Effects of continuous negative airway pressure on lung volume and respiratory resistance

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Lorino, Anne Marie, Kamel Hamoudi, Frédéric Lofaso, Estelle Dahan, Christian Mariette, Alain Harf, and Hubert Lorino. Effects of continuous negative airway pressure on lung volume and respiratory resistance. J. Appl. Physiol. 87(2): 605–610, 1999.—This study was designed to determine the responses of lung volume and respiratory resistance (Rrs) to decreasing levels of continuous negative airway pressure (CNAP). Twenty normal subjects were studied in the basal state and under CNAP levels of −5, −10, and −15 hPa. Rrs was measured by the forced oscillation technique (4–32 Hz). End-expiratory lung volume (EELV) and tidal volume (VT) were measured by whole body plethysmography. Rrs was extrapolated to 0 Hz (R0) and estimated at 16 Hz (R16) by linear regression analysis of Rrs vs. frequency. Specific Rrs, SR0 and SR16, were then calculated as R0 (EELV + VT/2) and R16 (EELV + VT/2), respectively. EELV significantly decreased, whereas R0, R16, S R0, and SR16 significantly increased, as the CNAP level decreased (P < 0.0001). Our results demonstrate that the CNAP-induced increase in R0 does not result from a direct lung volume effect only and strongly suggest the involvement of other factors affecting both intrathoracic and extrathoracic airway caliber.

forced oscillations; respiratory resistive impedance; upper airway resistance; lower airway resistance

IT HAS BEEN ESTABLISHED that total airway resistance measured at the mouth varies when lung volumes are voluntarily changed (4, 5, 26) and that there is a decreasing curvilinear relationship between airway resistance and lung volume (4, 5). Accordingly, specific airway resistance, which is defined as the product of airway resistance by lung volume, can be predicted to remain roughly constant over the physiological lung volume range (5).

A recent study relating to upper airway resistance demonstrated that the response of airflow resistance to passive decreases in lung volumes was different depending on whether a continuous negative airway pressure (CNAP) or a continuous positive extrathoracic pressure was applied (25). These results suggest that the response of airway resistance, measured at the mouth, to decreasing lung volumes might also vary with the way lung volume is reduced and that CNAP-induced decreases in lung volume might result in a larger increase in airway resistance than voluntary decreases in lung volume. This study was, therefore, designed to quantify the effects of CNAP application on lung volume and to investigate the associated changes in total and specific airway resistance. To this end, we used the combination of two methods easily applicable during CNAP application: the plethysmographic technique for lung volume measurement and the forced oscillation (FO) technique for respiratory resistance (Rrs) measurement. This methodological approach allowed a quantification of the changes in Rrs that might occur independently of the decrease in lung volume.

MATERIALS AND METHODS

Subjects. Twenty asymptomatic healthy subjects (13 men and 7 women), aged 20–54 yr (mean 31 yr), with normal body weight and no upper or lower respiratory complaints, participated in the study. None of them was a habitual snorer, and none complained of diurnal or nocturnal symptoms seen with the sleep apnea syndrome. The experimental protocol was approved by the hospital Ethics Committee, and each subject gave informed consent.

Lung volume measurement. End-expiratory lung volume (EELV) and tidal volume (VT) were measured by whole body plethysmography using an improved method previously described (10, 16). In brief, the subject was asked to breathe spontaneously and then to pant against a mouth shutter closed at a lung volume level near EELV. Thoracic flow was obtained with a pressure-compensated flow plethysmograph and measured by a differential pressure transducer (±0.5 hPa, Validyne DP 45, Validyne, Northridge, CA). Mouth pressure (Pm) was measured with a differential pressure transducer (±50 hPa, Validyne MP 45). Signals were digitized at a rate of 15 Hz, and thoracic gas volume was calculated from linear regression analysis of thoracic flow against the first time derivative of Pm (10, 16).

Rrs measurement. Rrs was measured by the FO technique. The pseudorandom forced flow used in this study was composed of 29 harmonics (4–32 Hz) of the fundamental (1 Hz), with enhanced amplitudes at the lower frequencies, to limit the influence of spontaneous breathing. The phases were calculated to minimize the peak-to-peak amplitude of the excitation signal. The forced signal, generated by a digital-to-analog converter, excited, through a power amplifier, a 50-W loudspeaker (Audax HM 130 XO) enclosed in a 2.5-liter rigid chamber and placed in parallel with the CNAP device, as in the experimental setup described by Peslin et al. (20). The peak-to-peak amplitude of the resulting flow was ~0.2 l/s. Mouth flow was measured with a screen pneumotachograph (resistance = 0.35 hPa·l−1·s; Jaeger, Wurzburg, Germany) connected to a differential pressure transducer (±70 hPa, Sensym SCX 01D, Sunnyvale, CA), and Pm was measured by a similar pressure transducer referenced to the atmosphere. The pneumotachograph and the tubing were flushed by a
constant bias flow (0.5 l/s of compressed air). Pm and mouth flow data were collected over 16-s periods and high-pass filtered (3rd order, cutoff frequency = 3.5 Hz) to eliminate the low harmonics of the breathing noise. A fast Fourier transform algorithm was applied to adjacent 4-s periods. Impedance data were calculated from the auto- and cross-spectra and retained for analysis when they corresponded to a coherence value >0.9 (17). Rrs was submitted to linear regression analysis against frequency over the 4- to 16- and 17- to 32-Hz frequency range. Rrs extrapolated to 0 Hz (R0) was derived from the first linear regression analysis, and Rrs estimated at 16 Hz (R16) was derived from the second linear regression analysis (15). The indexes adopted to evaluate airway resistance were R0, R16, and the difference, ∆R = R0 − R16. Specific Rrs, SR0 and SR16, were then calculated as R0 (EELV + Vt/2) and R16 (EELV + Vt/2), respectively.

Experimental protocol. Each subject was successively studied under four conditions: in the basal state (CNAP0) and under decreasing levels of CNAP of −5, −10, and −15 hPa (CNAP5, CNAP10, and CNAP15, respectively) applied at the mouth. CNAP was generated by an adjustable vacuum source set at the negative pressure required before the subject was connected to the breathing circuit and continuously monitored with a manometer. Subjects were asked to breathe quietly under each condition and not to fight the different applied pressures. A 5-min period was allowed to pass after release from CNAP before the next CNAP application.

Subjects, sitting in the plethysmograph, wearing a nose clip, and firmly supporting their cheeks with their hands, breathed through a mouthpiece linked to a three-way valve that allowed connection either to both the CNAP and FO devices placed in parallel or to the mouth shutter. The subject was first connected to the CNAP and FO devices, and, after a 30-s period of adaptation to CNAP, FOs were applied during spontaneous breathing. Then, while the subjects were still under CNAP, the three-way valve was turned, and the subjects were connected to the mouth shutter against which they performed their panting maneuver. The four to five cycles of spontaneous breathing preceding the panting maneuver, including those during which FOs were applied, were used to calculate the EELV level and the Vt amplitude. In that way, Rrs and lung volume were estimated simultaneously.

Under each condition, three to four measurements of lung volumes and Rrs were performed, and EELV, Vt, R0, R16, ΔR, SR0, and SR16 were taken as the average of their respective basal values.

Data analysis. Values are means ± SE, except when otherwise indicated. Statistical analysis of data was performed by using one-factor analysis of variance for repeated measures, completed as necessary by modified Student's paired t-test, and two-factor analysis of variance. A value of P < 0.05 was considered statistically significant.

RESULTS

EELV significantly decreased as the CNAP level was lowered (P < 0.0001) down to 71 ± 3% of its basal value at CNAP15 (Fig. 1). No significant change was observed in Vt (P > 0.07), which had mean values of 1.01 ± 0.08 liter at CNAP0, 1.04 ± 0.08 liter at CNAP5, 1.09 ± 0.08 liter at CNAP10, and 1.13 ± 0.10 liter at CNAP15.

A typical response of Rrs to decreasing CNAP levels, obtained in a representative subject, is shown in Fig. 2. No significant difference between R0 and R16 was observed in the basal state. R0 and R16 significantly increased as the CNAP level decreased (P < 0.0001 for both) and reached 198 ± 13 and 175 ± 9% of their respective basal values at CNAP15 (Fig. 3). ΔR significantly increased as the CNAP level decreased (P < 0.004). No significant difference was observed between men and women regarding the R0 and R16 basal values (P > 0.08 and P > 0.10, respectively) and the R0 and R16 responses to decreasing CNAP levels (P > 0.37 and P > 0.14, respectively).

No significant difference between SR0 and SR16 was observed in the basal state. SR0 and SR16 significantly increased as the CNAP level decreased (P < 0.0001 for both) and reached 152 ± 13 and 135 ± 10% of their respective basal values at CNAP15 (Fig. 4). The CNAP-induced increase in SR0 was significantly larger than the one in SR16 (P < 0.04).

DISCUSSION

The effects of subatmospheric airway opening pressures on EELV (2, 23) and upper airway resistance (1, 2, 22, 24) have been widely studied, but, to our knowledge, CNAP-induced changes in total and specific air-
way resistance have never been investigated. Our methodological and technical approach, which combines simultaneous measurements of lung volume and Rrs, allowed quantification of the changes in Rrs that might occur independently of the decrease in lung volume. Our results demonstrate that specific Rrs, which mainly reflects specific airway resistance, increases under decreasing CNAP levels and that, consequently, the CNAP-induced increase in Rrs does not solely result from a direct lung volume effect.

The FO technique allows noninvasive measurements of Rrs, the changes of which have been shown to fairly reflect those in airway resistance (8). We chose two indexes of Rrs, namely $R_0$ and $R_{16}$, because they may provide complementary information regarding airway resistance. Indeed, $R_{16}$ is roughly constant from 4 to 32 Hz in patients with normal lungs but exhibits a negative frequency dependence when alteration in the distribution of gas flow occurs, as a result of series or parallel inhomogeneities (21). As most of this frequency dependence occurs $<16$ Hz, $R_{16}$ reflects Newtonian airway resistance, whereas $R_0$ reflects total airway resistance, i.e., Newtonian resistance plus the delayed resistance resulting from gas redistribution, when present (3, 15). Consequently, any increase in the difference $\Delta R = R_0 - R_{16}$ can be interpreted in terms of occurrence or development of gas redistribution.

When airway resistance is assessed by plethysmography, the reference volume used to calculate specific airway resistance is the lung volume around which the panting is performed. In our study, in which the FO technique was applied during spontaneous breathing and provided a mean estimate of Rrs over the entire VT, the corresponding mean lung volume, namely EELV + Vt/2, was taken as the reference volume for the calculation of specific Rrs.

Fig. 3. Mean ± SE values (n = 20 subjects) in Rrs extrapolated to 0 Hz ($R_0$; A) and estimated at 16 Hz ($R_{16}$; B) in basal state (CNAP = 0) and under CNAP levels of −5, −10, and −15 hPa.

Fig. 4. Mean ± SE values (n = 20 subjects) in specific Rrs extrapolated to 0 Hz ($SR_0$; A) and estimated at 16 Hz ($SR_{16}$; B) in basal state (CNAP = 0) and under CNAP levels of −5, −10, and −15 hPa. NS, not significant.
The relatively high VT values, which are in the range of those previously reported by Leiter and Daubenspeck (13), are explained by the volume of the experimental dead space, which was ~200 ml because of the presence of the mouthpiece and the three-way valve. Indeed, the bias flow had to be bypassed during the panting maneuver and, consequently, could not be placed between the mouthpiece and the three-way valve. However, it appeared to be very important to perform the measurements of Rrs and thoracic gas volume within the same period to obtain consistent specific resistance values. Because, in all subjects, VT was not affected by the CNAP level, it may be assumed that the VT values per se did not influence our results. This assumption is corroborated by the comparison between the present results and those obtained in a preliminary study in the same seven volunteers (unpublished observations). In this preliminary study, Rrs were measured without simultaneous estimation of lung volume, i.e., by a conventional FO technique device with an experimental dead space of ~50 ml. In these seven subjects, no significant difference was found between the R0 and R16 responses to CNAP observed with either experimental setup (P > 0.25 and P > 0.12, respectively). To further confirm this assumption, we measured R0 and R16 in six new volunteers who breathed under two conditions: in the basal conditions and through an additional dead space of 420 ml consisting of a cylindrical tube. Despite a significant increase in VT (0.92 ± 0.04 vs. 0.53 ± 0.03 liter, P < 0.001), no significant increase in R0 (2.4 ± 0.2 vs. 2.3 ± 0.2 hPa·l⁻¹·s, P > 0.49) and R16 (2.3 ± 0.3 vs. 2.2 ± 0.2 hPa·l⁻¹·s, P > 0.37) was observed, probably because the dead-space-induced increase in VT was associated with a decrease in functional residual capacity. Consequently, upper airway hysteresis apparently did not alter our Rrs estimates.

To determine whether the CNAP-induced increase in Rrs could be partly or totally explained by a direct lung volume effect, we calculated specific Rrs. We indeed reasoned that, if the increase in Rrs could be explained by a direct lung volume effect, specific Rrs should remain constant.

We are not aware that any direct measurement of EELV under CNAP has ever been made. Only changes in EELV have been previously assessed, either by conventional spirometry (18) or by inductive plethysmography (2, 24). The CNAP-induced decreases in EELV observed in the present study (Fig. 1) are explained by the decrease in transrespiratory pressure. Our decreases in EELV are in the range of those reported by Meessen et al. (18) at comparable CNAP levels but are markedly larger than those previously measured by Séries and Marc (25) at similar transrespiratory pressures. This discrepancy might be due to the experimental conditions, insofar as Séries et al. (23) studied their subjects in the supine position, which, in comparison with the sitting position, induces a mean 20–30% decrease in functional residual capacity (12).

As expected in our normal subjects who had no history of airway obstruction, R0 and R16 were comparable in the basal state, which illustrates the homogeneity of the distribution of gas flow within the respiratory system (21).

It must be stressed that our subjects were studied during mouth breathing, i.e., in an experimental condition that differed from most of those reported in the literature, in that the measured Rrs did not include nasopharyngeal and nasal airflow resistances. But mouth breathing was the required condition to perform the panting maneuver and thereby allow simultaneous measurements of Rrs and EELV.

Despite the anatomic and functional differences of the upper airways in men and women, the responses of R0 and R16 to decreasing CNAP levels were similar in both sexes. The significant increases in R0 and R16 presently observed in response to CNAP (Fig. 3) may be partly explained by the decrease in EELV. It has indeed been demonstrated that voluntary decreases in EELV affect both extrathoracic and intrathoracic airway caliber (1, 4–6, 26). However, the fact that specific airway resistances, which take the direct lung volume effect into account, significantly increased as the CNAP level decreased (Fig. 4) proves that, besides a direct lung volume effect, other factors affecting extrathoracic and/or intrathoracic airways were involved in the increase in Rrs. Our technique did not make it possible to partition total airway resistance into intrathoracic and extrathoracic (oropharyngeal plus laryngeal) airway resistances, but our results strongly suggest that, under CNAP, the caliber of both extrathoracic and intrathoracic airways was affected by factors other than a direct lung volume effect.

Indeed, that ΔR increased significantly as the CNAP level decreased demonstrates that CNAP application promotes the occurrence and development of series and/or parallel gas redistribution. Now the main source of series gas redistribution is upper airway shunt compliance, the influence of which on Rrs was probably reduced under CNAP because of the increased activity of upper airway dilating muscles (2). Consequently, parallel gas redistribution within intrathoracic airways is the most plausible explanation for the difference presently observed between the respective responses of R0 and R16 to decreasing CNAP levels, which corroborates the assumption that intrathoracic-specific airway resistance probably increased under CNAP. That the CNAP-induced increase in SR2 presently observed in SR0 was significantly larger than the one in SR16 suggests that the additional airflow resistance resulting from gas redistribution increased more than the Newtonian airway resistance when lung volume decreased.

Furthermore, the mathematical simulation proposed in the APPENDIX tends to further confirm this assumption. Indeed, supposing that 1) extrathoracic airway resistance accounts for one-third of the total airway resistance during mouth breathing (9), and 2) CNAP affected intrathoracic airway resistance via a direct lung volume effect only, i.e., intrathoracic airway-specific resistance remained constant, then an increase of roughly 260% in extrathoracic airway resistance would be necessary to explain the mean 50% increase in SR0 presently observed at CNAP15 (see APPENDIX). Such
an increase in extrathoracic airway resistance is higher than the increases previously reported for similar CNAP levels (24).

In the following paragraphs, we will, therefore, successively consider the CNAP-related factors that may induce increases in both extrathoracic and intrathoracic airway resistance, apart from the direct lung volume effect.

Among the factors that might affect extrathoracic airway caliber during CNAP application, one may cite an indirect effect of lung deflation, i.e., an additional increase in oropharyngeal resistance possibly resulting from an increase in upper airway collapsibility involving mechanical linkages between the thorax and the upper airway (27).

Another explanation for our results might just be a narrowing of extrathoracic airways directly resulting from the CNAP-induced decrease in upper airway transmural pressure and from the inefficiency of the dilating muscles in counterbalancing the tendency of the pharyngeal airway to collapse, despite their increased electromyographic activity. It has indeed been observed that, for a given transrespiratory pressure, supralaryngeal resistance increased more during CNAP than during continuous positive extrathoracic pressure (25) and that the CNAP threshold corresponding to the occurrence of inspiratory flow limitation was lower when the CNAP-induced decrease in EELV was prevented by applying a continuous negative extrathoracic pressure (24). Furthermore, significant increases in genioglossal electromyographic activity have been reported in humans not only during CNAP (2) but also during the combination of CNAP and continuous negative extrathoracic pressure (13), as well as increased preeactivation of upper airway dilating muscles relative to the onset of diaphragm activity in response to CNAP in dogs (28). However, it is worth noting that this compensatory increase in activity of the airway dilator muscles, which probably minimizes the sucking effect of CNAP on extrathoracic airways and the resulting increase in upper airway resistance, is confined to the inspiratory phase. Although our resistance values were determined over the entire ventilatory cycle and did not allow partitioning of airway resistance into inspiratory and expiratory resistances, one may assume that the CNAP-induced increase in upper airway resistance was dramatically higher during expiration than during inspiration.

Among the factors that might potentially affect intrathoracic airway caliber during CNAP application, airway closure is highly improbable, because in normal and young subjects this phenomenon occurs below 20% of vital capacity (7), i.e., at a lung volume level that was not reached in the present study, even at the lowest CNAP level.

On the contrary, airway congestion might be a factor contributing to the increase in intrathoracic airway resistance. Although no increase in thoracic blood volume has been observed under CNAP (22), a side effect of CNAP might be a pulmonary blood redistribution toward the airways as a result of both the decrease in lung volume and the negative intra-alveolar pressure (19). In addition, CNAP application induces a decrease in central venous pressure that falls toward zero at CNAP15 (11) and thereby an increase in venous return, which may have a potential vasodilating effect on the tracheobronchial vessels that belong to the systemic vasculature (14). Thus congestion of both central and peripheral airways might promote the CNAP-induced increase in airflow resistance.

In conclusion, this study demonstrates that the CNAP-induced increase in Rs does not exclusively result from a direct lung volume effect. Our results strongly suggest the involvement of other factors affecting not only extrathoracic but also intrathoracic airway caliber. Further investigations are still required to partition airflow resistance and thereby evaluate the respective contributions of intrathoracic and extrathoracic airways to the CNAP-induced increase in total airflow resistance.

APPENDIX

Let us denote EELV and intrathoracic and extrathoracic airway resistance at CNAP0 by V0, R0, and R0E, respectively; and EELV and intrathoracic and extrathoracic airway resistance at CNAP15 by V15, R15, and R15E, respectively. Specific airway conductances at CNAP0 (SR0) and CNAP15 (SR15) are then expressed as

\[ SR_0 = \left( R_0^1 + R_0^E \right) V_0 \]  
\[ SR_{15} = \left( R_{15} + R_{15}^E \right) V_{15} \]  

As SR15 was approximately equal to 150% SR0, it follows that

\[ (R_{15} + R_{15}^E) V_{15} = 1.5 \left( R_0^1 + R_0^E \right) V_0 \]  

Should intrathoracic airway-specific resistance remain constant, i.e., R0E V0 = R15E V15, Eq. A3 becomes

\[ R_{e,15} V_{15} = 1.5 R_0^E V_0 + 0.5 R_0^E V_0 \]  

Consequently

\[ R_{e,15} / R_0^E = \left( V_0 / V_{15} \right) [1.5 + 0.5 (R_0^1 / R_0^E)] \]  

Assuming that, during mouth breathing, R0E = 2 R0 (Ref. 9) and as V0 and V15 were ~3.3 and 2.3 liters, respectively, one can estimate the ratio of R15E to R0E at ~3.6, which roughly corresponds to a mean 260% increase in extrathoracic airway resistance at CNAP15.

REFERENCES


