV modes.

Figure 4 shows the results of blood gases for a simulated COPD patient. The model for COPD [21] was used for this experiment. The simulated patient had advanced COPD and the respiratory dead space was increased by 20% above normal. The NIV treatment for this patient consisted of a CPAP of 5 cm H_2O and oxygen supplementation at a fraction of inspired oxygen (F_{IO2}) of 30%. As shown in this figure, P_{aO2} rose from its initial low value of about 43 mm Hg (corresponding to an S_{aO2} value of 74%) to about 122 mm Hg (S_{aO2} of 99.2%) in about 1500 s. During the same time, P_{aCO2} rose from its initial value of about 43 mm Hg to around 50 mm Hg due to CO_2 retention demonstrating permissive hypercapnia.

4 | SUMMARY AND CONCLUSION

PS NIV with CCARV is a new proposed advanced modality, and AVAPS NIV is an advanced and newer modality for treatment

TABLE 1 Selected steady-state simulation results. P_{aCO2} and P_{aO2} are arterial partial pressures of carbon dioxide and oxygen in mm Hg respectively. S_{aO2} is arterial oxygen saturation, Q, Q_B and V_E are cardiac output, brain blood flow rate, and minute ventilation in L/min respectively, and F is breathing rate in breaths/min.

Test	Steady-state results							
	First 60 s	P_{aCO2} mm Hg	P_{aO2} mm Hg	S_{aO2}	Q L/min	Q_B L/min	V_E L/min	F breaths/min
Aver. Vol. Assured NIV EPAP = 4 cmH_2O, $F_{IO2} = 0.21$	Apnea	40.12	87.10	0.964	5.11	0.74	6.56	11.50
NIV with Cont. Cal. Aver. Req. Ven. EPAP = 4 cmH_2O, $F_{IO2} = 0.21$	Apnea	39.20	95.11	0.975	5.13	0.72	6.62	11.56
Advanced COPD EPAP = 5 cm H_2O, $F_{IO2} = 0.3$	Apnea	50.30	121.81	0.993	6.90	1.33	5.91	11.02

The ideal body weight of the simulated subject was 70.5 kg. In the simulation experiments of non-COPD patients, the respiratory elastance (reciprocal of compliance), α, was 10 cmH_2O/L, and, the respiratory airway resistance, β, was 7 $cmH_2O/L/s$. In the simulation experiments under COPD, the respiratory elastance was 34 cmH_2O/L, airway resistance was 12 $cmH_2O/L/s$, and the dead space was increased by 20% above normal. Significant acid-base shifting in Advanced COPD was assumed.
COPD, chronic obstructive pulmonary disease; EPAP, expiratory positive airway pressure; NIV, non-invasive mechanical ventilation.
[Correction added July 10, 2024, after first publication: test 1 description was aligned with the result values].

of sleep apnea. These modalities were evaluated in this study and were both found to be effective in normalizing breathing and blood gases in the simulation experiments. The results of this study are in line with the results of several clinical studies on the treatment of sleep apnea patients [18, 25, 26]. According to the simulation results of the present study, after each apneic period, it would take between 200 and 300 s for the blood gases to reach a steady state in the simulation experiments. Since apnea can cause hypoxemia and hypercapnia, requiring a higher level of ventilation than the resting levels, using PS NIV-CCARV would be more tolerable and less awakening if a smoothing factor of 40% to 50% in the level of ventilation in the first 3 to 5 cycles of breathing following apnea is adapted. In COPD patients, the optimal treatment is to apply nocturnal continuous low level of supplemental oxygen with low level of CPAP to mitigate the effects of both COPD and sleep apnea.

The simulation results of this study suggest that both AVAPS NIV and PS NIV-CCARV have the potential to be used in a wide range of patients with CSA or complex sleep apnea. Clinical evaluations are needed to assess the effectiveness and limitations of these NIV modalities for patients with disordered breathing and sleep apnea.

AUTHOR CONTRIBUTIONS

Fleur Tehrani: Methodology; mathematical modelling studies; literature search; writing original draft. **James Roum**: Clinical evaluations; review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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