RESEARCH ARTICLE

Nasal high flow reduces minute ventilation during sleep through a decrease of carbon dioxide rebreathing

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Pinkham M, Burgess R, Mündel T, Tatkov S. Nasal high flow reduces minute ventilation during sleep through a decrease of carbon dioxide rebreathing. J Appl Physiol 126: 863–869, 2019. First published February 7, 2019; doi:10.1152/japplphysiol.01063.2018.—Nasal high flow (NHF) is an emerging therapy for respiratory support, but knowledge of the mechanisms and applications is limited. It was previously observed that NHF reduces the tidal volume but does not affect the respiratory rate during sleep. The authors hypothesized that the decrease in tidal volume during NHF is due to a reduction in carbon dioxide (CO2) rebreathing from dead space. In nine healthy males, ventilation was measured during sleep using calibrated respiratory inductance plethysmography (RIP). Carbogen gas mixture was entrained into 30 l/min of NHF to obtain three levels of inspired CO2; 0.04% (room air), 1%, and 3%. NHF with room air reduced tidal volume by 81 ml, SD 25 (P < 0.0001) from a baseline of 415 ml, SD 114, but did not change respiratory rate; tissue CO2 and O2 remained stable, indicating that gas exchange had been maintained. CO2 entrainment increased tidal volume close to baseline with 1% CO2 and greater than baseline with 3% CO2 by 155 ml, SD 79 (P = 0.0004), without affecting the respiratory rate. It was calculated that 30 l/min of NHF reduced the rebreathing of CO2 from anatomical dead space by 45%, which is equivalent to the 20% reduction in tidal volume that was observed. The study proves that the reduction in tidal volume in response to NHF during sleep is due to the reduced rebreathing of CO2. Entrainment of CO2 into the NHF can be used to control ventilation during sleep.

NEW & NOTEWORTHY The findings in healthy volunteers during sleep show that nasal high flow (NHF) with a rate of 30 l/min reduces the rebreathing of CO2 from anatomical dead space by 45%, resulting in a reduced minute ventilation, while gas exchange is maintained. Entrainment of CO2 into the NHF can be used to control ventilation during sleep.

carbon dioxide; dead space; nasal high flow; sleep; ventilation disease (26, 35). Furthermore, NHF has a similar efficacy as noninvasive ventilation (NIV) in reducing the need for the escalation of treatment in some patients with acute respiratory failure (12, 16). The available evidence highlights a potential use of NHF therapy in a wide range of settings, from home to acute care (12, 16, 20, 26, 35).

One of the key mechanisms of NHF is the reduction of dead space (4, 5, 10). NHF reduces dead space by purging the expired air from the upper airways and replacing it with fresh gas (23, 24). Currently, there is a lack of explanation as to how NHF can reduce dead space rebreathing without affecting blood gases, as observed in some studies (29). To date, one study has measured gases directly in the trachea during NHF. Möller et al. (24) measured gases in the trachea of three tracheostomized patients using a side-stream gas analyzer. It was estimated that NHF at 15, 30, and 45 l/min decreased the rebreathing of CO2 and increased rebreathing of O2 by −1, 2, and 3 ml per breath, respectively, which corresponded to −20, 40, and 60 ml reduction of dead space (24). Mündel et al. (25) previously measured a substantial (20%) decrease in minute ventilation in response to NHF in sleeping healthy volunteers. The decrease in minute ventilation was mediated wholly by a reduction in tidal volume (25). Biselli et al. (5, 6) replicated these findings in both sleeping healthy volunteers and COPD patients and demonstrated that the reduced minute ventilation in response to NHF significantly lowered the work of breathing. The 20 to 60 ml of dead-space clearance estimated by Möller et al. (24) does not explain the approximate 20% reduction in tidal volume in response to NHF observed in these studies (25).

The responses to NHF may be dependent on the sleep/awake state. In wakefulness, most subjects produce slow and deep breathing during NHF therapy (18, 25), which can be favorable in patients with respiratory distress. However, behavioral influence on breathing can mask the metabolic-dependent control of breathing that determines the long-term trends in ventilation (8, 14).

During sleep, the chemoreceptors located in the carotid body are the primary driver of short-term changes in ventilation, and their input acts to maintain a constant arterial blood CO2 and O2 (8, 22). Therefore, sleep is the preferable setting to measure the effects of CO2 rebreathing on ventilation. To date, no studies have directly related CO2 rebreathing with changes in ventilation in response to NHF.

The above-mentioned findings led the authors to the hypothesis that an NHF-mediated reduction in the rebreathing of CO2
is entirely responsible for the decrease in tidal volume during sleep.

On the basis of the inconsistency between previous estimates of dead-space clearance and the magnitude of reduction in tidal volume during sleep (24, 25), the authors further hypothesized that the actual reduction of dead space by NHF is substantially larger than previously estimated.

MATERIALS AND METHODS

Subjects. Healthy males were recruited and considered eligible if they were between the ages of 18 and 40 yr, had a body mass index (BMI) of 20 to 30 kg/m², and had no abnormalities in sleep or respiratory function, such as sleep apnea, asthma, or allergies. The study was approved by the Massey University Human Ethics Committee and was performed according to the latest version of the Declaration of Helsinki, whereby written informed consent was obtained from each subject. Eleven subjects (Table 1) participated in this study. Data from two subjects were excluded because of their inability to sleep during the entire protocol. As can be seen from Table 1, subjects were all healthy men, with a mean age of 25 yr (SD 3) and a BMI of 25 kg/m² (SD 3).

Study design. NHF of room air was delivered at 37°C and fully saturated with water. Flow was generated by the AIRVO 2 (Fisher & Paykel Healthcare, New Zealand) with a humidifier to maintain a remote control of flow, and then the respiratory gas was conditioned by the MR850 respiratory humidifier (Fisher & Paykel Healthcare, Auckland, New Zealand). To alter the level of inspired CO₂, a carbogen gas mixture (6% CO₂-20.9% O₂-73.1% nitrogen; BOC Limited, Auckland, New Zealand) was entrained via the inlet oxygen port on the AIRVO 2 device. NHF was delivered through a nasal cannula (Optiflow + OPT944 Medium; Fisher & Paykel Healthcare), as illustrated previously (25).

Study protocol. The study consisted of a single overnight visit by each subject. A brief introductory session was held to familiarize all subjects with the interventions they would be receiving. The subjects went to sleep while wearing the nasal interface and maintained a supine position. Once the subject entered stage 2 of non-rapid-eye-movement (NREM) sleep, and the recordings were stable, the experimental protocol commenced. When the subject was in NREM sleep, tidal CO₂ was considered to be equivalent to the partial pressure of end-tidal CO₂ in the inspired gas. It was assumed that a constant metabolic production of CO₂ in the inspired gas. It was assumed that a constant metabolic production of CO₂ was maintained during the use of NHF (4, 31). Therefore, VCO₂ during NHF therapy was calculated using Eq. 1:

\[
V_A = V_T - V_D.
\]

For the purposes of the calculations, the partial pressure of end-tidal CO₂ was considered to be equivalent to the partial pressure of tissue CO₂ (3, 37). The end-tidal CO₂ fraction was then calculated from the partial pressure of tissue CO₂ (Table 2) with a mean atmospheric pressure during the study of 760.7 mmHg (SD 8). The volume of CO₂ excreted via the lungs per breath was calculated using Eq. 2:

\[
V_{CO_2} = V_A \cdot (f_{ex} - f_{in} - f_{ex} \cdot f_{in} \cdot V_A) / V_{CO_2}
\]

where \( V_{CO_2} \) is the volume of CO₂ excreted via the lungs per breath, \( f_{ex} \) is the end-tidal CO₂ fraction, and \( f_{in} \) is the fraction of CO₂ in the inspired gas. It was assumed that a constant metabolic production of CO₂ was maintained during the use of NHF (4, 31). Therefore, V_A during NHF therapy was calculated by rearranging Eq. 2:

\[
V_{A_{NHF}} = V_{CO_2} / (f_{ex} - f_{in} - f_{ex} \cdot f_{in} \cdot V_A)
\]

where \( V_{A_{NHF}} \) is the alveolar volume during NHF, \( f_{ex} \) is the end-tidal CO₂ fraction during NHF, and \( f_{in} \) is the fraction of CO₂ in the inspired gas during NHF. V_D during NHF was then calculated by rearranging Eq. 1:

\[
V_{D_{NHF}} = V_{T_{NHF}} - V_{A_{NHF}}
\]

where \( V_{D_{NHF}} \) is the dead-space volume during NHF and \( V_{T_{NHF}} \) is the V_T during NHF, which was measured during the study. On the basis of the ventilation parameters, it is possible to estimate the mean volume of inspired CO₂ (\( V_{in} \) CO₂) per breath using Eq. 5:

\[
V_{in} = (f_{ex} \cdot V_T) + (f_{ex} \cdot V_D).
\]

Table 1. Anthropometric data of subjects

| Subject | Age, yr | Height, cm | Weight, kg | BMI, kg/m² | Vt, ml |
|---------|---------|------------|------------|-------------|-------|
| A       | 22      | 186        | 85         | 25          | 181   |
| B       | 23      | 187        | 95         | 27          | 183   |
| C       | 28      | 185        | 100        | 29          | 178   |
| D       | 23      | 185        | 72         | 21          | 178   |
| E       | 23      | 179        | 72         | 21          | 164   |
| F       | 24      | 179        | 66         | 21          | 164   |
| H       | 21      | 181        | 90         | 25          | 169   |
| I       | 24      | 178        | 83         | 26          | 162   |
| J       | 31      | 171        | 70         | 24          | 146   |

Values are expressed as means (SD), BMI, body mass index; Vt, dead-space volume.
Data analysis. Analog signals were digitized by a 16-bit ADC converter (ADI PowerLab 16/30; ADInstruments, New Zealand), recorded, and then analyzed using ADI LabChart V.8 software. Results are expressed as the means (SD) unless otherwise stated. GraphPad Prism V5.01 (GraphPad Software, San Diego, CA) was used to perform the statistical analysis. Effects of intervention were examined by repeated-measures, one-way ANOVA with a Bonferroni post hoc test for comparisons. The comparison between awake and asleep variables was made using a paired Student’s t-test. The threshold for statistical significance was set at \( P < 0.05 \).

RESULTS

Ventilation changes in the transition to sleep. Ventilation responses are presented in Table 2. Before NHF was applied, the transition into sleep led to a nonsignificant change of breathing pattern, mean RR changed by -2 min\(^{-1}\) (SD 3), \( P = 0.07 \), and mean \( \dot{V}_E \) changed by 1.2 l/min (SD 1.6), \( P = 0.06 \). The partial pressure of tissue CO\(_2\) increased significantly with sleep by 3.7 mmHg (SD 1.9), \( P = 0.0009 \). Following the

Table 2. Tidal volume, respiratory rate, minute ventilation, peripheral capillary oxygen saturation, and transcutaneous partial pressure of carbon dioxide

|                | n | Tidal Volume, ml | Respiratory Rate, breaths/min | Minute Ventilation, liters/min | \( \text{SpO}_2 \), % | \( \text{TcCO}_2 \), mmHg |
|----------------|---|-----------------|-------------------------------|-----------------------------|----------------|-----------------|
| Wakefulness    | 9 | 418 (46)        | 17.4 (2)                      | 7.33 (1.5)                  | 96 (1)         | 40 (3)          |
| NHF OFF        | 9 | 415 (114)       | 15.2 (2)                      | 6.16 (1.3)                  | 94 (2)         | 44 (4)          |
| NHF ON         | 9 | 334 (108)*      | 14.6 (3)                      | 4.70 (1.2)*                 | 94 (2)         | 44 (4)          |
| NHF + 1% CO\(_2\) | 9 | 393 (111)*†     | 14.6 (2)                      | 5.61 (1.4)*                 | 94 (2)         | 44 (4)          |
| NHF + 3% CO\(_2\) | 9 | 570 (155)*†‡    | 14.5 (1)                      | 8.19 (2.0)*‡                 | 96 (2)*†       | 45 (5)*†        |
| REM sleep      |   |                 |                               |                             |                |                 |
| NHF OFF        | 3 | 539 (47)        | 13.7 (2)                      | 7.31 (0.6)                  | 92 (1)         | 44 (3)          |
| NHF ON         | 3 | 508 (92)        | 12.9 (1)                      | 6.40 (0.2)                  | 92 (1)         | 44 (3)          |
| NHF + 1% CO\(_2\) | 3 | 515 ± 113       | 13.8 (2)                      | 7.01 (0.5)                  | 94 (4)         | 44 (2)          |
| NHF + 3% CO\(_2\) | 3 | 776 ± 53        | 13.9 (1)                      | 10.75 (0.6)                 | 94 (3)         | 45 (4)          |

Data are expressed as means (SD). Values were first obtained during wakefulness during normal breathing. Once subjects entered stage 2 non-rapid-eye-movement (NREM) sleep, values were obtained before nasal high flow (NHF) was applied (NHF OFF) and then during NHF at 30 l/min with room air (NHF ON), NHF with 1% CO\(_2\) in the inspired air (NHF + 1% CO\(_2\)), and NHF with 3% CO\(_2\) in the inspired air (NHF + 3% CO\(_2\)). In three subjects, ventilation parameters were measured during rapid-eye-movement (REM) sleep. \( \text{SpO}_2 \), oxygen saturation; \( \text{TcCO}_2 \), transcutaneous partial pressure of carbon dioxide.

*Significant difference from NHF OFF, \( P < 0.05 \); †Significant difference from NHF ON, \( P < 0.05 \); ‡Significant difference from NHF + 1% CO\(_2\), \( P < 0.05 \).
transition into sleep, ventilation stabilized, and irregularities only occurred during arousals or REM periods.

**Ventilatory responses to NHF during sleep.** In response to NHF, \( V_T \) decreased by 81 ml (SD 25), \( P < 0.0001 \), and the RR was unchanged, \( P = 0.103 \). As a result, \( V_E \) decreased by 1.5 l/min (SD 0.7), \( P = 0.0002 \). The reduction in \( V_T \) occurred within 1 min of NHF being applied and then remained stable at the new level until NHF was turned off, at which point \( V_T \) returned to baseline. Arterial \( O_2 \) saturation and tissue \( CO_2 \) levels remained stable following the application of NHF at 30 l/min (Table 2).

Three subjects entered REM sleep during testing; the average duration of REM sleep while recording was 29 (SD 9) min, and the protocol was shortened accordingly. The responses to NHF during REM sleep were similar to responses in NREM sleep, but the reduced group number limited the authors’ ability to test statistical significance (Table 2). The subjects typically remained asleep during the application of NHF, although flows greater than 25 l/min occasionally caused arousals.

**Increasing the fraction of inspired \( CO_2 \) during NHF.** As shown in Fig. 2, \( V_T \) increased as the level of inspired \( CO_2 \) increased; 1% \( CO_2 \) in the inspired gas increased \( V_T \) by 57 ml (SD 23), \( P < 0.0001 \), slightly below the pre-NHF level; 3% \( CO_2 \) in the inspired gas increased \( V_T \) by 236 ml (SD 66), which was significantly greater when compared with pre-NHF level (\( P = 0.0004 \)), NHF with room air (\( P < 0.0001 \)), and NHF with 1% of \( CO_2 \) (\( P < 0.0001 \)).

The partial pressure of tissue \( CO_2 \) was maintained constant as the concentration of inspired \( CO_2 \) was increased to 1%, but it was increased in response to 3% \( CO_2 \) by 1.2 mmHg (SD 1.0, \( P = 0.007 \)) (Table 2). The blood \( O_2 \) saturation was unchanged at 1% \( CO_2 \), but was increased in response to 3% \( CO_2 \) by 2% (SD 3), \( P = 0.007 \) (Table 2).

Peak inspiratory flow was calculated by differentiation of calibrated RIP. Peak inspiratory flow in NREM sleep during baseline (NHF OFF) was 21.91 l/min (SD 4.8), NHF ON was 19.8 l/min (SD 5.6), NHF ON + 1% \( CO_2 \) was 20.78 l/min (SD 4.0), and NHF ON + 3% \( CO_2 \) was 29.48 l/min (SD 5.96). During REM sleep, peak inspiratory flow greatly exceeded the NHF rate of 30 l/min during entrainment of 3% \( CO_2 \) [32 l/min (SD 10)] but was below 30 l/min while entraining 1% \( CO_2 \).

**DISCUSSION**

The primary findings of the current study are: 1) 30 l/min of NHF in healthy male subjects reduces the rebreathing of \( CO_2 \) from anatomical \( V_T \) by ~45%, and 2) entrainment of \( CO_2 \) into the NHF can be used to control ventilation during sleep. The study proves that the reduction in \( V_T \) in response to NHF during sleep is due to the reduced rebreathing of \( CO_2 \) from the anatomical \( V_T \).

In patients, a reduction of RR is the most frequently reported physiological outcome related to NHF, and it is cited as indirect evidence for reduced \( V_E \) (9, 20, 30, 34). During NHF, breathing flow and volume are typically not recorded, as these are technically challenging to measure due to the lack of a seal between the nasal cannula and the airways. Previously, in a research setting, calibrated RIP was used to indirectly measure breathing parameters during NHF (4, 25). Mündel et al. (25)
first observed in three sleeping healthy volunteers that NHF
with a rate of 30 l/min reduced VT by ~20% but did not affect RR. These results were replicated by Biselli et al. (5) in sleeping COPD patients and healthy controls using calibrated RIP (4) and direct measurements of breathing flow. In sleeping COPD patients, NHF at 20 l/min reduced the work of breathing, pressure time product, and esophageal pressure swings, but not lung compliance or airway resistance, leading the authors to conclude that the reduced work of breathing was due to reduced VT and V5 (5). In the current study, NHF at 30 l/min reduced VT from 415 ml (SD 114) to 334 ml (SD 108), without a change in RR or gas exchange in nine sleeping healthy volunteers, reproducing the results of Mündel et al. (25) and Biselli et al. (4).

It is technically complex to quantify the rebreathing of expired gas during NHF therapy. Measurement of CO2 re-breathing typically requires a side-stream gas analyzer placed in the stream of respiratory gas (e.g., from the trachea, or using a tight-fitting mask) while simultaneously measuring breathing flow and volume. Along with the complexity in directly quantifying respiratory flows and volumes in an open system such as NHF, it can be very difficult to synchronize the input from the gas analyzer with the breathing flows. Instead, the authors used CO2 entrainment into the respiratory gas provided by the NHF. The results during sleep indicate that VT is responsive to changes in CO2 rebreathing, but RR is not, at least in the range tested. These findings are consistent with those by Haldane et al. (13), who showed in awake subjects that elevating the level of inspired CO2 causes a selective increase in VT. In the current study, increasing the fraction of inspired CO2 reversed the effects of NHF by increasing VT and V5. Therefore, the approximate 20% decrease in VT in response to NHF during sleep is consistent with a substantial reduction in CO2 rebreathing (4, 5, 25).

During NHF, breathing is spontaneous, and the responses rely on the physiological control of ventilation, which can present in a multitude of ways. Awake subjects can respond to the NHF-mediated expiratory resistance by prolonging expiration and increasing VT, a response not observed during sleep at flows up to 30 l/min (4, 5, 25). The variable responses to NHF may explain the contrast in the clinical findings, in which some studies have shown no effect on tissue/arterial CO2 (4, 10, 12, 16, 20), and others have shown a reduction (11, 19, 26). For example, Pilcher et al. (29) applied 30 min of NHF therapy to 24 hypercapnic patients and reported a small decrease in tissue CO2 of only 2 mmHg. The authors questioned the clinical significance of the small reduction in tissue CO2. They observed a marginal change in RR of ~2 breaths/min but did not measure VT. The current study highlights that alveolar ventilation and gas exchange may remain constant in response to NHF despite a reduction in dead-space ventilation (5).

NHF delivered 30 l/min, or 500 ml/s, of fresh gas. Assuming that the nasal cavity is approximately one-third of anatomical Vdp, then the volume of fresh gas delivered per second by the NHF was ~9 × the volume of the nasal cavity. The current results demonstrate a 45% reduction in CO2 rebreathing due to 30 l/min NHF and suggest that the clearance of anatomical VD would extend beyond the volume of the nasal cavity. This observation supports Möller et al. (24), who demonstrated that NHF up to 45 l/min clears a radioactive tracer gas from as distal as the trachea in healthy subjects. Studies are required to better understand how the complex geometry of the upper airways, position of the soft palate, and vocal chords can influence the clearance of anatomical VT by NHF.

The reduction in CO2 rebreathing is dependent on the leak around the cannula in the nostrils and the open/close position of the mouth (28). In an upper airway model in which variiances in leak can be controlled, NHF cleared a greater volume of expired gas in the upper airways in the open mouth setting versus the closed mouth (28). It was observed that some subjects opened their mouths during sleep while receiving NHF. However, the degree of leak through the mouth could not be quantified, and it is not possible to comment on the effect this may have had on the results.

Use of CO2 in the inspired gas has been proposed as a therapy for Cheyne-Stokes breathing (33); however, technical constraints of CO2 supplementation have restricted the practical implementation (2). Entrainment of a carbogen mixture rather than pure CO2 delivered via NHF could serve as a feasible and safe alternative to closed systems, such as continuous positive airway pressure (CPAP) or NIV to manage hypoventilation due to various causes. Subjects typically displayed stable sleep during the experimental protocol; however, occasionally an increase of CO2 from 1% to 3% was associated with arousals. CO2 supplementation of 3% significantly increased the partial pressure of tissue CO2 from 44 ± 4 mmHg to 45 ± 5 mmHg, and increased SpO2 from 94 ± 2% to 96 ± 2%. These findings are consistent with previous observations in studies investigating the use of CO2 supplementation for treating Cheyne-Stokes breathing (2, 33). The increase of arterial O2 saturation may be explained by the CO2-induced increase in VT, and clinical significance of this effect could be explored in patients with hypoxemia.

Limitations. The study was performed in healthy male volunteers. However, the reduction in anatomical VD should be similar in patients with respiratory disease, and the results can be extrapolated. Previous research shows that patients respond to NHF during sleep with a reduction in VT and V5, but stable RR (4, 5). A number of assumptions were made in the calculations, although the values are within physiological norms. For example, it was estimated that the pre-NHF VD/VT was 0.41, which is consistent with direct measures of dead-space ventilation in healthy volunteers during sleep using the Bohr equation (31, 36).

The authors assumed that the fraction of inspired CO2 measured in the NHF circuit was the same as that inspired by the subject. NHF at 30 l/min delivers the respiratory gas at greater flow rates than the peak inspiratory flow in healthy subjects at rest, thereby precluding the entrainment of room air (21); this is supported by data on peak inspiratory flow that was substantially lower than NHF of 30 l/min with room air, 1% CO2, and 3% CO2. Indirect measurement of VT with calibrated RIP has been shown as a reliable method in a number of the above-mentioned studies. Direct measurement of breathing flow during NHF therapy is complex and may introduce additional errors due to increased resistance and rebreathing; consequently, RIP is an appropriate method for quantifying ventilation during NHF treatment.

The study results during REM sleep were less extensive than during NREM sleep. However, similar responses to NHF were observed during REM sleep in the three subjects with REM. In previous research, V5 during REM sleep has been similar or
slightly reduced compared with during NREM sleep (36). The three subjects who were recorded during REM sleep displayed higher-than-average $V_e$ during NREM sleep, 7.2 l/min (SD 1.5), which was similar to the volumes recorded in the same subjects during REM sleep, 7.3 l/min (SD 0.6). The RR during NREM in the three subjects, 14 breaths/min (SD 1), was also similar as seen during REM sleep, 14 breaths/min (SD 2). The results indicate that NHF therapy is effective in reducing $V_e$ throughout the sleep stages.

**Physiological and clinical implications.** The results demonstrate a 45% decrease of rebreathing from anatomical $V_d$, which resulted in a 20% reduction in $V_T$ (81 ml, SD 25), reducing the $V_d/V_T$ from 0.41 to 0.26 in healthy males. It has been shown that even small increases in the dead-space fraction are associated with increased mortality in patients with acute respiratory distress (27); a reduction in the dead-space fraction and CO$_2$ rebreathing could be beneficial in these patients. By decreasing the rebreathing of expired air from the anatomical $V_d$, NHF reduces wasted ventilation, and gas exchange can be maintained with a lower $V_e$. This increase in breathing efficiency should unload the respiratory muscles and reduce the work of breathing (5). A reduction in the work of breathing may alleviate respiratory muscle fatigue and the requirement to escalate care in various respiratory-compromised patients. This may be one mechanism that explains clinical findings that show NHF therapy to be as effective as NIV in preventing the escalation to invasive ventilation in some patients with respiratory failure (12, 16).

The findings that NHF reduces the rebreathing of CO$_2$ from anatomical $V_d$, while $V_a$ remains unchanged; this must be considered when interpreting clinical findings during NHF therapy, particularly, in the context of hypercapnia or hypoxemia and when $V_T$ is unknown. The energy cost of breathing in patients with respiratory disease is more sensitive to changes in $V˙E$ when compared with healthy individuals (7); a decrease in the required $V_e$, such as in response to NHF, may be particularly beneficial in patients. It is possible that the reduction in work of breathing over a long period of time can reduce the O$_2$ consumption and CO$_2$ production by the respiratory muscles, which may further reduce the required $V_e$. The findings help to explain clinical studies in acute- and chronic-care patients who received respiratory support with NHF therapy and displayed a reduced escalation of care and an improved health-related quality of life when compared with conventional O$_2$ therapy (12, 17, 20, 26, 35).

**Conclusion.** The study proves that the reduction in tidal volume in response to NHF during sleep is due to the reduced rebreathing of CO$_2$. Entrainment of CO$_2$ into the NHF can be used to control ventilation during sleep.

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**DISCLOSURES**

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**AUTHOR CONTRIBUTIONS**

T.M. and S.T. conceived and designed research; M.I.P., T.M., and S.T. performed experiments; M.I.P. and R.B. analyzed data; M.I.P., R.B., T.M., and S.T. interpreted results of experiments; M.I.P. and S.T. prepared figures; M.I.P. and S.T. drafted manuscript; M.I.P., R.B., T.M., and S.T. edited and revised manuscript; M.I.P., R.B., T.M., and S.T. approved final version of manuscript.

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