Submental negative pressure application decreases collapsibility of the passive pharyngeal airway in nonobese women

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Submitted 18 February 2014; accepted in final form 19 January 2015

Kato S, Isono S, Amemiya M, Sato S, Ikeda A, Okazaki J, Sato Y, Ishikawa T. Submental negative pressure application decreases collapsibility of the passive pharyngeal airway in nonobese women. J Appl Physiol 118: 912–920, 2015. First published January 22, 2015; doi:10.1152/japplphysiol.00158.2014.—The pharyngeal airway is surrounded by soft tissues that are also enclosed by bony structures such as the mandible, maxilla, and cervical spine. The passive pharyngeal airway is therefore structurally analogous to a collapsible tube within a rigid box. Cross-sectional area of the tube is determined by transmural pressure, the pressure difference between intraluminal and extraluminal pressures. Due to a lack of knowledge on the influence of extraluminal soft tissue pressure on the human pharyngeal airway patency, we hypothesized that application of negative external pressure to the submental region decreases collapsibility of the passive pharynx, and that obese individuals have less response to the intervention than nonobese individuals. Static mechanical properties of the passive pharynx were compared before and during application of submental negative pressure in 10 obese and 10 nonobese adult women under general anesthesia and paralysis. Negative pressure was applied through use of a silicone collar covering the entire submental region and a vacuum pump. In nonobese subjects, application of submental negative pressure (−25 and −50 cmH2O) significantly decreased closing pressures at the retropalatal airway by 2.3 ± 3.2 cmH2O and 2.0 ± 3.0 cmH2O, respectively, and at the retroglossal airway by 2.9 ± 2.7 cmH2O and 3.7 ± 2.6 cmH2O, respectively, and the intervention stiffened the retroglossal pharyngeal airway wall. No significant mechanical changes were observed during application of submental negative pressure in obese subjects. Conclusively, application of submental negative pressure was found to decreases collapsibility of the passive pharyngeal airway in nonobese Japanese women.

OBSTRUCTIVE SLEEP APNEA (OSA) is characterized by repetitive episodes of pharyngeal airway narrowing and closure during sleep (26). Pharyngeal airway size is determined by the interaction between neural regulation of pharyngeal airway dilator muscle activity and structural properties of the pharyngeal airway (7, 29). Under suppression of neural control mechanisms, the cross-sectional area of the passive pharynx decreases exponentially with static reduction of the luminal pressure, and the static pressure-area curve is steep near closing pressure and flat at higher luminal pressures, suggesting the passive pharynx is a highly collapsible airway conduit (10). Static mechanical properties are well able to predict dynamic behavior of the passive pharynx (9, 10).

We previously proposed an artificial collapsible tube in a rigid chamber as a mechanical model analogous to the atonic or hypotonic human pharyngeal airway (7, 8, 33). In this model, the luminal size of the collapsible tube is determined by the tube law, representing the intrinsic mechanical properties of the tube and transmural pressure (\(P_{\text{tm}}\)). \(P_{\text{tm}}\) is the pressure difference between pressures inside the tube (\(P_{\text{lumen}}\)), defined as the lateral wall pressure acting on the luminal surface of the tube, and outside the tube (\(P_{\text{tissue}}\), defined as the tissue pressure acting on the outer surface of the tube (\(P_{\text{tm}} = P_{\text{lumen}} - P_{\text{tissue}}\)). Influences of \(P_{\text{lumen}}\) on human pharyngeal airway patency have been extensively investigated and are rational for effectiveness of nasal continuous positive airway pressure (CPAP) treatment of OSA (31). Contrastingly, a series of animal studies (16–19) directly measured \(P_{\text{tissue}}\), and several human studies indirectly assessed the contribution of \(P_{\text{tissue}}\) to the pathophysiology of pharyngeal obstruction (14, 25). Although no studies have directly measured \(P_{\text{tissue}}\) in humans due to the difficulty in manipulating and measuring \(P_{\text{tissue}}\), these studies strongly suggest the effectiveness of \(P_{\text{tissue}}\) reduction on improvement of pharyngeal airway patency. In fact, one canine study demonstrated negative pressure surrounding the neck significantly decreased upper airway resistance (35).

Negative pressure applied to the submental region, where no bony structure encloses the soft tissue, may transmit to the soft tissue surrounding the pharyngeal airway and decrease \(P_{\text{tissue}}\) in humans, although pressure transmission may be impeded by soft tissue volume. Accordingly, the purpose of this study was to investigate effects of negative external pressure (NEP) application to the submental region through use of a newly designed submental collar attached to a vacuum source on pharyngeal airway collapsibility in humans (Fig. 1). We hypothesized that submental NEP application would improve collapsibility of the passive pharynx, and that response to the intervention is less in obese individuals compared with nonobese individuals. Comparison of static pressure-area relationships before and during submental NEP application in obese and nonobese individuals was executed under anesthesia and paralysis.

METHODS

Subjects. Twenty-one women [11 nonobese; 10 obese, body mass index (BMI) ≥25 kg/m² by the Japanese definition of obesity] undergoing elective surgery, mostly for breast cancer under general anesthesia, were included. One nonobese patient was excluded due to low pharyngeal image quality (Table 1). Patients undergoing upper airway, head, neck, or lung surgery; those with severe comorbidities, allergies for muscle relaxants or propofol, apparent upper airway structural abnormality, difficult mask fit, or full dentures were excluded from the study. Sleep-disordered breathing was assessed by a
portable monitor measuring respiratory airflow and \( \text{SaO}_2 \) (SAS2100; Nihon Kohden, Tokyo, Japan). The aim and potential risks of the study were fully explained to each subject, after which written informed consent was obtained. The investigation was approved by the institutional review board (Graduate School of Medicine, Chiba University: 1579) and registered in the University Hospital Medical Information Network Clinical Trial Registry as UMIN000010555.

Subject preparation. Each subject was placed in the supine position under standard cardiorespiratory monitoring. General anesthesia was induced and maintained by intravenous infusion of propofol. Intravenous injection of rocuronium produced complete paralysis throughout the experiment while the subject was ventilated through a modified nasal CPAP mask with positive pressure through an anesthetic machine. A slim endoscope (FB-10V, 3.4 mm OD; Pentax, Tokyo, Japan) was inserted through the center of a soft silicone cork in the nasal CPAP mask without air leakage to visualize the retroptalatal (RP) and retroglossal (RG) airways. The inserted endoscope was moved to visualize the different pharyngeal segments but insertion length of the endoscope was kept constant for each pharyngeal segment. A closed-circuit camera (ETV8; Nisco, Saitama, Japan) connected to the endoscope recorded pharyngeal images on a video-tape along with Plumen readings from a water manometer. An appropriate-sized silicone collar (cNEP; 5i Science, Carlsbad, CA) determined by the fitness to the submental region and space between the collar and the submental skin during NEP application was worn without air leakage (Fig. 1). A smaller collar limits displacement of the submental soft tissues in contact with the submental skin, whereas a larger collar produces massive air leakage leading to difficulty in maintaining NEP. The upper and lower ridges of the collar were placed on the mandible and thyroid cartilage, respectively, and the lateral ridges extended beyond the mandibular angles. Consequently, the entire submental region, including the hyoid, was subject to negative pressure and these structures moved in relation to each other as negative pressure was applied. Pillow height was adjusted accordingly for proper fit, and was elevated in obese subjects. The collar was connected to a vacuum source to produce preselected constant negative pressures inside the collar.

Assessment of static pharyngeal mechanics. The nasal mask was disconnected from the anesthetic machine and reconnected to a pressure-control system capable of accurately manipulating a constant, preselected \( P_{\text{lumen}} \) ranging from 20 to –20 cm H\(_2\)O in steps of 1 cm H\(_2\)O. Cessation of mechanical ventilation resulted in apnea caused by complete muscle paralysis. \( P_{\text{lumen}} \) was immediately increased and maintained at 20 cm H\(_2\)O. While the subject remained apneic for 2–3 min, \( P_{\text{lumen}} \) was slowly reduced from 20 cm H\(_2\)O to a pressure at which complete RP airway closure occurred, as evident on a video screen. In this experimental setting, RG \( P_{\text{lumen}} \) was not reduced below the RP \( P_{\text{lumen}} \). The airway images were kept in the center of the screen by manipulating the angle of the endoscope to maintain the angle between the camera and the targeted cross-sectional area. This procedure of experimentally induced apnea allowed construction of the static pressure-area relationship of the visualized pharyngeal segment (11–15). Recordings were made for the RP and RG airways. Distance between the tip of the endoscope and the Narrowing site was measured by using a wire passed through an aspiration channel of the endoscope to determine image magnification at the atmospheric airway pressure. The subject was manually ventilated for at least 1 min before and after the apneic test. The measurements were repeated during submental NEP application of 0 cm H\(_2\)O (NEP\(_{\text{ZERO}}\)), –25 cm H\(_2\)O (NEP\(_{25}\)), and –50 cm H\(_2\)O (NEP\(_{50}\)), randomly selected for each pharyngeal segment.

Data analysis. The technique and accuracy of conversion of the video pharyngeal image to an absolute value of cross-sectional area are evident in previous reports (11–15) and in our study, which produced digitized endoscopic images. A frame for each 1 cm H\(_2\)O \( P_{\text{lumen}} \) step was selected and image distortions due to fisheye lens of

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**Table 1. Anthropometric characteristics and results of sleep studies for each group**

<table>
<thead>
<tr>
<th></th>
<th>Nonobese</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>10 women</td>
<td>10 women</td>
</tr>
<tr>
<td>Age, yr</td>
<td>57.4 ± 11.5</td>
<td>56.3 ± 11.2</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.55 ± 0.08</td>
<td>1.53 ± 0.07</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>49.9 ± 5.9</td>
<td>76.5 ± 14.7**</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>20.8 ± 1.9</td>
<td>32.8 ± 6.7**</td>
</tr>
<tr>
<td>Neck circumference, cm</td>
<td>31.8 ± 1.4</td>
<td>37.9 ± 3.8**</td>
</tr>
<tr>
<td>Mallampati class, I/II/III/IV</td>
<td>6/2/1/1</td>
<td>1/0/2/1</td>
</tr>
<tr>
<td>SDB symptoms, 0/1/2/3/4†</td>
<td>3/0/0/1/1</td>
<td>0/2/3/0/0*</td>
</tr>
<tr>
<td>3% Oxygen desaturation index, h(^{-1})</td>
<td>7.0 ± 8.8</td>
<td>20.9 ± 12.6*</td>
</tr>
<tr>
<td>4% Oxygen desaturation index, h(^{-1})</td>
<td>4.6 ± 7.3</td>
<td>15.0 ± 10.3*</td>
</tr>
<tr>
<td>Time spent ( \text{SaO}_2 ), &lt;90%</td>
<td>0.8 ± 1.9</td>
<td>5.0 ± 5.4*</td>
</tr>
<tr>
<td>Apnea hypopnea index, h(^{-1})</td>
<td>7.5 ± 9.9</td>
<td>20.5 ± 13.1*</td>
</tr>
<tr>
<td>Patients with SDB</td>
<td>5/10</td>
<td>10/10*</td>
</tr>
</tbody>
</table>

SDB, sleep-disordered breathing. *P < 0.05, **P < 0.01 vs. nonobese group, respectively. †Number of clinical symptoms suggesting SDB including habitual snoring, daytime sleepiness, witnessed apnea, and presence or treatment of hypertension.
the endoscope were corrected (Photoshop Creative Suite 6; Adobe Systems, San Jose, CA). Magnification of the imaging system was estimated at 1.0-mm interval distances between the endoscopic camera and the object (1 cm² grid) in range of 5 to 30 mm, producing a relationship between distance and pixels corresponding to 1 cm². At a defined value of Plumen, each pharyngeal lumen image was manually traced on the computer screen with particular reference to its contrast and relative position of the pharyngeal structures observed in the image. A pixel count within the traced area was executed (ImageJ; National Institutes of Health, Bethesda, MD). The pixel number was converted to the pharyngeal cross-sectional area according to the distance measured at atmospheric pressure and the distance-magnification relation for the imaging system assuming the distance between the camera and the targeted area does not change during an apneic test. Accuracy of cross-sectional area measurements was previously tested by use of known diameter tubes (12). For constant distance, the measured areas were consistently deviated from actual areas; underestimation by 11% for a large area and overestimation by 13% for a small area (12). Image distortion correction by the computer program adopted in this study decreased the measurement error due to the fisheye lens of the endoscope from 5% to 1% (10 mm distance).

The measured luminal cross-sectional area was plotted as a function of Plumen. Maximum area (A_max) was determined as the mean of the mean values of areas at the highest three Plumen (18, 19, and 20 cmH₂O). The relationship of each pharyngeal segment was expressed as an exponential function, \( A = A_{\text{max}} - B \cdot \exp(-K \cdot \text{Plumen}) \), where B and K denote constants, and A denotes cross-sectional area. A non-linear least-squares technique was used for the curve fitting, and the quality of the fitting was denoted as coefficient \( r^2 \). A regression estimate of \( P_{\text{close}} \), which corresponds to an intercept of the curve on the Plumen axis, was calculated from the following equation for each pharyngeal segment: \( P_{\text{close}} = \ln(B/A_{\text{max}}) \cdot K^{-1} \). The shape of the pressure-area relation was denoted as K. When the pressure-area relation is curvilinear, compliance of the pharynx, defined as a slope of the curve, varies with changes in Plumen. Therefore, a single value of compliance calculated for a given Plumen does not represent collapsibility of the pharynx for entire ranges of Plumen. By contrast, K represents the rate of slope changes of the curve. When K is high, a small reduction of Plumen results in a significant increase of compliance, leading to a remarkable reduction in the cross-sectional area. Accordingly, collapsibility of the pharynx increases with increased K value. 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. Reproducibility of the \( P_{\text{close}} \) estimation for both pharyngeal segments was tested in 10 subjects randomly selected from our database (13). Differences between the first and second measurements of \( P_{\text{close}} \) ranged from +0.2 cmH₂O to −0.9 cmH₂O (mean ± SD, +0.2 ± 0.3 cmH₂O) at the RP segment and from +0.4 cmH₂O to −2.3 cmH₂O (mean ± SD, +0.2 ± 0.8 cmH₂O) at the RG segment.

Statistical analysis. Our previous study indicates that a maximum SD of our primary variable, \( P_{\text{close}} \) of patients with OSA, is 2.8 cmH₂O (11). Submental NEP was expected to decrease \( P_{\text{close}} \) by greater than 3 cmH₂O, which would require nine or more subjects for detection of the expected change, assuming 0.05 (two-tailed) and 80% power (SigmaPlot 12.0; Systat Software, Point Richmond, CA). To avoid a type 1 error for the second hypothesis, the appropriate sample size was determined to be 20 or more. All values are expressed as means ± SD. Outliers defined as the values below or above 2 SDs were excluded from the analyses. The one-way repeated variance measurement analysis was used to examine the effects of the submental NEP applications. All pairwise multiple comparisons were performed with the Student-Newman-Keuls test, comparisons between obese and nonobese groups were performed by unpaired t-test, and Pearson correlation analysis was used to identify correlation between the variables. Stepwise regression analyses were performed to identify independent variable(s) to explain changes in the static mechanics. \( P < 0.05 \) was considered significant.

RESULTS

Subjects in the obese group were revealed to have higher BMI than those in the nonobese group by definition (Table 1). Obese subjects had larger neck circumference and more disordered breathing episodes during sleep than nonobese subjects, although age and height were matched between the groups. Endoscopic measurements of static pressure-area relationships of RP and RG airways were successfully performed during submental NEP applications, aside from one obese patient whose measurement at RP during −25 cmH₂O NEP application was unattainable due to a technical difficulty.

Figure 2 presents representative changes of RP airway patency during apneic testing, and static pressure-area relationships before and during submental NEP application in a nonobese subject without sleep-disordered breathing (BMI 20.8 kg/m², apnea hypopnea index 3.1 h⁻¹). Although almost no change was observed in the RP airway images at the higher Plumen range, the airway progressively narrowed below 5 cmH₂O and closed at −2 cmH₂O Plumen during NEPZERO. In contrast, RP airway narrowing during step Plumen changes was gradual even near atmospheric pressure during NEPZERO, and −7 cmH₂O Plumen was required to close the airway. Distance between the tip of the endoscope and the narrowing site was 11 mm, and 15,151 pixels of the digitized image corresponded to 1.0 cm². To obtain static pressure-area relationships of the airway and static mechanical variables, the measured RP cross-sectional areas and the corresponding Plumen values were plotted on a coordinate plane. Only a slight change in A_max measurements was obtained during submental NEP application. The relationships were well fitted by the exponential function with relatively high \( r^2 \). The curve shifted to the left and became less steep at application of submental NEP (−50 cmH₂O), decreasing the \( P_{\text{close}} \) and K values.

Figures 3 and 4 show examples of endoscopic pharyngeal images during step Plumen changes in a nonobese subject and an obese subject, respectively. Application of −50 cmH₂O submental NEP increased the airway size, particularly at lower Plumen in both RP and RG airways in the nonobese subject with a BMI of 19.8 kg/m². In contrast, the −50 cmH₂O submental NEP application did not improve airway patency in either RP or RG airways in the obese subject with a BMI of 35.2 kg/m².

Effects of submental NEP application on static pharyngeal mechanics. The pharyngeal pressure-area curves obtained by exponential curve fitting for each subject are presented in Figures 5 and 6, demonstrating changes of the static pressure-area relationships before and during submental NEP. To clarify the changes in \( P_{\text{close}} \) during submental NEP, Plumen was normalized by the \( P_{\text{close}} \) during NEPZERO. In the nonobese subject group (Fig. 5), submental NEP shifted the static pressure-area curves to the left and produced less steep curves, indicating decrease of the closing pressures and airway wall compliance at the RP and RG airways. In the obese subject group (Fig. 6), changes in the static pressure-area curves in response to submental NEP were slight and insignificant.

Table 2 presents static pharyngeal mechanics obtained by curve-fitting analyses for the pressure-area relationships during submental NEP applications. As indicated by the high \( r^2 \) values, the relationships were reasonably well fit by the expo-
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Retropalatal

P_lumen [cmH2O] 20 16 12 8 4 0 -2
NEP_ZERO

NEP_25

NEP_50

Retroglossal

P_lumen [cmH2O] 20 16 12 8 4 0 -2
NEP_ZERO

NEP_25

NEP_50

In the nonobese group, submental NEP significantly reduced RP-P\(_{close}\), whereas \(A_{max}\) and K were unchanged. NEP effects were more evident in the RG airway than the RP airway. In fact, in addition to a significant reduction in RG P\(_{close}\), RG-K significantly decreased, and RG-A\(_{max}\) was only slightly but significantly increased in response to submental NEP application. No difference was observed in the effects of NEP\(_{50}\) from those of NEP\(_{25}\) in the variables. In contrast, no statistically significant changes in pharyngeal mechanics were evident in the obese groups.

Table 3 presents comparisons of the pharyngeal mechanics change in response to submental NEP between nonobese and obese groups. No difference in changes in A\(_{max}\) (\(\Delta A_{max}\)) was observed between the groups. Improvements in both K (\(\Delta K\))

Fig. 2. Representative changes of retropalatal (RP) airway patency during the apneic test and RP static pressure-area relationships before and during submental application of NEP in a nonobese subject without sleep-disordered breathing [body mass index (BMI) 20.8 kg/m\(^2\), apnea hypopnea index 3.1 h\(^{-1}\)]. Maximum area (\(A_{max}\)) was determined as the mean value of the highest three airway pressures (P\(_{lumen}\)). Each RP pressure-area relationship was fitted by the exponential function A\(_{RP}\) = \(A_{max} - B*exp(-K*P_{lumen})\), where B and K are constants and A\(_{RP}\) is the RP cross-sectional area. Quality of the fitting was provided by the coefficient \(r^2\). P\(_{close}\) = estimated closing pressure calculated by ln(B/A\(_{max}\))K\(^{-1}\).

Fig. 3. Endoscopic pharyngeal images during step changes of the pharyngeal airway pressure (P\(_{lumen}\)) before (NEP\(_{ZERO}\)) and during application of -50 cmH\(_2\)O negative pressure application to the submental region (NEP\(_{25}\)) in an anesthetized and paralyzed nonobese subject (BMI 19.8 kg/m\(^2\)). The pharyngeal area is outlined in white. Note increase of RP and retroglossal (RG) cross-sectional areas at lower P\(_{lumen}\).
and $P'_{\text{close}}$ at the RG airway region were significantly greater in the nonobese group compared with the obese group as is clearly evident in the scatter plot between $\Delta K$ and $\Delta P'_{\text{close}}$ (Fig. 7). Notably, significant association between $\Delta K$ and $\Delta P'_{\text{close}}$ was evident in the nonobese group ($r = 0.645$), suggesting mechanical linkages between airway closure and airway wall stiffness in the RG airway region in response to submental NEP application, whereas no such relationship was observed in the obese group ($r = 0.007$).

Factors possibly influencing the effectiveness of submental NEP application on pharyngeal collapsibility. Pearson correlation analyses between the pharyngeal mechanics variables listed in Table 3 and patients’ backgrounds listed in Table 1 using all subject data ($n = 20$) revealed four factors such as age, BMI, neck circumference, and apnea hypopnea index might influence a change in RG airway collapsibility (Table 4). Among the factors, noteworthy is that smaller neck circumference consistently contributes to improvement of both RG-1 and RG-$P'_{\text{close}}$. In fact, stepwise regression analyses with using the four variables listed in Table 4 identified neck circumference to be an independent factor for RG-$P'_{\text{close}}$ and RG-$\Delta K$. Interestingly, age was identified as an independent factor for decreasing RG-$\Delta K$ during NEP50 despite no significant difference in age between individuals in the nonobese and obese groups. Notably, RP-$\Delta K$ was significantly associated with RP-K ($r = 0.891$, $P < 0.001$).
whereas no such correlation was found between other mechanics variables.

**DISCUSSION**

To date, there have been no studies that have demonstrated an improvement in airway closing pressures and airway wall stiffness of the passive pharynx, particularly at the RG airway region in response to submental NEP application in human subjects. Obese individuals responded to the intervention less than nonobese individuals. The results clearly support involvement of $P_{\text{tissue}}$ in the pathophysiology of pharyngeal obstruction and indicate reduction in $P_{\text{tissue}}$ as a promising alternative approach for treatment of pharyngeal obstruction and sleep-disordered breathing.

**Mechanical actions of submental NEP.** The results of this study agree with those of the animal study in which application of ~5 cmH$_2$O negative pressure surrounding the neck significantly decreased the upper airway resistance in anesthetized, spontaneously breathing dogs (35). Our results indicate that submental NEP produces two different, though possibly interrelated, mechanical effects on the pharyngeal airway (Fig. 8).

First, $P_{\text{close}}$ decreased during submental NEP. A possible explanation may be displacement of soft tissue surrounding the pharyngeal airway, which improves anatomical balance within the maxilla-mandibular bony enclosure and possibly decreases mechanical properties of the soft tissue. In fact, the amount of soft tissue surrounding the pharyngeal airway is significantly

**Table 2. Static pharyngeal mechanics during submental NEP applications**

<table>
<thead>
<tr>
<th></th>
<th>Nonobese, n = 10</th>
<th>Obese, n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_{\text{max}}$-NEP$_{\text{ZERO}}$, cm$^2$</td>
<td>1.75 ± 0.79, 2.31 ± 0.75</td>
<td>1.66 ± 0.83, 3.47 ± 0.84</td>
</tr>
<tr>
<td>$A_{\text{max}}$-NEP$_{25}$, cm$^2$</td>
<td>1.82 ± 0.92, 2.45 ± 0.79</td>
<td>1.74 ± 0.88, 3.83 ± 0.88</td>
</tr>
<tr>
<td>$A_{\text{max}}$-NEP$_{50}$, cm$^2$</td>
<td>1.87 ± 0.78, 2.60 ± 0.85*</td>
<td>1.80 ± 0.85, 3.78 ± 0.98</td>
</tr>
<tr>
<td>K-NEP$_{\text{ZERO}}$</td>
<td>0.23 ± 0.10, 0.19 ± 0.04</td>
<td>0.18 ± 0.04, 0.22 ± 0.05</td>
</tr>
<tr>
<td>K-NEP$_{25}$</td>
<td>0.19 ± 0.09, 0.12 ± 0.03**</td>
<td>0.16 ± 0.03, 0.23 ± 0.05</td>
</tr>
<tr>
<td>K-NEP$_{50}$</td>
<td>0.15 ± 0.06, 0.13 ± 0.03**</td>
<td>0.18 ± 0.06, 0.20 ± 0.04</td>
</tr>
<tr>
<td>$P_{\text{close}}$-NEP$_{\text{ZERO}}$, cmH$_2$O</td>
<td>−2.2 ± 1.3, −1.2 ± 2.1</td>
<td>−0.8 ± 1.1, −1.5 ± 1.7</td>
</tr>
<tr>
<td>$P_{\text{close}}$-NEP$_{25}$, cmH$_2$O</td>
<td>−4.9 ± 4.6*, −3.7 ± 3.5**</td>
<td>−2.1 ± 1.4, −2.4 ± 0.8</td>
</tr>
<tr>
<td>$P_{\text{close}}$-NEP$_{50}$, cmH$_2$O</td>
<td>−3.7 ± 3.4*, −4.5 ± 3.4**</td>
<td>−1.9 ± 1.3, −2.2 ± 0.9</td>
</tr>
<tr>
<td>$r^2$-NEP$_{\text{ZERO}}$</td>
<td>0.95 ± 0.03, 0.95 ± 0.03</td>
<td>0.96 ± 0.04, 0.93 ± 0.06</td>
</tr>
<tr>
<td>$r^2$-NEP$_{25}$</td>
<td>0.94 ± 0.04, 0.93 ± 0.03</td>
<td>0.95 ± 0.04, 0.92 ± 0.05</td>
</tr>
<tr>
<td>$r^2$-NEP$_{50}$</td>
<td>0.94 ± 0.05, 0.93 ± 0.03</td>
<td>0.95 ± 0.05, 0.95 ± 0.03</td>
</tr>
</tbody>
</table>

$A_{\text{max}}$, maximum cross-sectional area; B and K, constants obtained by fitting the pressure/area relationship of each pharyngeal airway to an exponential function, $A = A_{\text{max}} - B \cdot \exp(-K \cdot P_{\text{tissue}})$, where $A$ and $P_{\text{tissue}}$ denote the cross-sectional area of the pharyngeal airway and airway pressure, respectively; NEP, negative external pressure; NEP$_{25}$, ~20 cmH$_2$O submental NEP; NEP$_{50}$, ~50 cmH$_2$O submental NEP; $P_{\text{close}}$, estimated closing pressure calculated by ln(B/A$_{\text{max}}$)K$^{-1}$; RG, retroglossal airway; RP, retropalatal airway. Quality of the fit is provided by the coefficient $r^2$. *$P < 0.05$, **$P < 0.01$ vs. NEP$_{\text{ZERO}}$, respectively.

**Table 3. Comparisons of changes in the pharyngeal mechanics during submental NEP applications between nonobese and obese groups**

<table>
<thead>
<tr>
<th></th>
<th>Nonobese n = 10</th>
<th>Obese n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_{\text{max}}$-NEP$_{25}$, cm$^2$</td>
<td>0.01 ± 0.17, 0.14 ± 0.20</td>
<td>0.03 ± 0.31, 0.19 ± 0.32</td>
</tr>
<tr>
<td>$A_{\text{max}}$-NEP$_{50}$, cm$^2$</td>
<td>0.12 ± 0.27, 0.29 ± 0.37</td>
<td>0.14 ± 0.24, 0.31 ± 0.32</td>
</tr>
<tr>
<td>K-NEP$_{25}$</td>
<td>0.06 ± 0.10, 0.06 ± 0.05*</td>
<td>0.02 ± 0.06, 0.01 ± 0.02</td>
</tr>
<tr>
<td>K-NEP$_{50}$</td>
<td>0.08 ± 0.09, 0.06 ± 0.04*</td>
<td>0.03 ± 0.04, 0.01 ± 0.04</td>
</tr>
<tr>
<td>$P_{\text{close}}$-NEP$_{25}$, cmH$_2$O</td>
<td>2.3 ± 3.2, 2.9 ± 2.7</td>
<td>0.7 ± 0.8, 1.4 ± 1.7</td>
</tr>
<tr>
<td>$P_{\text{close}}$-NEP$_{50}$, cmH$_2$O</td>
<td>2.0 ± 3.0, 3.7 ± 2.6*</td>
<td>1.1 ± 1.2, 1.0 ± 1.9</td>
</tr>
</tbody>
</table>

* $P < 0.05$ vs. obese group.
This markedly contrasts with the fact that a relatively small application retroglossal airway collapsibility during submental NEP may shift the hyoid bone caudally, which increases pharyngeal airway length; consequently stretching the pharyngeal airway wall to the caudal direction and thus increasing longitudinal tension of the pharyngeal airway as indicated by significant K value reduction (Fig. 7) (11). This explains the changes in the shape of the tube law in response to submental NEP as demonstrated in Figs. 5 and 6. To our knowledge, no previous study has directly demonstrated changes in pharyngeal airway wall stiffness in response to submental and peripharyngeal mass loading, although its significance in pharyngeal airway obstruction has been reported both in human and animal studies (1, 4, 11). From our results, inhomogeneity of the soft tissue elastic properties surrounding the pharyngeal airway may be a possible explanation for the changes in pharyngeal wall stiffness in response to submental NEP. As discussed above, occurrence of increased stiffness by tissue deformation is very rare in obese subjects with redundant fatty tongue base (higher Young’s elastic modulus) during submental NEP, as illustrated in Fig. 4. In contrast, stiffness of the RG airway increases in nonobese subjects with less redundant tongue base

decrease while submental NEP stretches the skin. This nonlinear elastic property of the skin may explain the decrease in submental NEP effectiveness while increasing the NEP levels, which produced the ceiling effect of submental NEP observed in this study.

Second, soft tissue displacement outside of the maxilla-mandible enclosure during submental NEP application may shift the hyoid bone caudally, which increases pharyngeal airway length; consequently stretching the pharyngeal airway wall to the caudal direction and thus increasing longitudinal tension of the pharyngeal airway as indicated by significant K value reduction (Fig. 7) (11). This explains the changes in the shape of the tube law in response to submental NEP as demonstrated in Figs. 5 and 6. To our knowledge, no previous study has directly demonstrated changes in pharyngeal airway wall stiffness in response to submental NEP. As discussed above, occurrence of increased stiffness by tissue deformation is very rare in obese subjects with redundant fatty tongue base (higher Young’s elastic modulus) during submental NEP, as illustrated in Fig. 4. In contrast, stiffness of the RG airway increases in nonobese subjects with less redundant tongue base

Fig. 8. Possible mechanical actions of submental NEP are illustrated. Top: in nonobese subjects, movement and deformation of the soft tissue during submental NEP result in a reduction in tissue pressure \( P_{\text{tissue}} \) near the pharyngeal airway and an increase in longitudinal tension of the pharyngeal airway wall. Location and pattern of soft tissue displacement are well explained by inhomogeneous mechanical properties of soft tissue surrounding the pharyngeal airway. Note the possibility of the caudal and anterior shift of the hyoid bone and epiglottis in response to the application of NEP. Bottom: displacement of fatty tongue base in obese subjects is expected to be difficult because of relative higher Young’s elastic modulus at the tongue base, accounting for no collapsibility changes in obese subjects during submental NEP.

| Table 4. Factors possibly influencing changes in retroglossal airway collapsibility during submental NEP application |
|-----------------|--------|--------|--------|
| Retroglossal \( \Delta P'_{\text{close}} \) (cmH\(_2\)O) | Age | BMI | NC | AHI |
| NEP\(_{25}\) | -0.228 | -0.408 | -0.518*† | -0.289 |
| NEP\(_{50}\) | -0.222 | -0.502*† | -0.506*† | -0.587* |
| Retroglossal \( \Delta K \) | Non-obese, \( r=0.645 \) | Obese, \( r=0.007 \) |
| NEP\(_{25}\) | -0.325 | -0.545*† | -0.568*† | -0.425 |
| NEP\(_{50}\) | -0.558*† | -0.538*† | -0.573*† | -0.390 |

AHI, apnea hypopnea index; BMI, body mass index; NC, neck circumference; \( \Delta K \), difference in pharyngeal wall stiffness before and during submental NEP. * \( p < 0.05 \) by Pearson’s correlation analysis. † Independent variable identified by stepwise regression analysis using the four variables (\( P < 0.05 \)).
(smaller Young’s elastic modulus) during submental NEP. This suggests that a more mobile tongue base could result in improvement of both RG $P_{\text{close}}$ and stiffness during submental NEP, similar to the finding that tongue displacement augmented the tracheal traction effect on upper airway collapsibility and airflow dynamics in animal preparation (27). Furthermore, the finding that RP airway with an originally high K value, despite the lengthy distance from the submental region, responded well to submental NEP may be an outcome of the physical response of RP soft tissue with smaller Young’s elastic modulus (higher elasticity) to submental NEP. In the future, these considerations may be tested through a sophisticated tagged magnetic resonance imaging technique (3).

**Limitations of the study.** There are various methodological limitations in this study. First, the study was performed only in adult Japanese women. Menstrual cycle and menopause significantly influence breathing during sleep and collapsibility of the pharyngeal airway (5, 36). We did not assess these conditions in our subjects, although 75% of the subjects were over 50 years old. In addition to craniofacial characteristics, fat distribution and compositions of soft tissue within the maxilla-mandible enclosure and the tongue differ between genders and among races (30); therefore, different results may have been obtained with male subjects and different races.

Second, the subjects were anesthetized and paralyzed to assess pure mechanical properties of the pharyngeal airway; therefore, potential effects of submental NEP on the neuromuscular mechanisms were not considered in this study. However, these mechanisms are highly unlikely, considering the study by Wolin et al. in which recruitment of the alae nasi electromyogram was not evident in response to negative pressure surrounding the neck in anesthetized dogs (35).

Third, during mask ventilation with airway maneuvers between apneic testing and NEP device readjustment, slight alterations of the head and mandible positions may have occurred, which could have influenced the results of this study.

Fourth, the results significantly depend on the efficacy of the devices, particularly the submental silicone collar design, although device testing is not the purpose of this study. Wearing a collar may even have changed the pharyngeal collapsibility. In fact, only 5 out of 14 subjects with an apnea hypopnea index greater than 5 had positive $P_{\text{close}}$ during NEPZERO, probably due to the positional effects of the collar. Maintaining the sniffing position is expected to reduce $P_{\text{close}}$ during NEPZERO, probably due to the positional effects of the collar. The ineffectiveness of submental NEP application in obese subjects could be, although highly unlikely, due to technical failure, because submental soft tissue was observed. Because the soft tissue displacement volume was not measured in this study, the volumes between nonobese and obese subjects could not be compared; however, space between the silicone collar and submental skin was confirmed during the intervention, which indicates that submental NEP was unquestionably applied on the entire submental region.

Finally and most importantly, the cross-sectional area measurements in human pharyngeal airway is challenging and may be less accurate than estimated in known diameter tubes. The human pharyngeal airway is curved and has various complicated structures with irregular surfaces. Mucus on the surface sometimes causes a deterioration in image quality. Also, its shape and size change with a change in luminal pressure. Because we manually traced the area on the computer screen with particular reference to its contrast and relative position of the pharyngeal structures observed in the image, changes in position and angle of the endoscope introduced technical difficulties in correctly outlining the area, although our efforts to minimize these might have helped to some extent. Interestingly, as evident from Figs. 2–4, pharyngeal structures appear to move cranially with decreasing the $P_{\text{lumen}}$, which possibly impairs consistent measurements of the cross-sectional area. This systematic phenomenon is unable to be explained by the technical errors mentioned above and may reflect mechanical influence of lung volume reduction and/or inhomogeneous mechanical properties of the pharyngeal structures. These technical difficulties and mechanical influences need to be managed to obtain more accurate static pressure-area relationship of the passive pharyngeal airway in the future.

**Clinical implications of the study.** Nasal CPAP effectively reverses and prevents upper airway obstruction by increasing $P_{\text{lumen}}$ and lung volume during sleep in patients with OSA (2, 31). Despite its effectiveness, not all patients accept the treatment, limiting its clinical usefulness (21). Alternative treatments need to be developed for further patient health care improvement and safety in critical situations. Submental NEP tested in this study significantly improved pharyngeal airway collapsibility, and hence may be useful in clinical applications such as treatment of OSA and upper airway maintenance during sedation and anesthesia. Although the clinical usefulness of this treatment should be determined in real clinical settings from the standpoints of breathing stability, patient acceptance, ease and difficulty in maintaining proper collar positioning during sleep or sedation, and potential adverse effects, our results clearly provide pathophysiological evidence for clinically testing submental NEP in various clinical situations.

In this study, improvement of the passive pharyngeal airway collapsibility during submental NEP was demonstrated to be most likely caused by a tissue pressure decrease around the pharyngeal airway, particularly in nonobese subjects. The difference in submental NEP responses can be well explained by inhomogeneous mechanical characteristics of the soft tissue surrounding the pharyngeal airway.

**ACKNOWLEDGMENTS**

We thank Richard Rose, president of 5i Science, Carlsbad, CA, for providing the silicone collars and a vacuum source used in this study. Dr. Sara Shimizu helped improve the language of the manuscript. This work is attributed to the Department of Anesthesiology, Graduate School of Medicine, Chiba University.

**GRANTS**

Support for this study was provided by Grant-in-Aid 24390363 from the Ministry of Education, Culture, Sports, Science and Technology, Tokyo, Japan.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.
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