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Early View

Original article

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Reductions in dead space ventilation with Nasal High Flow depend on physiologic dead space volume - Metabolic hood measurements during sleep in patients with COPD and controls

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Abstract

Background: Nasal high flow (NHF) reduces minute ventilation and ventilatory loads during sleep but mechanisms are not clear. We hypothesized NHF reduces ventilation in proportion of the physiologic but not anatomic dead space. **Methods:** 11 subjects (5 Controls and 6 COPD) underwent a polysomnography with transcutaneous CO_2 ($tcCO_2$) monitoring under a metabolic hood. During stable NREM 2 sleep, subjects received NHF (20 L/min) intermittently for periods of 5-10 min. We measured CO_2 production and calculated dead space ventilation. **Results:** Controls and patients with COPD responded similarly to NHF. NHF reduced minute ventilation (5.6±0.4 L/min to 4.8±0.4 L/min, $p<0.05$) and tidal volume (0.34±0.03 to 0.3±0.03 L, $p<0.05$) without a change in energy expenditure, $tcCO_2$ or alveolar ventilation. There was a significant decrease in dead space ventilation (2.5±0.4 L/min to 1.6±0.4 L/min, $p<0.05$) but not respiratory rate. The reduction in dead space ventilation correlated with baseline physiologic dead space fraction ($r^2= 0.36$, $p<0.05$) but not respiratory rate or anatomic dead space volume. **Conclusion:** During sleep, NHF decreases minute ventilation due to an overall reduction in dead space ventilation in proportion to the extent of baseline physiologic dead space fraction.

Introduction

Nasal high flow (NHF) is a method of ventilatory support increasingly used in several clinical settings. During NHF, warm and humidified air is delivered to patients' nose at high flow rates (2 to 60 L/min) [1]. NHF can assist ventilation and prevent intubation in both adults and children with respiratory failure [2–5]. Several mechanisms have been proposed to explain the responses observed with the use of this therapy. NHF could lead to improvements in respiratory mechanics [6], better humidification of airways [7], reductions in anatomic dead space [8, 9], increases in end expiratory lung volume [10–12] and decreases in ventilatory demand due to reduction in work of breathing [4, 9, 13–15]. The decrease in ventilatory demand has been attributed to washout of the anatomic nasal dead space [8], however, dynamic measures of dead space volume and CO_2 production during tidal breathing were not performed, leaving the actual mechanism of action for the effects produced by NHF still unknown.

Sleep is a unique opportunity to study physiologic mechanisms of NHF since we avoid potential conscious confounders. We have previously shown that ventilatory responses to NHF are different during wakefulness and sleep [16]. These differences may explain the heterogeneous responses reported when examining mechanisms of NHF in the clinical setting. In fact, when controlled for sleep, we observed a more homogeneous response to NHF. Both minute ventilation and work of breathing (WOB) decrease while CO_2 levels remain constant [9]. The reduction in ventilation is possibly due to a decrease in dead space ventilation due to nasal dead space washout [8, 17]. However, by decreasing work of breathing, NHF can also decrease CO_2 production and, therefore, reduce the amount of minute ventilation required to maintain constant levels of CO_2.

To determine whether the reduction in minute ventilation is driven by the decrease in work of breathing or by a reduction in dead space ventilation, we measured the effects of NHF on CO_2 production during sleep in controls and patients with COPD. Specifically, using a metabolic hood and standard polysomnography with CO_2 monitoring, we measured CO_2 production and calculated alveolar ventilation with and without the use of NHF during stable sleep. We hypothesized that NHF would reduce dead space ventilation and that the amount of the reduction would depend on the extent of dead space. We also hypothesized that, in contrast to controls, patients with COPD would show a reduction in CO_2 production, thereby also reducing alveolar ventilation.

Methods

Participants were recruited from the Johns Hopkins pulmonary clinics and surrounding community. Subjects older than 18 years old and consenting to participate were included. Exclusion criteria were exacerbation of COPD or severe illnesses within 8 weeks prior to the study, severe heart and liver disease, home use of oxygen and/or chronic use of opioid, benzodiazepines or other sedatives.

In a previous study[9], we detected a 30 to 40% reduction in minute ventilation, work of breathing and tidal volume with the use of NHF. Since we planned to investigate whether changes in metabolic rate contributed to minute ventilation reduction, we estimated that 10 patients would be required to reproduce the previously observed effect on ventilation and to study the contribution of variation in metabolic rate.

The study was approved by the Johns Hopkins Medical Institution Human Investigation Review Board.

Equipment setup

Subjects enrolled underwent an overnight sleep study under a metabolic hood to measure CO_2 production while using NHF. During the study, we collected standard polysomnography signals including transcutaneous CO_2 (TCM3, Radiometer Medical Aps, Bronshoj, Denmark). Ventilation was monitored with respiratory inductive plethysmography (Respitrace Corp, New York, NY, USA). At the beginning of the protocol, subjects wore a face mask attached to a pneumotachograph [18] and end-tidal CO_2 monitor (Vacumed, Ventura, CA, USA). Subjects breathed through the mask for approximately 30 seconds to calibrate the respiratory inductive plethysmography with the integrated pneumotachograph signal. Additionally, participants performed a slow exhalation maneuver to elicit an accurate end-tidal CO_2 reading. We scaled the transcutaneous CO_2 measurement to the obtained end-tidal CO_2 values.

After calibration procedures, the mask was removed and subjects wore only a nasal cannula for the intermittent delivery of NHF.

Once participants were fully monitored and comfortable in bed, we placed a metabolic hood (Quark RMR, Cosmed, Rome, Italy) covering their head and chest to collect the air exhaled by the subject (**Figure 1**). This system allows the measurement of O_2 consumption and CO_2 production in an individual without wearing a mask. The long sheets attached to the hood rest around the upper part of subject's body, avoiding air leaks. A pump continuously aspirates air from the hood to the analysis equipment, directing the exhaled air towards the hood exit and away from other potential leak points. The exhaled air is collected and analyzed to compute CO_2 production, O_2 consumption and energy expenditure.

In our setting, we sought to determine CO_2 production and energy expenditure during the NHF therapy, which would alter the flow delivered to the interior of the hood. Therefore, a high flow rate at the pump collecting air from the hood (50 L/min) was maintained to avoid leaks and to ensure constant experimental conditions. The incoming flow to the hood was the sum of the NHF flow (20 L/min) and a room air inlet flow (30 L/min). Whenever the NHF to the subjects' nose was turned off, we initiated the delivery of an equal flow to the subjects' chest via a secondary cannula, maintaining the overall flow to the interior of the hood constant (**Figure 1**). Since it was important to maintain a constant flow to the metabolic hood, we performed a series of pilot experiments using a constant source of CO_2 to ensure that alternating NHF would not interfere with metabolic measurements.

Study Protocol

Patients were admitted to the sleep center at approximately 7 p.m. for getting accustomed to the experimental procedures and to standardize level of activity prior to the sleep studies. Once participants were fully monitored, we started the delivery of a flow of 20 L/min, 85% humidity and 32 ^{o}C through a nasal cannula during wakefulness for acclimatization. We used a modified S8 CPAP Machine (ResMed, Bella Vista, New South Wales, Australia) that was able to generate constant flows up to 30 L/min. The device was also designed with a special hose with active heating that maintained the delivered air warm and humid. Between 10 and 11 p.m., patients initiated sleep with NHF on at 20 L/min. When subjects were in stable stage 2 NREM sleep, we alternated periods of NHF on/off at 5 to 10-minute intervals (**Figure 2**). During the periods when NHF was turned off, the flow to the second cannula (to subjects' chest) was turned on at the same rate, humidity and temperature of the NHF. For each subject, pairs of on/off NHF trials were selected when intervals were absent of interruptions in sleep and there was no significant reduction in pulse wave amplitude of more than 50% from baseline as a marker for cortical activity or skin nerve activity. On average, 3 pairs of NHF on/off for each subject were obtained. Measurements were summarized to produce one mean value of 'NHF off' and 'NHF on' for each patient, which were used for the statistical comparisons.

Parameters calculation and statistical analysis

Data were recorded using a PSG recording station (Remlogic Natus, Pleasanton, CA, USA) and transferred to a data analysis software (IgorPro WaveMetrics, Lake Oswego, OR, USA). We derived minute ventilation, respiratory rate and tidal volume from the calibrated respiratory inductive

plethysmography signal. Physiologic dead space ventilation was calculated using the equation for alveolar ventilation:

$pCO_2 = 0.863 * VCO_2 / (MV – DS)$ [19],

where pCO_2 is arterial pCO_2, for which calibrated transcutaneous CO_2 measurements were used; VCO_2 is CO_2 production, measured with the metabolic hood; MV is minute ventilation; and DS is the physiologic dead space ventilation per minute.

Tidal dead space volume was calculated dividing dead space ventilation by respiratory rate. Dead space fraction was computed as dead space volume divided by tidal volume. Anatomic dead space volume was estimated from participants' height, as previous described [20–22].

Measurements with and without NHF were compared by using paired-T test. The degree of the response in controls and patients with COPD was compared by non-paired T-test. The correlation of changes in dead space to baseline dead space was analyzed using Pearson correlation coefficient. We considered p values lower than 0.05 as statistically significant.

Results

Twelve participants were recruited (6 controls and 6 with COPD), but one subject (with COPD) could not sleep under the metabolic hood and was excluded. **Table 1** shows the demographics of the population enrolled.

We detected an awakening in 12 of the 98 on/off NHF trials, some of them apparently induced by the transition of the state of NHF (on to off, or vice versa). Once an arousal was detected, we waited longer periods until patients reached stable sleep or excluded the analysis on that segment if sleep was not resumed.

Effect of Nasal High Flow on respiratory pattern during sleep in a metabolic hood

In **Figure 2**, we show the effect of NHF *on* and *off* on ventilation during sleep in one individual (COPD1). One can notice that our experimental setup of turning NHF *on* and *off* during sleep (see vertical downward arrows, upper trace) did not disturb sleep continuity (see EOG, EEG and EMG traces) or lead to an activation of the autonomic nerve activity, as illustrated by the stability of the heart rate (pulse) and pulse wave amplitude (PWA) in this patient. The effects of NHF on ventilation are illustrated by comparing tidal volume signal (Respiratory plethysmography trace) with the oxygen saturation (SaO_2), transcutaneous CO_2 ($tcCO_2$), CO_2 consumption (VCO_2) and energy expenditure. While tidal volumes increased during the NHF *off* condition (middle panel), there was no change in $tcCO_2$, oxygen saturation, CO_2 production (VCO_2) or energy expenditure (EE), indicating that alveolar ventilation and did not change.

Effect of Nasal High Flow on ventilation

Pooled data are shown **Figure 3**. At baseline, compared to controls, patients with COPD had a slightly but not statistically significant higher minute ventilation (Control: 4.9 ± 0.5 L/min, COPD: 6.4 ±

0.6 L/min, p= NS), respiratory rate (Control: 15.8 ± 1.0 rpm, COPD: 18.4 ± 1.3 rpm, p=NS) and dead space ventilation (Control: 1.8 ± 0.3 L/min, COPD: 3.2 ± 0.6 L/min, p=NS).

In response to NHF, we noticed a significant reduction in minute ventilation in all subjects, as shown in the far left panel in **Figure 3** (NHF off: 5.6 ± 0.4 L/min, NHF on: 4.8 ± 0.4 L/min, $p<0.05$). The reduction in ventilation was associated with a reduction in tidal volumes (middle left panel) from NHF off (340 ± 30 ml) to NHF on (300 ± 30 ml, $p<0.05$). There was no significant change in respiratory rates (middle right panel) and a minimal reduction in transcutaneous CO_2 (far right panel) which fell from NHF off (41.7±1.1 mmHg) to NHF on (41.3±1.2 mmHg, $p<0.05$). Changes in these parameters in response to NHF were similar for controls and patients with COPD. Off note, there was one participant, who had moderate COPD (female, 55 years, FEV1 38% of predicted) who reduced minute ventilation from NHF off (7.7 L/min) to NHF on (6.7 L/min) due to a 16% fall in respiratory rate from 19 to 16 rpm without a significant change in her tidal volume (413 to 433 ml).

In **Figure 4,** we show pooled data for alveolar ventilation (left panel) which remained unchanged in controls and COPD subjects. However, there was a substantial (~40%) reduction in dead space ventilation (middle left panel, NHF off: 2.5 ± 0.4 L/min, NHF on: 1.6 ± 0.4 L/min, $p<0.05$), dead space fraction (middle right panel, NHF off: 0.42 ± 0.03, NHF on: 0.31 ± 0.05, $p<0.05$) and dead space volume (far right panel, NHF off: 144 ± 19 ml, NHF on: 98 ± 22 ml, $p<0.05$) with the use of NHF. The reduction in dead space ventilation was similar for both controls and patients with COPD. Of note, the individual with moderate COPD who reduced the respiratory rate from 19 rpm to 16 rpm on NHF, as mentioned above, did not have a significant change in either alveolar ventilation (NHF off: 3.3 L/min, NHF on: 3.4 L/min) or transcutaneous CO_2 (NHF off: 40.3 mmHg, NHF on: 39.5 mmHg). However, she had a substantial reduction in dead space ventilation (1.1 L/min) that was due to both the reduction in respiratory rate and a reduction in tidal dead space volume (NHF off: 236 ml, NHF on: 214 ml).

Determinants of reductions in dead space ventilation

There was no correlation between baseline respiratory rate, minute ventilation or anatomic dead space volume with either the reduction in dead space ventilation or reduction in tidal dead space volume. In contrast, the degree of physiologic dead space at baseline correlated with the reduction of dead space ventilation with NHF: the greater the dead space fraction of an individual at baseline, the greater the reduction in dead space ventilation with NHF. As it can be seen in **Figure 5,** for each 10 % increase in dead space fraction there is a 208 ml/min reduction in dead space ventilation with the use of NHF ($r^2=0.36$, $P<0.05$).

Discussion

In the present work, we evaluated the effects of the use of Nasal High Flow (NHF) during sleep on ventilation and directly measured CO_2 production using a metabolic hood and polysomnography. We first observed that responses in ventilation to NHF during sleep were similar in COPD and controls. Second, the use of NHF led to a substantial decrease in minute ventilation due to a reduction in dead space ventilation without a significant change in alveolar ventilation, CO_2 production, energy expenditure and transcutaneous CO_2. Third, the reduction in dead space ventilation depended on the amount of physiologic dead space fraction and not anatomic dead space volume, respiratory rate or minute ventilation at baseline off NHF. Although we did not observe a reduction in either alveolar

ventilation or CO_2 production during our short trials of NHF, it is still possible that longer trials of NHF may also affect these parameters.

Several previous studies have demonstrated a washout of the anatomical dead space with nasal high flow using imaging techniques in upper airway models [8] or human upper airway in volunteers [17]. These studies, however, could not elucidate the effect of NHF on dead space clearance because of technical restrictions and did not evaluate CO_2 production and metabolism [17]. We were able to show baseline physiologic dead space volume is related to the amount of dead space washout at a given flow rate. Physiologic dead space is known to directly correlate with the tidal volume [23]. We now show that the lower the tidal dead space fraction the lower was the reduction in dead space ventilation with NHF. Thus, it appears that individuals with higher tidal volumes due to increases in dead space fraction benefit more from the use of NHF compared to those with lower dead space fraction.

NHF has been extensively used for treating respiratory failure in different clinical settings. The warming and humidification of the air allow the delivery of higher flows, creating a low level of PEEP and increasing end expiratory lung volume [10–12]. Further, NHF reduces minute ventilation during both sleep and wakefulness, without increasing CO_2 levels [9, 16, 24, 25]. The respiratory pattern response to NHF apparently differs when individuals are awake or sleeping [16], thus explaining potential differences in respiratory rate responses between individuals [16]. To exclude this confounder, we determined ventilatory responses during sleep and showed that NHF reduced minute ventilation and dead space ventilation similarly in controls and patients with mild to moderate COPD. Moreover, the reduction in dead space ventilation was associated with no change in alveolar ventilation, CO_2 production and transcutaneous CO_2. This is in contrast to previous studies, in which we and others have shown a significant reduction in work of breathing following the reduction in minute ventilation [4, 9, 13–15].

There are several explanations for these discrepancies. First, it is possible that our trials on and off NHF were too short to translate into changes in CO_2 production and energy expenditure. Second, during sleep, energy expenditure is low and for individuals with low amount of ventilation, we expect a low level of energy expenditure related to the respiratory muscle activity. Thus, changes in work of breathing could have been too small to be detected by measurements of energy expenditure. Third, ventilatory responses to NHF were similar in controls and COPD, which suggests that breathing mechanics were not markedly different between these groups. Additionally, the number of patients enrolled was small to exclude minor differences between the responses in patients with COPD and controls. We also could not compare the differential responses between genders. The complexity of the experimental design prevented the enrollment of a larger sample. Further, our patients did not have severe obstruction. Patients with more severe COPD disease may have shown a differential response to NHF.

There are also several strengths in our study. First, this study performed on/off experiments in a very controlled setting without influencing the variables of the metabolic hood. Second, polysomnography was used to control for biologic variables related to changes in sleep stages, movements and conscious influences. As a consequence, we obtained data from stable NREM 2-3 sleep in which breathing pattern and metabolism are very regular, allowing the detection of even small changes in CO_2 production. Third, we quantified ventilation with calibrated respiratory inductive plethysmography, which is void of any artificial changes in ventilation that may arise with the use of either nasal or face masks. Taken together, our data indicate that the immediate ventilatory responses to NHF are due to a reduction in dead space ventilation. Whether these changes translate into

reductions in energy expenditure may depend on NHF being used over prolonged periods of time or in patients with high ventilatory demands.

Our study has immediate clinical implications. First, we demonstrate that alveolar ventilation remains constant during the use of NHF and the driver for the reduction in minute ventilation is a reduction in dead space ventilation. Therefore, NHF could be particularly useful in patients with large dead space ventilation, maximizing its potential for unloading the respiratory system. Second, we now provide an explanation for heterogeneous response to NHF observed in previous studies. While some individuals lowered their arterial CO_2 in response to NHF, others did lower their respiratory rate [24]. We hypothesize that individuals with higher physiologic dead space ventilation showed reduction in arterial CO_2. Finally, although CO_2 production remained constant during our short on/off trials of NHF, it is possible that longer use of NHF would lead to reductions in work of breathing, CO_2 production and could prevent nocturnal hypercapnia. However, studies with longer exposure to NHF are required to further evaluate these hypotheses.

Conclusion

In the present work, we show that the mechanism for minute ventilation reduction during short term use of NHF during sleep is not related to a reduction in CO_2 production. Rather it is caused by the reduction in dead space ventilation. The degree of the reduction in minute ventilation is correlated to the amount of baseline physiologic dead space, measured as dead space fraction. Therefore, NHF could be used to unload the respiratory system, particularly in patients with very high dead space fraction.

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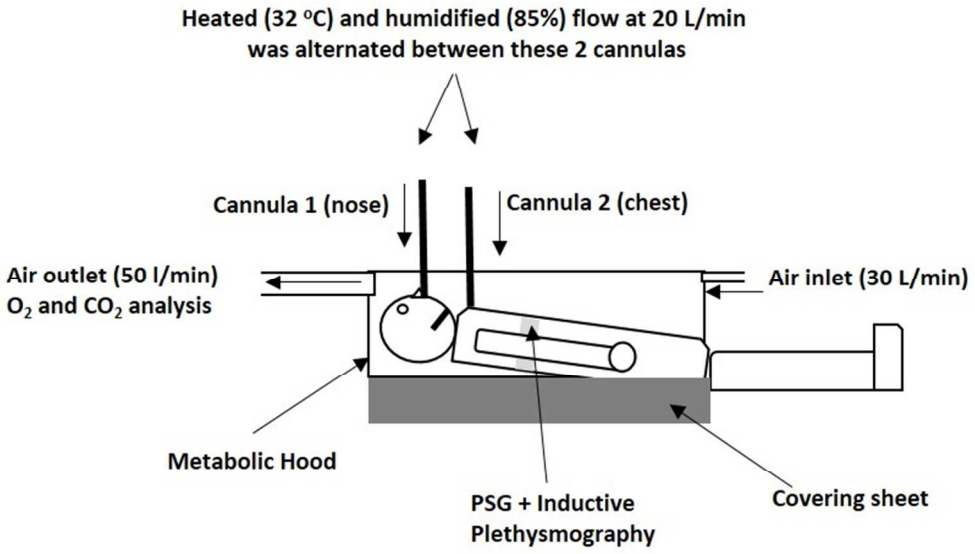

Figure 1 - Schematic representation of the experimental setting. Subjects underwent a polysomnography study in which we monitored electrocardiogram, electooculogram, electroencephalogram, electromyogram, pulse oximetry and transcutaneous CO_2. Ventilation was monitored with respiratory inductive plethysmography, calibrated with a flow sensor at the beginning of the experiment. Once subjects were monitored, we placed a Metabolic Hood covering the subjects' upper body. The system consisted of a rigid plastic transparent cover attached to a plastic sheet, which sat around the subject upper body. The sheet created a high resistance area around the subject, avoiding leak. Additionally, a pump aspirated air from inside the hood, directing the flow to the analysis equipment and away from other points of leak. Air could enter into the hood through air inlet or through system for high nasal flow delivery. We maintained a high aspirating flow from the hood to minimize leaks. O_2 consumption and CO_2 production were measured at the outlet flow. Participants wore a nasal cannula (cannula 1) for the intermittent delivery of high flow therapy (20 L/min, 85% humidity, 32 °C). An additional cannula was placed in subjects' chest (cannula 2) for delivery of the high flow whenever the nasal high flow was turned off. Therefore, we maintained a constant flow to the hood interior.

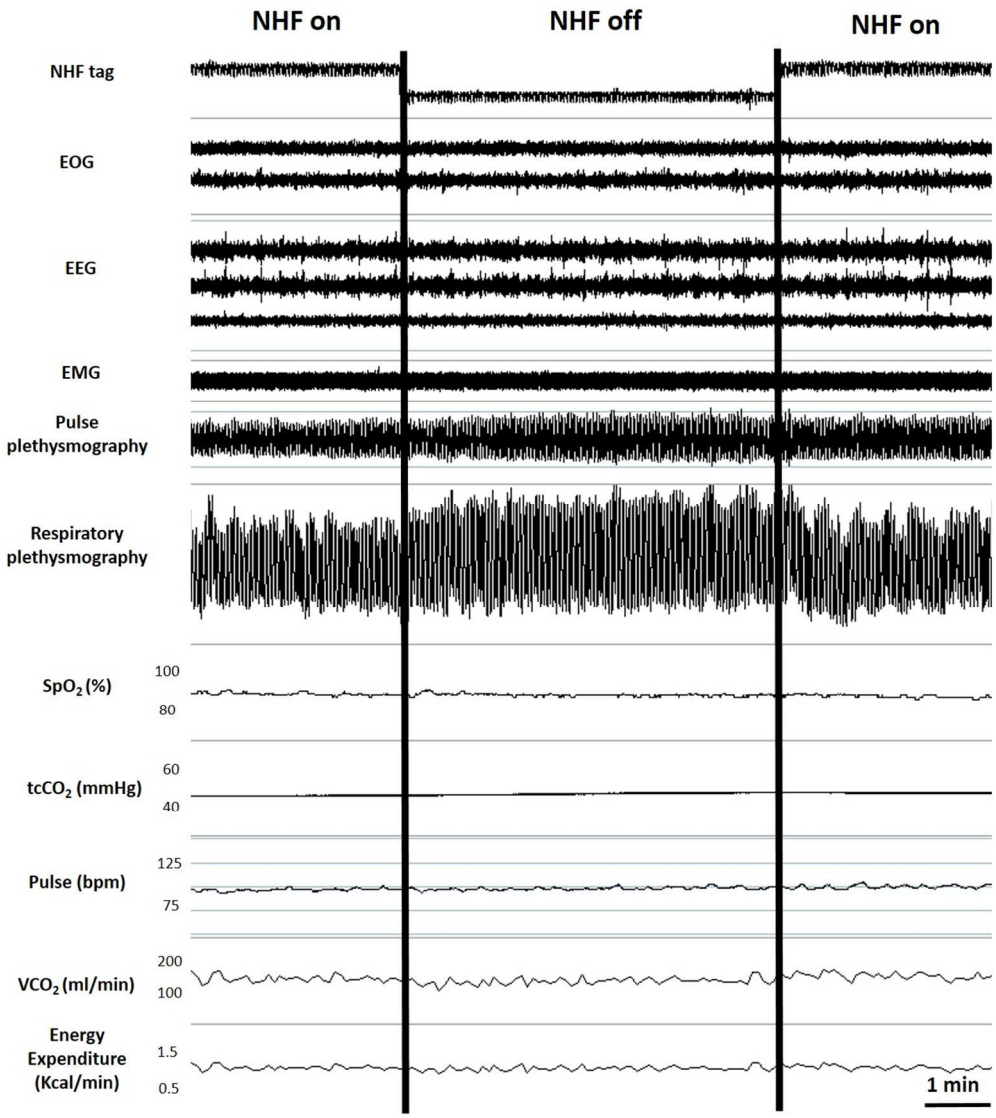

Figure 2 - Experimental protocol. Participants slept under NHF (20 L/min, 85% humidity, 32 ^{o}C) for acclimatization. Once achieving stage 2 NREM sleep, we alternated NHF delivery (NHF on) with no flow delivered (NHF off) to the nose. During NHF off period, we delivered the same flow to the subjects' chest to maintain constant the flow delivery to the hood interior. We selected periods without arousals or changes in sympathetic activity. During periods of NHF on, we could observe a reduction in ventilation, but no change in CO_2 production or energy expenditure.

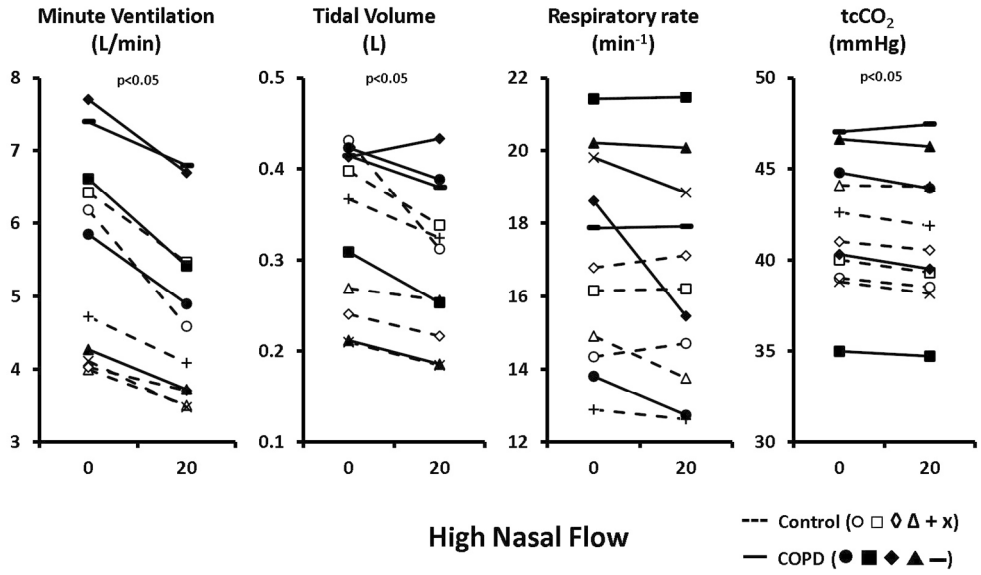

Figure 3 - Ventilatory response to NHF. The plots display average individual values for each parameter under the two conditions (NHF off / NHF on). Solid traces represent patients with COPD and dashed traces represent controls. Individuals are identified by different symbols and the coding is maintained for the subsequent graphs (e.g., black square is the same individual in figures 3 to 5). We observed a significant reduction in minute ventilation for all patients (NHF off: 5.6 ± 0.4 L/min, NHF on: 4.8 ± 0.4 L/min, $p<0.05$ for paired T-test) with the use of NHF. Tidal volumes were also reduced by the use of NHF in all but one patient (NHF off: 340 ± 30 ml, NHF on: 300 ± 30 ml, $p<0.05$ for paired T-test). Overall, respiratory rate did not change, but it is noteworthy to observe a reduction in respiratory rate for the one individual with no reduction in tidal volume. We noticed a slight, but statistically significant, reduction in transcutaneous CO_2 with the use of NHF (NHF off: 42.6±1.2 mmHg, NHF on: 42.1±1.2 mmHg, $p<0.05$ for paired T-test).

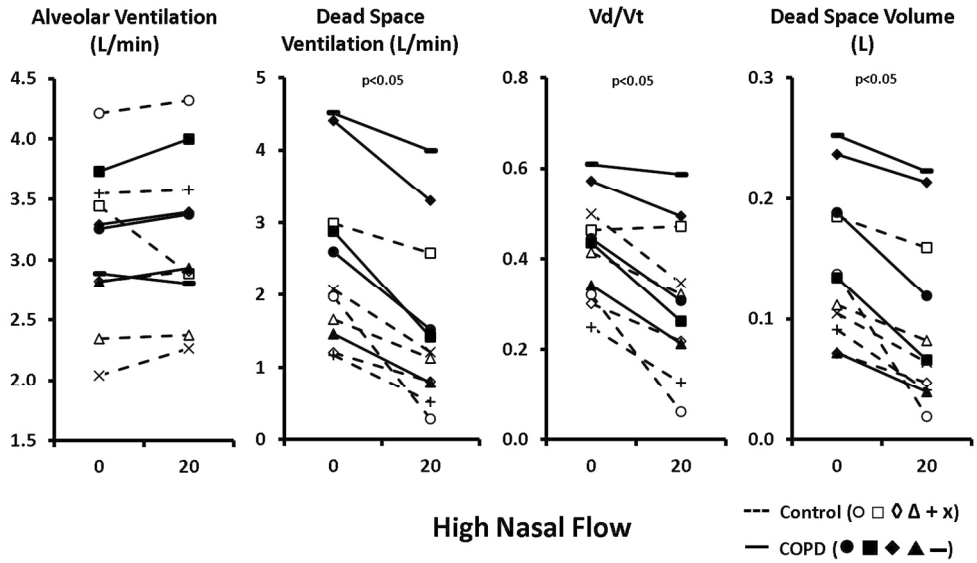

Figure 4 - Alveolar ventilation and dead space with NHF. The plots display average individual value for each parameter under the two conditions (NHF off / NHF on). Solid traces represent patients with COPD and dashed traces represent controls. Individuals are identified by different symbols and the same coding system is used in figures 3 to 5. There was no change in alveolar ventilation with the use of NHF. However, in all subjects NHF produced a significant reduction in dead space ventilation (NHF off: 2.5 ± 0.4 L/min to 1.7 ± 0.3 L/min, $p<0.05$ for paired T-test), dead space fraction (NHF off: 0.43 ± 0.03, NHF on: 0.33 ± 0.04, $p<0.05$ for paired T-test) and dead space volume (NHF off: 150 ± 20 ml, NHF on: 100 ± 20 ml, $p<0.05$ for paired T-test).

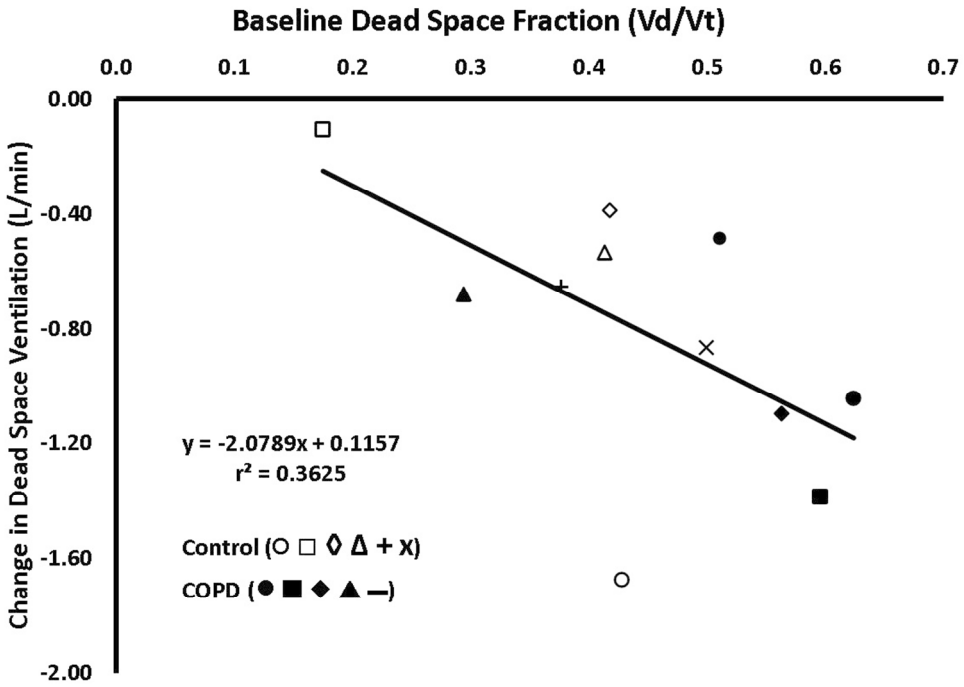

Figure 5 - Dead space fraction correlation. The points represent individual averages for patients with COPD and controls. Individuals are identified by different symbols and the same coding system is used in figures 3 to 5. We noticed an inverse correlation of the amount of the reduction NHF produced in dead space fraction with the values of baseline dead space fraction (measured with NHF off).

	Control	COPD
Demographics		
n	6	5
Age (years)	44.2 ± 18.4	59 ± 7.5
Gender	2 Males; 4 Females	1 Male; 4 Females
Weight (Kg)	70.3 ± 15.4	81.3 ± 11.0
Height (cm)	164.8 ± 12.4	167.6 ± 6.8
BMI (Kg/cm2)	25.3 ± 6.0	28.3 ± 3.2
Lung Function		
FEV_1/FVC (%)	83.5 ± 14.9	55.0 ± 6.3
FEV_1 (% of predicted)	86.8 ± 15.4	53.8 ± 10.4
Baseline Values		
Pulse (bpm)	69.3 ± 11.1	76.4 ± 16.0
SaO_2 (%)	95.2 ± 2.3	97 ± 0.7
End-tidal CO_2 (mmHg)	40.9 ± 2.1	42.7 ± 5.1

Table 1 - Demographics of participants. We enrolled 6 controls and 5 patients with COPD. Our sample consisted of more females in both groups. Patients with COPD were older, but with similar BMI. FEV_1 was lower for patients with COPD, as determined by enrollment, but there was no difference in SaO_2 and end-tidal CO_2 during baseline measurements at the beginning of the protocol.