Lung volume and collapsibility of the passive pharynx in patients with sleep-disordered breathing

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Tagaito Y, Isono S, Remmers JE, Tanaka A, Nishino T. Lung volume and collapsibility of the passive pharynx in patients with sleep-disordered breathing. J Appl Physiol 103: 1379–1385, 2007.—Lung volume dependence of pharyngeal airway patency suggests involvement of lung volume in pathogenesis of obstructive sleep apnea. We examined the structural interaction between passive pharyngeal airway and lung volume independent of neuromuscular factors. Static mechanical properties of the passive pharynx were compared before and during lung inflation in eight anesthetized and paralyzed patients with sleep-disordered breathing. The respiratory system volume was increased by applying negative extrathoracic pressure, thereby leaving the transpharyngeal pressure unchanged. Application of $-50 \text{cmH}_2\text{O}$ negative extrathoracic pressure produced an increase in lung volume of 0.72 (0.63–0.91) liter [median (25–75 percentile)], resulting in a significant reduction of velopharyngeal closing pressure of 1.22 (0.14–2.03) cmH$_2$O without significantly changing collapsibility of the oropharyngeal airway. Improvement of the velopharyngeal closing pressure was directly associated with body mass index. We conclude that increase in lung volume structurally improves velopharyngeal collapsibility particularly in obese patients with sleep-disordered breathing.

obstructive sleep apnea; pathophysiology; upper airway; closing pressure

OBESITY IS A CHARACTERISTIC feature of patients with obstructive sleep apnea (OSA) and is associated with reduction of lung volume. Hoffstein et al. (10) clearly demonstrated lung volume dependence of pharyngeal airway patency in awake obese patients with obstructive sleep apnea. A lung volume increase during non-rapid eye movement (REM) sleep was reported to decrease sleep-disordered breathing (SDB) events in obese OSA patients (9, 18). These evidences suggest involvement of lung volume in the pathogenesis of OSA. The current concept of pharyngeal airway maintenance suggests that interaction between intrinsic mechanical properties of the pharynx (anatomic mechanisms) and neural regulation of pharyngeal dilator muscle activities (neural mechanisms) determines the size of the pharynx (13). Therefore, lung volume dependence of pharyngeal airway patency could be due to structural alteration and/or increase in the pharyngeal dilator muscle activities. Van de Graaff (21) demonstrated reduction of upper airway resistance during inspiration in anesthetized dogs with upper airway muscle denervation, suggesting structural alteration of upper airway patency in response to lung volume increase. Begle et al. (2), and recently Stanchina et al. (19) reported no increase in genioglossus muscle activity despite reduction of airway resistance in response to lung inflation during sleep in normal subjects. Although these studies suggest a contribution of the anatomic mechanisms to the lung volume dependence, conclusive evidence can be provided only when separating the neural and anatomic mechanisms. Accordingly, the purpose of this study was to assess involvement of anatomical mechanisms in the lung volume dependence of pharyngeal airway collapsibility.

Our laboratory has previously described a simple method for evaluating anatomic properties of the pharynx independently of neural mechanisms (12–14, 22). Total muscle paralysis produced by administration of muscle blockade under general anesthesia is used to completely eliminate pharyngeal muscle contraction and assess static mechanical properties of the passive pharynx. Under such circumstances, anatomic differences between different lung volumes should be manifested as differences of static mechanical properties of the passive pharynx. We, therefore, undertook this study to compare static mechanical properties of the passive pharynx before and during lung inflation in anesthetized and paralyzed patients with SDB and to test the hypothesis that lung volume increase improves collapsibility of the passive pharynx.

MATERIALS AND METHODS

Subjects and overnight oximetry. The study included eight male patients with SDB (Table 1). Six patients were obese and two were overweight according to the Japanese definitions of obesity [body mass index (BMI) $\geq 25 \text{kg/m}^2$] and overweight (23 kg/m$^2 \leq \text{BMI} < 25 \text{kg/m}^2$), whereas only one patient was obese (BMI $\geq 30 \text{kg/m}^2$) and five were overweight (25 kg/m$^2 \leq \text{BMI} < 30 \text{kg/m}^2$) according to the World Health Organization definitions (5, 23). All had histories of excessive daytime sleepiness, habitual snoring, and witnessed repetitive apnea. Evaluation of SDB was achieved by one-night pulse oximetry with a pulse oximeter (Pulsox-5, Minolta, Tokyo, Japan). All subjects were instructed to attach an oximetry finger probe before sleep and to remove the probe on awakening. Digital readings of arterial oxygen saturation ($\text{Sa}_o$) and pulse rate were stored every 5 s in a memory card. The stored data were displayed on a computer screen to check quality of the recordings. The computer calculated oxygen desaturation index (ODI), defined as the number of oxygen desaturation exceeding 4% from the baseline, and the percent of time spent at $\text{Sa}_o < 90\%$ (CT$_{90}$). Although the oximetry evaluation alone does not clarify the nature of SDB, we believe that all patients can be safely diagnosed as having OSA based on the oximetry results and clinical symptoms (6). The diagnosis of SDB was confirmed by a standard polysomnogram or nocturnal respiratory monitoring measuring respiratory airflow and $\text{Sa}_o$ (Apmomonitor, Chest, Tokyo, Japan) in five patients. Individual sleep study data are provided in Table 1.

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All subjects were free from pulmonary diseases, and none experienced symptoms suggesting lower respiratory tract infection within a month before the study. None had medications possibly influencing upper airway collapsibility and lung function. The aim and potential risks of the study were fully explained to each subject, and informed consent was obtained from each. The investigation was approved by the hospital ethics committee of our institution (Graduate School of Medicine, Chiba University).

Static pharyngeal mechanics assessment under general anesthesia.

Each subject was initially premedicated with 0.5 mg of atropine, and he was placed in the supine position on an operating table where a modified tight-fitting nasal mask was attached. Care was taken to prevent air leaks from the mask, particularly when the airway was pressurized above 20 cmH2O. General anesthesia was induced and maintained by intravenous infusion of propofol, and intravenous injection of a muscle relaxant (vecuronium 0.2 mg/kg) produced complete paralysis throughout the experiment. Positive pressure ventilation was performed with a ventilator with an initial setting of 15 cycles/min of respiratory rate, and 15 ml/kg of tidal volume while the airway was maintained by mandible advancement and neck extension. PaCO2 was not measured, PaCO2 was not considered to increase before the apneic test. Apnea tolerance time was estimated to be ~3 min at SaO2 of 90%, even in obese subjects (3). The apneic test was terminated when SaO2 decreased to <95%. Although arterial PCO2 (PaCO2) was not measured, PaCO2 was not considered to increase above 50 Torr at the end of the apneic test, because PacO2 has been reported to increase by 3–6 Torr/min during apnea (16). Accordingly, we considered that such a mild increase in PaCO2 would not significantly affect each subject’s safety.

Data analysis. To convert the monitor image to an absolute value of the pharyngeal cross-sectional area, magnification of the imaging system was estimated at 1.0-mm interval distances between the endoscopic tip and the object in range of 5–30 mm. At a defined value of Paw, the image of the pharyngeal lumen was traced and pixels included in the area were counted (SigmaScan Pro 5, Systat Software, Point Richmond, CA). The pixel number was converted to pharyngeal cross-sectional area according to the distance-magnification relationship. Using known-diameter tubes, the accuracy of the cross-sectional area measurements was tested. For constant distance, the measured areas were systematically deviated from actual areas; the largest-known area tested (0.95 cm2) was underestimated by 11% due to image deformation of the outer image area, and the smallest-known area tested (0.03 cm2) was overestimated by 13% due to reduction of the image resolution (12).

The measured luminal cross-sectional area was plotted as a function of Paw. The closing pressure was defined as pressure corresponding to the zero area. At high values of Paw, relatively constant cross-sectional areas were revealed; therefore, maximum area (Amax) was determined as the mean value of highest three Paw (18, 19, and...
The pressure-area relationship of each pharyngeal segment was fitted by an exponential function: $A = A_{\text{max}} - B \cdot \exp(-K \cdot \text{Paw})$, where $B$ and $K$ are constants. A nonlinear least squares technique was used for the curve fitting, and the quality of the fitting was provided by coefficient $R^2$ (SigmaPlot 9.0; Systat Software). A regressional estimate of closing pressure ($P'_{\text{close}}$), which corresponds to an intercept of the curve on the Paw axis, was calculated from the following equation for each pharyngeal segment: $P'_{\text{close}} = \ln(B/A_{\text{max}})K^{-1}$. $K$ denotes the shape of the pressure-area relationship. When pressure-area relationship is curvilinear, compliance of the pharynx, defined as a slope of the curve, varies with changes in Paw; therefore, a single value of compliance calculated for a given Paw does not represent collapsibility of the pharynx for the entire Paw range. In contrast, $K$ represents the rate of changes in the slope of the curve; therefore, when $K$ is high, a small reduction in Paw results in a significant increase in compliance, leading to remarkable reduction in cross-sectional area. Consequently, collapsibility of the pharynx increases with increasing $K$. We suggest that both $P'_{\text{close}}$ and $K$ values represent collapsibility of the pharynx, whereby the former determines the position of the exponential curve, and the latter characterizes the shape of the curve. Improvement of $P'_{\text{close}}$ in response to lung inflation was assessed by the difference of $P'_{\text{close}}$ before and during NETP application ($\Delta P'_{\text{close}}$). Positive $\Delta P'_{\text{close}}$ supports the hypothesis. Because of variable $\Delta LV$ among the patients, $\Delta P'_{\text{close}}$ per unit changes in the lung volume was also calculated.

All values are expressed as median (25–75 percentiles). The Wilcoxon’s signed-rank test was used to examine the effect of NETP (SigmaStat 3.1, Systat Software). Spearman rank order correlation was used to identify correlation between the variables. $P < 0.05$ was considered significant.

![Figure 1](image-url)

Fig. 1. Static pressure-area relationships of passive velopharyngeal airway are exhibited for all subjects. $\bullet$ (control) and $\circ$ (application of negative extrathoracic pressure [NETP]) represent measured pressure-area data points. Curves represent results of curve-fitting analysis by an exponential function. Paw, airway pressure; BMI, body mass index (kg/m²), $\Delta P'_{\text{close}}$, estimated closing pressure (cmH₂O); $\Delta LV$, lung volume change in response to application of −50-cmH₂O NETP (liter). Fractional area (FA) was used for the relations during NETP in patient 3.
RESULTS

Application of −50-cmH\textsubscript{2}O NETP caused significant increases in lung volume in all patients [ΔLV = 0.72 (0.63–0.91) liter] at atmospheric pressure, whereas the amount of ΔLV varied among the patients (Table 1). ΔLV tended to be indirectly associated with BMI (R = −0.667, P = 0.059).

Endoscopic measurements of static pressure-area relations of the VP and OP were successfully performed before and during NETP application in all but one patient, whose \( A_{\text{max}} \) at the VP was not obtained due to a technical difficulty. \( P'_\text{close} \) values were in good agreement with observed closing pressure at the velopharynx (\( R = 0.964, P < 0.0001 \)), whereas no comparison was possible at the oropharynx because of no complete closure observed at the oropharyngeal airway in this study. Figure 1 shows individual pressure-area relationships of the VP together with ΔP\textsubscript{close} and ΔLV. The pressure-area curves during NETP application locate left to control pressure-area curve. ΔP\textsubscript{close} was positive in all patients, indicating reduction of VP \( P'_\text{close} \). In fact, VP \( P'_\text{close} \) significantly decreased by application of NETP, resulting in ΔP\textsubscript{close} by 1.22 cmH\textsubscript{2}O, whereas \( A_{\text{max}} \) and \( K \) values did not significantly change (Table 2). \( A_{\text{max}} \) and \( K \) value at the VP before NETP were not statistically correlated with age, height, weight, BMI, and severity of SDB. Because of the variable ΔLV among the patients, ΔP\textsubscript{close} was normalized by ΔLV. As illustrated in the Fig. 3, ΔP\textsubscript{close} at the VP per unit change in the lung volume was significantly associated with BMI (\( R = 0.717, P = 0.025 \)), whereas OP ΔP\textsubscript{close} per unit change in the lung volume was not significantly associated with BMI (\( R = 500, P = 0.153 \)).

DISCUSSION

This is the first study, to our knowledge, examining influences of lung inflation on the static mechanical properties of the passive pharyngeal airways in anesthetized and paralyzed patients with SDB. The study has two methodological strengths: 1) it examines the passive pharynx, thereby eliminating the action of neuromuscular factors; and 2) it uses negative extrathoracic pressure to increase lung volume, thereby examining the confounding effects of changes in transpharyngeal pressure. The results indicated that 1) lung inflation decreased closing pressures of the passive velopharyngeal airway, and 2) improvement of the velopharyngeal collapsibility resulting from lung inflation was directly associated with BMI.

Limitations of the study. Neither absolute lung volume nor changes in lung volume were measured during static pharyngeal mechanics measurements; and lung volume was assumed to be constant during the experiment. Absence of lung volume measurements makes interpretation of our results difficult. Lung volume is known to decrease by −0.5 liter shortly after induction of general anesthesia (7) while it also decreases during sleep by −280–440 ml (1, 11). The anesthesia-induced lung volume reduction was demonstrated to be more severe and progressive in morbidly obese patients (4). Thus we assessed the influence of reversal of reduced lung volume, which is known to have greater influences on upper airway patency (17, 19), under general anesthesia. Our method of measuring static pharyngeal mechanics in itself includes the process of lung deflation because we measure cross-sectional area while decreasing the airway pressure. Accordingly, lung volume during static mechanics measurements may have varied at a lower range in obese OSA patients than in nonobese OSA patients. Our experimental procedures could have further augmented the lung volume effect. Future studies need to compare static pharyngeal mechanics at different lung volumes with variable NETP application while maintaining the lung volume constant during airway pressure reduction.

Negative extrathoracic pressure of −50 cmH\textsubscript{2}O appears to be much greater than that applied in previous studies while the amount of lung volume changes is similar (9, 17–19). Differences in experimental conditions and technique of lung inflation may account for the discrepancy. In this study, a cuirass-type shell without attachments along the neck for transmission of NETP to avoid potential influences of the device on pharyngeal patency, while many previous studies used a

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<th>Table 2. Static mechanics of the velopharynx and the oropharynx before (control) and during application of −50 cmH\textsubscript{2}O negative extrathoracic pressure</th>
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* Values are medians (25–75 percentiles). \( A_{\text{max}} \), maximum cross-sectional area; \( B \) and \( K \), constants obtained by fitting the pressure-area relation of each pharyngeal airway to an exponential function; \( A = A_{\text{max}} - B \exp(-K \cdot P_{\text{cm}}) \), where \( A \) and \( P_{\text{cm}} \) denote cross-sectional area of the pharyngeal airway, and airway pressure. Quality of the fit is provided by coefficient \( R^2 \). \( P'_\text{close} \), estimated closing pressure calculated by \( \ln(B/A_{\text{max}})K^{-1} \cdot \Delta P'_\text{close} \) \( \cdot \Delta P'_\text{close} \) changes in response to application of NETP. \( \Delta P'_\text{close}/100 \text{ml} \), \( \Delta\text{L.V.} \) reduction of the estimated closing pressure at the velopharynx or oropharynx per 100-ml increase in lung volume. \( *P < 0.05 \) vs. control.

J Appl Physiol • VOL 103 • OCTOBER 2007 • www.jap.org
head-out rigid shell, which could more efficiently increase the lung volume with minimal NETP. Furthermore, during NETP application, the abdominal compartment was noticed to expand more than the thoracic compartment, probably due to significant increase of abdominal compliance under general anesthesia and paralysis. Accordingly, it is possible that the artificially increased lung volume is less effective on pharyngeal mechanics compared with physiological lung volume changes.

The accuracy of cross-sectional area measurements in known-diameter tubes ranges from 11 to 13% by our technique (12). Accurate pharyngeal area measurements may be further impaired by irregularities of the pharyngeal lumen, curved airway, and presence of mucosal secretion. In addition, significant extrapolation of static oropharyngeal pressure-area relationships at lower airway pressure range may have made estimation of oropharyngeal closing pressure inaccurate.

Site specificity of the lung volume dependence of pharyngeal airway collapsibility. The site specificity of lung volume dependence at pharyngeal collapsibility was demonstrated, and the velopharyngeal airway was the only site responding to the lung volume changes. This is a significant contrast to other mechanical interventions such as mandibular advancement, and head and neck positioning, which were demonstrated to have equal influences on both the velopharynx and oropharynx (14, 15). Similarly, unlike other mechanical interventions, $A_{\text{max}}$ and compliance ($K$) of the velopharynx were not influenced by the lung volume change, indicating parallel leftward shift of the static pressure-area curve with decreasing $P_{\text{close}}$ without changing its shape. Although speculative at present, mechani-

Fig. 2. Static pressure-area relationships of passive oropharyngeal airway are exhibited for all subjects.● (control) and ○ (application of NETP) represent measured pressure-area data points. Curves represent results of curve fitting analysis by an exponential function.
The linkages among obesity, lung volume and velopharyngeal airway collapsibility are suggested in consequence of the facts that $P_{\text{close}}$ at VP was associated with BMI and that obese OSA patients revealed a collapsible site exclusively at VP (23). A tendency of increased lung volume influences of the OP with increasing BMI, shown in Fig. 3, indicates that the relatively small and limited effects of the lung volume may be due to the small sample size or to the less obese patient population examined in this study. Alternatively, significant extrapolation of the OP measurements may explain the lack of statistical significance.

**BMI dependence of the lung volume influence on the pharyngeal collapsibility.** Our results suggest that lung volume dependence of the pharyngeal airflow is more evident in obese SDB patients, although conclusive evidence needs comparison between obese SDB patients and nonobese control subjects. This finding may explain seemingly discrepant results regarding the magnitude of lung volume influences on pharyngeal airflow patency between nonobese normal subjects and obese OSA patients recently reported (8, 19). Stanchina et al. (19) demonstrated a significant increase in pharyngeal collapsibility, by 1.1 cmH$_2$O, assessed by brief negative pressure pulses to the airway during 582-ml lung volume reduction in nonobese normal subjects (mean BMI = 24.7 kg/m$^2$) during non-REM sleep. The magnitude of changes in pharyngeal collapsibility and body habitus are similar to our study. In contrast, Heinzer et al. (8) reported more significant influences of the lung volume changes in a study performed on obese OSA patients (mean BMI = 31.9 kg/m$^2$) during non-REM sleep. They found that the CPAP level needed to prevent flow limitation increased from 11.9 to 17.1 cmH$_2$O in response to 567-ml reduction of the lung volume, whereas it is possible that changes of optimal CPAP level possibly overestimated the actual closing pressure change. According to Fig. 3, the closing pressure increase by roughly four times in patients with a BMI of 32 kg/m$^2$ compared with those with BMI of 25 kg/m$^2$ possibly explains the significant influences of the lung volume in the study of Heinzer et al.. The BMI dependence of the lung volume influences suggests pathophysiological differences between obese and nonobese patients with OSA and its limited contribution to obese OSA patients.

**Mechanisms of the lung volume dependence of pharyngeal airway collapsibility.** Lung volume dependence of pharyngeal closing pressure was evident in this study while we did not directly assess the relationship between lung volume and pharyngeal closing pressure. Because lower lung volume is expected in obese OSA patients than nonobese OSA patients due to lower thoracopulmonary compliance with increasing BMI, different working ranges on a unique linear lung volume-closing pressure relation between obese and nonobese OSA patients may account for the results of this study (Fig. 4A), although unlikely, since lung volume increase in response to

![Fig. 3.](http://jap.physiology.org/) Relationship between body mass index and reduction of the estimated closing pressure (Δ$P_{\text{close}}$) at the velopharynx and oropharynx per 100-ml increase in lung volume. Note the statistically significant association between them at the velopharynx.

![Fig. 4.](http://jap.physiology.org/) Schematic explanations for three possible mechanisms (A, B, and C) of different lung volume dependence of the pharyngeal closing pressure between obese and nonobese obstructive sleep apnea (OSA) patients. See text for detailed explanation.
NTEP tended to be smaller in obese OSA patients. Assuming that BMI reflects absolute lung volume, the direct association between BMI and changes in $\Delta P_{\text{close}}$ per unit change in lung volume (Fig. 3) indicates progressive increases in the slope of a relationship between lung volume and pharyngeal closing pressure with decreasing lung volume as schematically shown in Fig. 4B. Different working ranges on a unique alinear relationship between obese and nonobese OSA patients may explain the BMI dependence of the lung volume influences on pharyngeal closing pressure. This mechanism is supported by the direct correlation between $V'_{\text{close}}$ before NETP and BMI observed in this study. However, this mechanism does not agree with our previous observation that the $V'_{\text{close}}$ values of obese OSA patients significantly overlap with those of nonobese OSA patients (22). The alinear relationship of lung volume and pharyngeal closing pressures may change its position and shape with changing BMI (Fig. 4C). The relationship curve of obese OSA patients may locate left to that of nonobese OSA patients with being steeper than that of nonobese OSA patients. Because closing pressure before lung inflation is expected to be greater in obese OSA patients, the lung volume dependency of pharyngeal closing pressure may be more evident in obese OSA patients than nonobese OSA patients. Lower lung volume and lower thoracopulmonary compliance, however, possibly limit the lung volume increase and improvement of closing pressure in obese OSA patients. Longitudinal tracheal traction increased by lung inflation is reported to improve mechanical properties of the pharyngeal airway (20, 21). Accordingly, profound reduction of the longitudinal tracheal traction is speculated to occur on significant lung volume decrease in obese OSA patients. Again, all these speculations need to be elucidated in the future by comparing static pharyngeal mechanics between obese and nonobese OSA patients at different lung volumes.

In conclusion, lung volume dependence of pharyngeal airway collapsibility is evident in anesthetized and paralyzed patients with SDB. The lung volume influence was more prominent in obese SDB patients and at the velopharyngeal airway.

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