Changes in lung volume and upper airway using MRI during application of nasal expiratory positive airway pressure in patients with sleep-disordered breathing

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Braga CW, Chen Q, Burschtin OE, Rapoport DM, Ayappa I. Changes in lung volume and upper airway using MRI during application of nasal expiratory positive airway pressure (nEPAP) delivered with a disposable device (Provent, Ventus Medical) has been shown to improve sleep-disordered breathing (SDB) in some subjects. Possible mechanisms of action are 1) increased functional residual capacity (FRC), producing tracheal traction and reducing upper airway (UA) collapsibility, and 2) passive dilatation of the airway by the expiratory pressure, carrying over into inspiration. Using MRI, we estimated change in FRC and ventilation, as well as UA cross-sectional area (CSA), in awake patients breathing on and off the nEPAP device. Ten patients with SDB underwent nocturnal polysomnography and MRI with and without nEPAP. Simultaneous images of the lung and UA were obtained at 6 images/s. Image sequences were obtained during mouth and nose breathing with and without the nEPAP device. The nEPAP device produced an end-expiratory pressure of 4–17 cmH2O. End-tidal Pco2 rose from 39.7 ± 5.3 to 47.1 ± 6.0 Torr (P < 0.01). Lung volume changes were estimated from sagittal MRI of the right lung. Changes in UA CSA were calculated from transverse MRI at the level of the pharynx above the epiglottis. FRC determined by MRI was well correlated to FRC determined by N2 washout (r = 0.76, P = 0.03). nEPAP resulted in a consistent increase in FRC (46 ± 29%, P < 0.001) and decrease in ventilation (50 ± 15%, P < 0.001), with no change in respiratory frequency. UA CSA at end expiration showed a trend to increase. During wakefulness, nEPAP caused significant hyperinflation, consistent with an increase in tracheal traction and a decrease in UA collapsibility. Direct imaging effects on the UA were less consistent, but there was a trend to dilatation. Finally, we showed significant hypoventilation and rise in Pco2 during use of the nEPAP device during wakefulness and sleep. Thus, at least three mechanisms of action have the potential to contribute to the therapeutic effect of nEPAP on SDB.

obstructive sleep apnea; obstructive sleep apnea therapy; resistance valves; tracheal traction

BECAUSE OF THE HIGH PREVALENCE (24) and morbidity (11, 24) associated with obstructive sleep apnea hypopnea syndrome (OSAHS), its diagnosis and treatment are important public health issues. The current gold-standard therapy for OSAHS is continuous positive airway pressure (CPAP), and although it is effective, acceptance of CPAP is frequently suboptimal (22). Alternative therapies, such as oral appliance therapy (4) and upper airway (UA) surgery (15), have variable efficacy and are expensive and/or invasive. Recently, a simple disposable device (Provent, Ventus Medical) that appears to be effective in a significant number of patients with OSAHS has been approved by the US Food and Drug Administration (1, 3, 16, 21). The device consists of a pair of valves secured in the nostrils by an external adhesive strip. Upon inspiration, negative airway pressure opens the valves, allowing for unimpeded airflow. Upon expiration, the valves close, increasing the resistance of the device and producing substantial (5–20 cmH2O) nasal expiratory positive airway pressure (nEPAP) (14). This increase in expiratory positive airway pressure (EPAP) is closely associated with effectiveness of the valve (14), but the physiological mechanisms underlying the benefits of EPAP are not fully understood. Two possible explanations are as follows: 1) the end-expiratory pressure results in an increased functional residual capacity (FRC), which causes increased traction on the trachea and UA and reduces collapsibility of the critical segment of the UA, and 2) the expiratory pressure in the UA results in passive (i.e., nonmuscular) dilatation of the airway just prior to inspiration, with carryover of this larger size into the period of collapse during inspiration. Furthermore, it is possible that an impediment to ventilation by the valves will cause an increase in Pco2, increasing respiratory drive. This increased respiratory drive could increase UA muscle tone and help maintain UA patency. All these mechanisms would improve OSAHS.

In a previously published study to evaluate the mechanisms of action of these nEPAP devices, we speculated that the progressive buildup of pressure when subjects fall asleep and begin breathing through the nose was consistent with an increase in FRC similar to that seen in “auto-positive end-expiratory pressure” (14). However, in this previous study (14), the effect of the device on lung volumes was not directly measured. Furthermore, Pco2 was measured only during use of the device and could not be directly compared with starting levels during wakefulness and without nEPAP.

The present study was designed 1) to assess the change in FRC and cross-sectional area (CSA) of the UA induced by breathing through the nEPAP device and 2) to measure changes in Pco2 resulting from any change in ventilation or ventilatory pattern. Because MRI was used to provide direct imaging of the UA and lung volume, these preliminary data are limited to effects during wakefulness and may need to be further investigated during sleep.
MATERIALS AND METHODS

Patient Selection

Ten patients [7 male, 3 female; 30–62 yr old, 34.9 ± 8.8 kg/m² body mass index (BMI)] with clinical OSAHS (n = 8) or significant snoring complicated by excessive daytime sleepiness (n = 2) were recruited for the study from patients presenting to the New York University Sleep Disorders Center for evaluation of sleep-disordered breathing (SDB). The respiratory disturbance index (RDI), defined as the number of apneas, hypopneas, and respiratory effort-related arousals per hour of sleep, was 4.1–69.9/h (mean 26.9/h). Patients with significant nasal congestion/obstruction, central sleep apnea, or other untreated major systemic or acute illnesses (other than obesity) were excluded.

Study Procedures

Diagnostic nocturnal polysomnogram. All patients underwent a full in-laboratory nocturnal polysomnogram (NPSG) performed according to standard clinical guidelines. Monitoring included frontal, central, and occipital EEG, electrooculogram, and submental electromyogram (EMG) to monitor sleep; an anterior tibialis EMG to monitor leg movements; a unipolar electrocardiogram to monitor cardiac activity; pulse oximeter to measure O₂ saturation; Pro-Tech zRIP system to detect chest and abdominal movements; and a multiposition sensor (Pro-Tech) switch to determine sleep position. A nasal cannula-pressure transducer system (model PTAF2, Pro-Tech, Wood-inville, WA) was used to measure airflow, with an additional tap introduced to simultaneously sample end-tidal PCO₂ (Novametrix Medical System) during the diagnostic polysomnogram. An oral thermistor was used to detect oral airflow.

Therapeutic (nasal valve device) polysomnography procedure. On a separate night, a full NPSG that was identical to the diagnostic NPSG, except for respiratory monitoring, was performed. Nasal flow was recorded with a pneumotachograph (Hans Rudolph, Kansas City, MO) attached to a unpressurized nasal mask placed over the nasal valve device, producing a signal essentially identical to the signal from the nasal cannula used in the diagnostic NPSG (14). During this therapeutic night of testing, the patients wore the nasal valve device (measured resistance 80 cmH₂O·s·l⁻¹ at a flow rate of 100 ml/s), which consists of two separate adhesive valves designed to produce nEPAP, on each nostril. The standard Provent nEPAP device was modified by Ventus Medical to allow monitoring of intranasal pressure (recorded from inside one naris) and end-tidal PCO₂ (recorded from inside the other naris).

The mask and pneumotachograph had a measured dead space of <110 ml, similar to most systems used for respiratory monitoring, and are unlikely to contribute to significant rebreathing (7). Furthermore, to prevent even this volume from acting as a significant dead space, a bias “washout” flow was created by application of a low level of suction to tubing attached to a side port on the mask. This bias flow was adjusted in preliminary studies to produce ∼15 l/min of flow through the mask and was independent of the mask pressure. During our data acquisition, a continuous trace of PCO₂ was monitored, and PCO₂ returned to 0 Torr prior to inspiration. The lowest effective nEPAP was determined, as previously reported (14), as the lowest pressure at end expiration during supine stage N2 sleep that effectively eliminated SDB for ≥2 min of documented sleep. In addition, for each patient, the end-expiratory pressure established in the nasal cavity by stable nasal breathing through the nEPAP device during wakefulness was recorded. End-tidal PCO₂ during quiet wakefulness in the supine position was recorded with and without the nEPAP valve in place. This measurement was obtained from the patients during a brief period of breathing through the nose (with the mouth closed). These measurements were also obtained during sleep. Intranasal end-tidal PCO₂ values are the average of values obtained from three consecutive breaths during wakefulness and 10 consecutive breaths during sleep. In Fig. 1, traces from one patient breathing through the nasal device show that nasal positive pressure is generated by the valves during expiration, but not during inspiration.

Diagnostic and therapeutic (nEPAP) NPSG scoring. For the NPSG data, sleep, arousals, and periodic leg movements were scored as recommended by the American Academy of Sleep Medicine (8). Respiratory events were scored manually as follows. 1) Apneas were identified when the airflow amplitude on the nasal cannula was <10% of baseline and no flow occurred on the oral thermistor. 2) Hypopneas4% were identified when airflow amplitude was reduced by >30% from baseline followed by 4% O₂ desaturation. 3) Respiratory effort-related arousals occurred when airflow amplitude was reduced by >30% from baseline followed by an EEG arousal within 5 s. 4) RDI was calculated as the sum of apneas, hypopneas4%, and respiratory effort-related arousals divided by total sleep time, as recommended by the American Academy of Sleep Medicine (8).

Lung volumes. Standard spirometry and body plethysmography (Sensormedics, Yorba Linda, CA) were performed in patients in the sitting position during a separate daytime session to determine forced expiratory volume in 1 s, forced vital capacity, FRC, expiratory reserve volume, and total lung capacity in each patient. FRC was also determined by N₂ washout in the sitting and supine positions.

MRI. nEPAP devices were applied ≥20 min prior to the MRI scan. After the patient was habituated to breathing through the device, two time series MRIs, capturing data with the patient lying in the supine position, were acquired simultaneously (alternate images): 1) a sagittal section of the right lung to allow an estimate of lung volume...
The cross section of the upper airway (UA) at the level of the pharynx (Fig. 2C) was scanned at 6 frames/s, providing a time resolution of ~3 images/s for each of the time series using a gradient echo sequence with a very short TR/TE. Patients were instructed to breathe quietly with normal tidal breaths through the nose (with nEPAP) for ~1 min prior to image acquisition. Scan data were then acquired for ~90 s (~300 frames). During the first 30 s, the patient was instructed to continue breathing through the nose, then (on command via a microphone) to switch to mouth breathing for 30 s and then switch back to nose breathing for an additional 30 s. A total of 300 images were acquired during the entire sequence for each of the lung volume and UA data collections. After this scanning sequence, the nEPAP valves were removed, with care taken not to allow patients to change their position, and an identical scanning sequence was performed without nEPAP. Again, the patient breathed for 30 s through the nose, then through the mouth, and again through the nose (all without nEPAP). All scans were conducted on a 3-T whole body MR scanner (Magnetom TIM Trio, Siemens) with a maximal gradient strength of 45 mT/m and maximal slew rate of 200 mT·m⁻¹·s⁻¹ using the following parameters: TR/TE = 1.6 ms/0.7 ms, fractional anisotropy = 5°, matrix size = 192 × 128–192, bandwidth = 965 Hz/pixel, and slice thickness = 16 mm, with (6/8) partial Fourier and field of view = 420–460 mm. In 5 of the 10 patients, each sequence of images (on and off nEPAP) was obtained twice to test reproducibility, and once validated, sequences were obtained only once in the remaining patients.

MRIs were analyzed off-line using DICOM custom software (DICOM Works, INVIWEB, Philippe and Loic Boussel, 2000–2008) and ImageJ (National Institutes of Health). The extracted data consisted of the area of lung on the sagittal sections (approximately proportional to lung volume; see RESULTS) and CSA of the UA at each time point. The outline of the lung/airway was manually identified, and each MRI was converted to a black-and-white image using a threshold level of signal. Figure 3 shows the lung volume by MRI as a function of time during two sequences of imaging lasting ~90 s. In Fig. 3A, the patient switched from nose to mouth to nose

Fig. 2. MRIs. A: sagittal section of the right lung. B: threshold level of signal in sagittal slice of the lung with outline, without (off) and with (on) nEPAP. C: transverse section of the upper airway (UA) at the level of the pharynx. D: outline of UA cross-sectional area (CSA), without and with nEPAP.

Fig. 3. MRI data obtained from 300 images as a function of time during 2 interdigitated sequences of imaging. N, nose breathing; M, mouth breathing; Ne, nose breathing with nEPAP device on the nose; Me, mouth breathing with nEPAP device on the nose, but outside the route of breathing. A: functional residual capacity (FRC, sagittal area) with the patient breathing through the nose (~100 images), mouth (~100 images), and nose (~100 images) without nEPAP. B: FRC data during a sequence with nEPAP. C and D: UA CSA without and with nEPAP.
breathing without nEPAP; in Fig. 3B, the patient performed the same maneuver while wearing the nEPAP device on the nose. In each sequence, the switch from nose to mouth breathing occurred at approximately slice 100 and the switch back to nose breathing at approximately slice 200.

In all measurements without nEPAP (10 of 10) and in 8 of 10 measurements with nEPAP, the FRC values obtained during the two periods of nasal breathing before and after the switch to mouth breathing were within 10% of each other. In the remaining two cases, the ventilatory pattern on nEPAP did not stabilize within the imaging interval, but values were averaged and were 50% higher than the FRC during mouth breathing. For all 20 measurements, FRC is the average of the end-expiratory volume of the two to three breaths that were not part of the transition from mouth to nose breathing.

On transverse scans timed to end inspiration and end expiration, UA CSA was measured at the level of the pharynx (just above the epiglottis). These images of the UA were collected with and without nEPAP to determine whether lung volume changes are related to UA changes.

Figure 3, C and D, shows UA data under conditions similar to those described for Fig. 3, A and B.

Statistical Analysis

All comparisons between baseline (off nEPAP) and with the nEPAP device were done using paired t-tests. Correlation between FRC<sub>MRI</sub> and FRC at sleep stage N2 was tested using Pearson’s correlation. Correlations between end-expiratory pressure developed with the nEPAP device during wakefulness (Pawake), BMI, FRC<sub>MRI</sub>, and change in end-tidal PCO<sub>2</sub> with nEPAP were tested using Pearson’s correlation. Therapeutic response to the nEPAP device during sleep was defined using the data from the therapeutic and diagnostic NPSGs. A reduction of the RDI by 50% and to <20/h was considered an acceptable therapeutic response, whereas meeting neither of these conditions was considered no therapeutic response. RDI = 20/h was chosen on the basis of previous data showing that this value lies at the upper limit of normal in asymptomatic individuals (6).

The protocol was approved by the Institutional Review Board of the New York University School of Medicine; all patients provided informed consent.

RESULTS

Table 1 summarizes demographics for the 10 patients. The mean baseline RDI was 27/h (range 4.1–69.9/h). During the therapeutic NPSG, the group mean RDI fell to 14.9 ± 17.3/h (P = 0.005), and 5 of the 10 patients showed a therapeutically acceptable response on the nEPAP device. Two patients had a diagnostic RDI in the normal range, despite RDIs of 13 and 16.9/h in previous sleep studies used for meeting inclusion criteria; in these patients, therapeutic response to nEPAP could not be evaluated, as RDI was normal at baseline. In one of these patients, no nEPAP data were collected, as the patient withdrew from the study before completing the protocol because of scheduling issues.

Pressure generated during breathing on the nEPAP device was measured during sleep and also during wakefulness. Neither measurement was obtained concurrent with the MRI. Pawake, obtained using a nEPAP device identical to that worn during the MRI, ranged from 4 to 17 cmH<sub>2</sub>O. Although these data were collected during a period remote from the MRI data collection, they provide an indication of the pressures whenever the valves are worn and were therefore taken as representative of all wakefulness periods during which the patients breathed through the valves. The lowest effective nEPAP (during sleep) was 2–19 cmH<sub>2</sub>O. As the definition of the lowest effective nEPAP was based on 2 min of stable breathing, it was available in all patients (including the nonresponders). The end-tidal PCO<sub>2</sub> on the diagnostic night (without nEPAP) was 39.7 ± 5.3 Torr during wakefulness and increased to 43.8 ± 5.1 Torr during sleep (P = 0.04). When nEPAP was used, the end-tidal PCO<sub>2</sub> increased from 39.7 to 47.1 ± 6.0 Torr (P = 0.009) during wakefulness. With the onset of sleep, end-tidal PCO<sub>2</sub> rose further to 50 ± 5.0 Torr [P = not significant (NS) compared with PCO<sub>2</sub> during wakefulness with nE-PAP]. End-tidal PCO<sub>2</sub> was significantly higher during sleep with nEPAP than during sleep without nEPAP (P = 0.02).

Validation of FRC<sub>MRI</sub>

The MRI lung sagittal area (representing FRC<sub>MRI</sub>) was collected for each patient during mouth or nose breathing (without nEPAP). There was no statistically significant difference between these conditions; therefore, for the purpose of comparing FRC<sub>MRI</sub> with FRC determined by conventional N<sub>2</sub> washout, the two MRI values were averaged. Figure 4 shows a strong linear correlation (r = 0.72, P = 0.04) between FRC<sub>MRI</sub> (arbitrary units) and FRC determined by N<sub>2</sub> washout (obtained

Table 1. Subject demographics

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<th>Diag, h</th>
<th>nEPAP, h</th>
<th>FRC, cmH&lt;sub&gt;2&lt;/sub&gt;O</th>
<th>Pawake, cmH&lt;sub&gt;2&lt;/sub&gt;O</th>
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BMI, body mass index; RDI, respiratory disturbance index; FRC, functional residual capacity; nEPAP, nasal expiratory positive airway pressure; Pawake, end-expiratory pressure developed with the nEPAP device during wakefulness; Diag, diagnostic study.
from a single slice), validating the use of MRI lung sagittal area as an index of the FRC. To test the reproducibility of the MRI data, we analyzed the difference between two duplicate series with and without nEPAP in five patients. The average difference between the two series was 0.2 ± 12.5% for FRC and 0.4 ± 9.9% for tidal volume, with a <10% difference in 9 of 10 measurements for FRC and tidal volume.

Table 2 shows raw data of FRCMRI measured during nose and mouth breathing, without and with the nEPAP device positioned on the nose, for each patient (percent change data are shown in Supplemental Tables S2–S5 in Supplemental Material for this article, available online at the Journal website). Pertinent comparisons are as follows. 1) Without the device in place, changing from mouth to nose (M vs. N) breathing had no significant effect on FRCMRI (P NS).

2) FRC was significantly higher when the patient breathed through the nEPAP device (Ne) than when the patient did not breathe through the device (i.e., nEPAP caused hyperinflation). The effect of nEPAP on FRC was significant compared with the reference of nose breathing without the device (33.9 ± 8.9 and 49.1 ± 14.6 units for N and Ne, respectively, P = 0.001, 46.8 ± 29.2% change) or compared with mouth breathing, which diverts airflow away from the nEPAP valve (35.9 ± 9.1 and 49.1 ± 14.6 units for Me and Ne, respectively, P = 0.001, 37.7 ± 22.4% change).

3) During mouth breathing, there was a small, but statistically significant, increase in FRC while the nEPAP device was in place on the nose but outside the route of breathing compared with while the nEPAP was not in place (34.1 ± 8.9 and 35.9 ± 9.1 units for Me and Ne, respectively, P = 0.001, 37.7 ± 22.4% change).

Comparisons between these observations are better appreciated in Fig. 5, which shows the percent change in FRCMRI and again shows the large effect of breathing through the valves compared with the small effect of changing from mouth to nose breathing on increasing FRC.

Figure 6 shows the large decrease in ventilation during breathing through the valve expressed as percent change. Raw data and percent change in tidal volume, frequency, and ventilation in each of the conditions (during nose and mouth breathing, without and with the nEPAP device positioned on the nose) are shown for each patient in Supplemental Tables.
S1–S5. Overall, there were no consistent changes in respiratory frequency. Tidal volume and ventilation changed as follows. J) Without the device in place, changing from mouth to nose breathing had no consistent or statistically significant effect on tidal volume or ventilation. 2) During breathing through the nEPAP device, tidal volume (13.0 ± 6.02 and 6.55 ± 3.10 units for N and Ne, respectively, \( P < 0.001 \), −48.1 ± 14.1% change) and ventilation (166 ± 52.2 and 80.3 ± 26.9 units for N and Ne, respectively, \( P < 0.001 \), −50.5 ± 14.6% change) fell significantly compared to breathing without the device (i.e., nEPAP caused hypoventilation). The effect of nEPAP on tidal volume and ventilation was significant whether compared with the reference of nose breathing without the device (N vs. Ne, \( P < 0.001 \)) and mouth breathing with the nEPAP device in place on the nose but outside the route of breathing (Me vs. Ne, \( P < 0.001 \)). 3) During mouth breathing (M vs. Me), there was no statistically significant change in tidal volume or ventilation with the nEPAP in place (but not in the path of breathing).

End-expiratory UA CSA for each patient during nose and mouth breathing, without and with the nEPAP device positioned on the nose, is shown in Table 2 and Supplemental Tables S2–S5. J) Without the device in place, changing from mouth to nose breathing had a highly variable effect on UA caliber (Table 2). There was, however, no statistically significant average change in the mean UA CSA for the group. 2) When the patients breathed through the nEPAP device (Table 2), end-expiratory UA CSA showed a trend to increase, but this did not reach statistical significance (1.81 ± 0.79 and 2.68 ± 1.1 cm² for N and Ne, respectively, \( P = 0.07 \), 74.4 ± 113.1% change). However, no dilatation was noted when end-expiratory UA CSA for breathing through the nEPAP valve was compared with mouth breathing with the nEPAP device in place on the nose but outside the route of breathing (2.99 ± 1.05 and 2.68 ± 1.1 cm² for Me and Ne, respectively, \( P = 0.07 \)). 3) During mouth breathing, there was a significant increase (2.12 ± 0.72 and 2.99 ± 1.05 cm² for M and Me, respectively, \( P = 0.03 \), 49.8 ± 59.2% change) in end-expiratory UA CSA while the nEPAP device was in place on the nose but outside the route of breathing.

These observations are summarized in Fig. 7, which shows the percent change in end-expiratory CSA with each intervention.

Figure 8 shows individual data from one patient and summary data for the group for CSA as a function of time (within the breath cycle). Data from periods of mouth and nose breathing are shown separately. Data from periods without and with the nEPAP device in place are also plotted. To pool the data, all CSAs for a given patient were referenced to the CSA of the nose at end expiration without nEPAP (100%) for that patient. Without nEPAP, there was little change in mean CSA during nose breathing over the respiratory cycle, although 6 of the 10 patients may have shown the expected increase during inspiration (data not shown). Although the temporal pattern during mouth breathing without the nEPAP device was similar to that during nose breathing without nEPAP, CSA was consistently larger during mouth breathing than during nose breathing (although data were not significant due to large variability). When only nose breathing is considered, the data suggest a trend to dilatation (1.81 ± 0.79 and 2.68 ± 1.1 cm² for N and Ne, respectively, \( P = 0.07 \)) of the UA resulting from the nEPAP that appears to drop off at the end of inspiration, suggesting that some of the end-expiratory dilatation may have been a pressure effect. The persistence of dilatation of the UA during mouth breathing (2.68 ± 1.1 and 2.99 ± 1.05 cm² for Ne and Me, respectively, \( P = 0.07 \)) is not consistent with a pressure effect (see discussion). All UA data were highly variable across patients.

We were not able to show any correlation between the effectiveness of the nEPAP during sleep (i.e., changes in RDI) and FRC at baseline, change in FRC with nEPAP, end-tidal PCO₂, or BMI (\( P = 0.07 \) for all pairs). However, an unexpected trend toward an inverse correlation between the pressure developed on nEPAP and the change in FRC was observed. Figure 9 shows that, in addition to the smallest change in FRC being associated with the highest \( P_{\text{awake}} \), it was also in the most obese patients that this occurred (\( r = -0.64, P = 0.06 \)).

**DISCUSSION**

The present study shows that application of a nasal device that results in 4–17 cmH₂O nEPAP produces significant hyperinflation during wakefulness. Whether this hyperinflation extends into sleep is not tested, but because of the consistency and size of the effect, it is likely that it persists during sleep. Hyperinflation by nEPAP provides a possible mechanism of action of the nEPAP device, since an increase in FRC causes tracheal traction that will transmit to the UA and decrease UA collapsibility. During wakefulness, the effects of the nEPAP device were more variable on UA CSA than on FRC.

Our measurements of lung volumes (FRC and tidal volume) were based on an imaging technique that has analogies to chest X-ray planimetry, which has been shown to provide acceptable measurements of lung volume (2). In addition, we validated the FRC MRI correlation with conventional FRC in our own patients. The reference value for FRC was the supine FRC obtained by \( N_2 \) washout during mouth breathing with noseclips in the supine position. In the MRI, we used the data without the nEPAP device while the supine patients breathed through the mouth or nose. These FRC determinations showed a good correlation to the \( N_2 \) washout data. This supports our use of single-lung MRI sagittal CSA as a surrogate for FRC.
Our data show that, at least during wakefulness, breathing through the nasal device produced a consistent increase in FRC. Although we did not directly measure volumes, we estimated this increase in volume by comparing the change in FRC with the change in volume representing stable tidal breathing. When both of these volumes are expressed in MRI units, the change in FRC (15 ± 10 arbitrary units) is of the same order of magnitude as the tidal volume (13 ± 6 arbitrary units), suggesting that the change in FRC induced by application of nEPAP was approximately the same as a normal tidal volume, or 500 ml. This is comparable to the change in FRC that has been reported by application of 10 cmH2O CPAP (13). A change of this magnitude has also been shown to affect UA collapsibility, expressed as a reduction in critical pressure (13, 20). Thus the observed increase in FRC induced by the nEPAP is consistent with the mechanism of an improved RDI with nEPAP being mediated through an effect on UA collapsibility through tracheal traction. Our data are in contrast to those obtained during sleep by Heinzer et al. (5), who showed only minimal changes in end-expiratory lung volume with application of 10 cmH2O EPAP during sleep. The possible reasons for differences in our data include differences in state (wakefulness vs. sleep), patient population (differences in BMI and FRC), range of nEPAP levels, and differences in technique used to generate nEPAP.

The trend toward an inverse relationship between the change in FRC on nEPAP and the nEPAP developed during breathing through the device was unexpected (Fig. 9). A trend for an inverse relationship was also present (r = 0.74, P = 0.05, see Supplemental Figure) between FRC (%predicted) and nEPAP. Our most obese patients were also those with the smallest change in FRC from nEPAP (Ne vs. N). All these observations are consistent with an effect of obesity acting through an increase in chest wall recoil. The nEPAP developed during passive expiration should be driven by total lung + chest wall recoil, which is probably higher in obese individuals. Tracheal traction, however, should be proportional to the percent predicted FRC, which is generally lower in obese individuals (9). Thus,
in lean subjects, expiratory pressure developed against the nEPAP device is low, because total recoil is low; however, this pressure affects FRC and transmits to tracheal traction. In contrast, in obese individuals, the large chest wall recoil generates a larger pressure against the nEPAP device, but FRC will be less affected because of mass loading by the chest wall, and there may be less tracheal traction. The balance of these effects is difficult to predict and may explain why nEPAP appears to improve SDB in lean and obese patients. It is also possible that the mechanism of action of nEPAP is different in lean and obese patients. In a recent study of 218 subjects (including the present series) (17), BMI was lower in subjects with than in those without a therapeutic response to nEPAP (30.9 ± 7.2 vs. 33.4 ± 6.3 kg/m², \( P = 0.007 \)). The analysis described above assumes that expiration remains passive on nEPAP, but we did not measure diaphragm or intercostal EMG activity, and our inability to exclude active expiratory effort is a limitation of the present study.

The effect of breathing through the nEPAP device on the UA was more variable than the effect on FRC across patients. Although end-expiratory CSA was not statistically different for the entire group, 6 of the 10 patients showed an increase in CSA on nEPAP, and only 1 patient showed a decrease, suggesting a trend toward dilatation at end expiration during nEPAP. Furthermore, the data during inspiration (Fig. 8) suggest that dilatation may have persisted into inspiration (at which point the device does not produce positive pressure). Caution is required in interpreting these data because of the variability of the response of UA CSA across patients. The reasons for this interpatient variability include differences in the awake behavior and reflexes induced by nEPAP but may also include differing indirect effects of the nEPAP (e.g., changes in \( P_{\text{CO}_2} \) and/or tracheal traction). Furthermore, while it is known that the effect of tracheal traction is to decrease collapsibility of the UA, it is not known whether the effect is associated with an increase or a decrease in CSA. Without the nEPAP device, our data show no statistically significant change in UA CSAs between mouth and nose breathing throughout the breathing cycle (Fig. 8). However, individual patients often showed large increases or decreases between mouth and nose breathing. We examined the anatomic landmarks to exclude a change in the level of the MRI slice and were not able to identify any such shift. However, jaw position does change, and this could have variably reoriented the axis of the airway between patients. An unexpected finding was a statistically significant increase in UA CSA at end expiration between periods when patients breathed with and without nEPAP but did so through the mouth (which takes the nEPAP out of the breathing path). This observation reemphasizes the more general role of route of breathing and/or jaw position on UA anatomy and, thus, on SDB. The increase in UA CSA during nEPAP mouth breathing observed in the present study may also have been due to the order in which experiments were done in each sequence of MRI data. Since a stable period of nEPAP nasal breathing always came first, there may have been a residual reflex or direct effect on control of breathing (as through elevated end-tidal \( P_{\text{CO}_2} \)) at the time of mouth breathing (i.e., residual hypercapnia from nose breathing through the nEPAP device may have carried over into the period of mouth breathing). It is unlikely that this was a persisting mechanical effect, as FRC (see prior data) had returned to baseline immediately on assumption of mouth breathing. Finally, since we did not measure UA muscle EMG activity, we cannot be sure that the application of nEPAP or the change in route of breathing from mouth to nose (18, 19) did not have an effect through neural activation, and these factors may have varied across individuals.

In addition to an effect on FRC, our data show that nEPAP caused a consistent drop in ventilation. This explains the increase in mean end-tidal \( P_{\text{CO}_2} \) with the nEPAP device, at least during wakefulness (Table 1). With nEPAP, there was also a trend for end-tidal \( P_{\text{CO}_2} \) to rise from wakefulness to sleep, but this did not reach significance. Without the nEPAP device, we observed the well-known rise in \( P_{\text{CO}_2} \) from wakefulness to sleep. On nEPAP, a limitation of our wakefulness data is that the end-tidal \( P_{\text{CO}_2} \) may not have been reflective of a steady state (data are based on the average of 3 breaths, as patients had difficulty breathing through the device during wakefulness). However, the essential observation is that the change in end-tidal \( P_{\text{CO}_2} \) from sleep without nEPAP to sleep with nEPAP was highly significant (from 43.8 to 50 Torr). Thus our data support the observation that nEPAP causes significant hypercapnia. This rise in \( P_{\text{CO}_2} \) may play a role in treatment of SDB with the nEPAP device. However, the effect of \( P_{\text{CO}_2} \) on stability of ventilation in the presence of SDB is complex. An increase in drive from hypercapnia could affect the UA muscles and increase stiffness due to greater baseline tone. However, an increase in \( P_{\text{CO}_2} \) in this setting has a complex effect on loop gain, in that it will increase the effect of changes in ventilation for a given FRC (increased plant gain), but, with a larger FRC, changes will have a lesser effect on \( P_{\text{CO}_2} \) (decreased plant gain). However, overall, it is suggested by the literature that increasing \( P_{\text{CO}_2} \) improves central apnea (23) and UA collapsibility (10, 12), so, in balance, the effect of increasing our patients’ \( P_{\text{CO}_2} \) would probably be in favor of a stabilizing effect on the UA.

Two patients had very low RDI on the diagnostic polysomnogram (4.1 and 7.2/h), despite having periods of sustained elevated UA resistance (inspiratory flow limitation). Prior sleep studies showed that both patients had significant SDB and continued to have symptoms of snoring and excessive daytime sleepiness, justifying their inclusion with the SDB patients. Deletion of their data did not change our findings for FRC, ventilation, or UA CSA change with nEPAP.

The present study investigated the effect of nEPAP, irrespective of the success of the therapy, to assess which mechanisms might contribute to a therapeutic effect and which were not present in any patient. Having found some increase in FRC in all patients, it becomes relevant to ask if this effect is a mechanism of action; unfortunately, only 2 of the 10 patients were clear nonresponders. In two other patients, RDI was too low to allow us to judge the effectiveness of the nEPAP. However, if we delete these four patients, the FRC in the remaining responders shows a 34% increase with nEPAP (\( P = 0.02 \)). Additional FRC data in “nonresponders” would be needed to address the correlation of change in FRC to therapeutic effect. In particular, one must separate mouth breathers [no nEPAP (14)] from nonresponders to generated EPAP.

Several additional limitations to our experiments, including the method used to assess lung volume using two-dimensional data from one lung, need to be mentioned. Because determination of tidal volume, FRC, and changes in FRC during...
nEPAP application may have independently (and inconsistently) affected anterior-posterior dimensions of the chest cavity, we may have underestimated changes in volume. Limited data in one additional normal subject were obtained to address this issue: transverse and sagittal scans of the chest obtained during the application of nEPAP (data not shown) showed little change in anterior-posterior diameter or transverse CSA during tidal breathing or FRC increase during application of nEPAP. Because of the maximum image acquisition rate (6 images/s), simultaneous transverse measurements of the chest were not added to our protocol, as this would have caused loss of temporal resolution, preventing accurate identification of the end-expiratory point in time.

A second limitation of our data collection is that intranasal pressure and CO$_2$ were not measured during MRI but, rather, at a separate session. Finally, and most importantly, all our data in the MRI relating to FRC and UA CSA changes with nEPAP were obtained during wakefulness. Extrapolation from wakefulness to sleep needs to be done with caution. During sleep, the loss of loading reflexes and the “wakefulness” drive could easily result in greater passive effects of nEPAP and, possibly, less variability in the UA measures. However, this remains to be investigated, and future measurements using other techniques (e.g., continuous lung volume measurement with magnetometers) are needed to confirm the effects of nEPAP on FRC, ventilation, and ventilatory pattern during sleep.

We were not able to show any correlation of the effectiveness of the nEPAP device during sleep (i.e., changes in RDI) to 1) FRC at baseline, 2) change in FRC with nEPAP, 3) end-tidal PCO$_2$, or 4) BMI. Although our findings of a change in FRC and possible UA CSA changes provide possible mechanisms for the effect of nEPAP during sleep, the lack of a clear dose-response relationship leaves some ambiguity as to whether these are the major mediators of any therapeutic benefit.

In conclusion, the present study uses a novel, noninvasive MRI approach to present estimates of FRC and measurements of UA CSA to observe these variables over multiple respiratory cycles and to examine the effect of application of nEPAP. Major impediments to making these measurements during sleep prompted us to begin by making measurements during wakefulness. We acknowledge the need to examine the effect of sleep directly to confirm that these are, indeed, the mechanisms of SDB improvement with nEPAP. The present studies demonstrate that significant hyperinflation (an increase in end-expiratory lung volume) occurs during breathing through the nEPAP device. In addition, there may be some trend to dilate expiratory lung volume) occurs during breathing through the UA during expiration, and this may carry over into inspiration. During sleep, the loss of loading reflexes and the “wakefulness” drive could easily result in greater passive effects of nEPAP and, possibly, less variability in the UA measures. However, this remains to be investigated, and future measurements using other techniques (e.g., continuous lung volume measurement with magnetometers) are needed to confirm the effects of nEPAP on FRC, ventilation, and ventilatory pattern during sleep.

We also thank Laura Young and Alex Sabile for assistance with pulmonary function testing and Ming Chen and Rakhi Kanevskaya (New York University Sleep Disorders Center) for data collection and scoring of the sleep studies. We also thank Ventus Medical for donating the nEPAP devices (Provent).

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