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

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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 decrease collapsibility of the passive pharyngeal airway in nonobese Japanese women.

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 (Ptm). Ptm is the pressure difference between pressures inside the tube (Plumen), defined as the lateral wall pressure acting on the luminal surface of the tube, and outside the tube (Ptissue), defined as the tissue pressure acting on the outer surface of the tube. Influences of Ptissue 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 Ptissue, and several human studies indirectly assessed the contribution of Ptissue to the pathophysiology of pharyngeal obstruction (14, 25). Although no studies have directly measured Ptissue in humans due to the difficulty in manipulating and measuring Ptissue, these studies strongly suggest the effectiveness of Ptissue 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 Ptissue 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
Subjects 10 women 10 women
Age, yr 57.4 ± 11.5 56.0 ± 11.2
Height, m 1.55 ± 0.08 1.53 ± 0.07
Weight, kg 49.9 ± 5.9 76.5 ± 14.7**
Body mass index, kg/m² 20.8 ± 1.9 32.8 ± 6.7**
Neck circumference, cm 31.8 ± 1.4 37.9 ± 3.8**
Mallampati class, I/II/III/IV 6/2/1 1/0/2/1
SDB symptoms, 0/1/2/3/4† 3/5/0/1 0/2/3/2/0* 
3% Oxygen desaturation index, h⁻¹ 7.0 ± 8.8 20.9 ± 12.6*
4% Oxygen desaturation index, h⁻¹ 4.6 ± 7.3 15.0 ± 10.3*
Time spent SaO₂ <90% 0.8 ± 1.9 5.0 ± 5.4*
Apnea hypopnea index, h⁻¹ 7.5 ± 9.9 20.5 ± 13.1*
Patients with SDB 5/10 10/10*

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 P_{lumen}, 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 P_{lumen}. Maximum area (A_{max}) was determined as the mean of the mean values of areas at the highest three P_{lumen} (18, 19, and 20 cmH₂O). The relationship of each pharyngeal segment was expressed as an exponential function, \( A = A_{max} - B \cdot \exp(-K \cdot P_{lumen}) \), 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 regressional estimate of \( P_{close} \), which corresponds to an intercept of the curve on the P_{lumen} axis, was calculated from the following equation for each pharyngeal segment: \( P_{close} = \ln(B/A_{max}) \cdot K \). 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 P_{lumen}. Therefore, a single value of compliance calculated for a given P_{lumen} does not represent collapsibility of the pharynx for entire ranges of P_{lumen}. By contrast, K represents the rate of slope changes of the curve. When K is high, a small reduction of P_{lumen} 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 \( P_{close} \) 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 \( P_{close} \) estimation for both pharyngeal segments was tested in 10 subjects randomly selected from our database (13). Differences between the first and second measurements of \( P_{close} \) 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, \( P_{close} \) of patients with OSA, is 2.8 cmH₂O (11). Submental NEP was expected to decrease \( P_{close} \) 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 P_{lumen} range, the airway progressively narrowed below 5 cmH₂O and closed at −2 cmH₂O P_{lumen} during NEP_ZERO. In contrast, RP airway narrowing during step P_{lumen} changes was gradual even near atmospheric pressure during NEP₀ and −7 cmH₂O P_{lumen} 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 P_{lumen} 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 \( P_{close} \) and K values.

Figures 3 and 4 show examples of endoscopic pharyngeal images during step P_{lumen} changes in a nonobese subject and an obese subject, respectively. Application of −50 cmH₂O submental NEP increased the airway size, particularly at lower P_{lumen} 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 \( P_{close} \) during submental NEP, P_{lumen} was normalized by the \( P_{close} \) during NEP_ZERO. 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-
nential function. In the nonobese group, submental NEP signifi-
cantly reduced RP-$P'_{\mathrm{close}}$, whereas $A_{\mathrm{max}}$ and $K$ were un-
changed. NEP effects were more evident in the RG airway than
the RP airway. In fact, in addition to a significant reduction in
RG-$P'_{\mathrm{close}}$, RG-$K$ significantly decreased, and RG-$A_{\mathrm{max}}$ was
only slightly but significantly increased in response to submen-
tal 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 $A_{\mathrm{max}}$ ($\Delta A_{\mathrm{max}}$) was
observed between the groups. Improvements in both $K$ ($\Delta K$)
and $A_{\mathrm{max}}$ ($\Delta A_{\mathrm{max}}$) were observed in the nonobese groups.

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 ($A_{\mathrm{max}}$) was determined as the mean value of the highest three airway pressures ($P_{\text{lumen}}$). Each RP pressure-area re-
lationship was fitted by the exponential func-
tion $A_{\mathrm{RP}} = A_{\max} - B \cdot \exp(-K \cdot P_{\text{lumen}})$,
where $B$ and $K$ are constants and $A_{\mathrm{RP}}$ is the RP cross-sectional area. Quality of the fitting
was provided by the coefficient $r^2$. $P'_{\mathrm{close}}$ was
estimated closing pressure calculated by
$\ln(B/A_{\max})K^{-1}$.

Fig. 3. Endoscopic pharyngeal images during step changes of the pharyngeal airway pressure ($P_{\text{lumen}}$) before (NEP$_{\text{ZERO}}$) and during applica-
tion of -50 cmH$_2$O negative pressure application to the submental region (NEP$_{50}$) in an anesthe-
tized 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 $P_{\text{lumen}}$. 

\begin{align}
A_{\mathrm{RP}} &= A_{\max} - B \cdot \exp(-K \cdot P_{\text{lumen}}) \\
P'_{\mathrm{close}} &= -\ln(B/A_{\max})K^{-1} \\
\end{align}

\begin{align}
\text{NEP}_{\text{ZERO}}: A_{\mathrm{RP}} &= 1.07 - 78.8 \cdot \exp(-0.21 \cdot P_{\text{lumen}}) \\
P'_{\mathrm{close}} &= -1.4 \text{ cmH}_2\text{O}, r^2 = 0.966 \\
\text{NEP}_{25}: A_{\mathrm{RP}} &= 1.01 - 54.4 \cdot \exp(-0.24 \cdot P_{\text{lumen}}) \\
P'_{\mathrm{close}} &= -2.6 \text{ cmH}_2\text{O}, r^2 = 0.964 \\
\text{NEP}_{50}: A_{\mathrm{RP}} &= 1.00 - 38.8 \cdot \exp(-0.15 \cdot P_{\text{lumen}}) \\
P'_{\mathrm{close}} &= -6.4 \text{ cmH}_2\text{O}, r^2 = 0.961
\end{align}
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-$P'_{\text{close}}$ and RG-$K$. In fact, stepwise regression analyses with using the four variables listed in Table 4 identified neck circumference to be an independent factor for RG-$\Delta P'_{\text{close}}$ 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-$K$ ($r = 0.891, P < 0.001$),
Submental Negative Pressure and Pharyngeal Collapsibility • Kato S et al.

917

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 $P_{tissue}$ in the pathophysiology of pharyngeal obstruction and indicate reduction in $P_{tissue}$ 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, $P_{close}$ 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 $P_{tissue}$ (32, 33) (Fig. 5). In addition to previous human studies assessing the pharyngeal anatomical balance (28, 32), animal studies also support this mechanism (17, 20, 34).

Kairaitis et al. increased peripharyngeal volume by inflating a balloon in anesthetized rabbits and found significant airway narrowing and an increase in directly measured $P_{tissue}$ in a nonuniform fashion (17), suggesting regional differences in 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>$A_{max}$-NEP$_{ZERO}$, 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>$A_{max}$-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>$A_{max}$-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$_{ZERO}$</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>$P_{close}$-NEP$_{ZERO}$, 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>$P_{close}$-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>$P_{close}$-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$_{ZERO}$</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 ± 0.03 0.95 ± 0.03</td>
</tr>
</tbody>
</table>

$A_{max}$, maximum cross-sectional area; B and K, constants obtained by fitting the pressure/area relationship of each pharyngeal airway to an exponential function, $A = A_{max} - B \exp(-K \cdot P_{tissue})$, where $A$ and $P_{tissue}$ 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; $P_{close}$, estimated closing pressure calculated by $\ln(B/A_{max}) + K^{-1}$; RG, retroglossal; RP, retropalatal airway. Quality of the fit is provided by the coefficient $r^2$, $*P < 0.05$, **$P < 0.01$ vs. NEP$_{ZERO}$, 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>$\Delta A_{max}$-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>$\Delta A_{max}$-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>$\Delta$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>$\Delta$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>$\Delta P_{close}$-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>$\Delta P_{close}$-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.
larger at the anterior pharyngeal wall than the lateral wall, possibly producing inhomogeneous $P_{\text{tissue}}$ (15). Furthermore, fat distribution also differs within the maxilla-mandible enclosure (23) and the tongue (24) with more fat at the tongue base indicating inhomogeneous soft tissue elasticity, which is a significant determinant of soft tissue movement and deformation. In general, Young’s elastic modulus of muscle (0.0675 MPa) is half of that of fat (0.182 MPa), suggesting that the middle part of the tongue body is more mobile than the tongue base and other fatty soft tissue in response to submental NEP (26a). This prediction is in agreement with the movements of the tongue musculature during hypoglossal nerve stimulation analyzed by a tagged magnetic resonance imaging technique in rats (3). Accordingly, obese subjects with redundant fatty tongue base hardly responded to submental NEP as was demonstrated in this study (22).

Relatively lower elasticity of the submental skin (0.85 MPa) may also be one explanation for the necessity of a large negative pressure to decrease $P_{\text{close}}$ for submental NEP (26a). This markedly contrasts with the fact that a relatively small increase in $P_{\text{tum}}$ directly changes collapsibility of the pharyngeal airway, possibly due to a smaller elastic modulus of soft tissue adjacent to the pharyngeal airway such as tongue musculature. The low elasticity of submental skin may further 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 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

Table 4. Factors possibly influencing changes in retroglossal airway collapsibility during submental NEP application

<table>
<thead>
<tr>
<th>Retroglossal $\Delta P'_{\text{close}}$</th>
<th>Age</th>
<th>BMI</th>
<th>NC</th>
<th>AHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEP25</td>
<td>0.228</td>
<td>-0.408</td>
<td>-0.518*</td>
<td>-0.297</td>
</tr>
<tr>
<td>NEP50</td>
<td>0.222</td>
<td>-0.502*</td>
<td>-0.506*</td>
<td>-0.587*</td>
</tr>
<tr>
<td>Retroglossal $\Delta K$</td>
<td>0.325</td>
<td>-0.545*</td>
<td>-0.568*</td>
<td>-0.425</td>
</tr>
<tr>
<td>NEP25</td>
<td>0.558*</td>
<td>-0.538*</td>
<td>-0.573*</td>
<td>-0.390</td>
</tr>
</tbody>
</table>

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 ($P < 0.05$).
Due to the positional effects of the collar. Maintaining the neck in anesthetized dogs (35). This effect surrounding the pharyngeal airway.

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**

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**DISCLOSURES**

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

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