Pharyngeal mucosal wall folds in subjects with obstructive sleep apnea

Kristina Kairaitis,1,3 Sheryl Foster,2,3 Jason Amatoury,1,3 Manisha Verma,1 John R. Wheatley,1,3 and Terence C. Amis1,3

1Ludwig Engel Centre for Respiratory Research, Westmead Millennium Institute, Westmead, New South Wales, Australia; 2Department of Radiology, Westmead Hospital, Westmead, New South Wales, Australia; and 3University of Sydney at Westmead Hospital, Westmead, New South Wales, Australia

Submitted 31 July 2014; accepted in final form 26 January 2015

Kairaitis K, Foster S, Amatoury J, Verma M, Wheatley JR, Amis TC. Pharyngeal mucosal wall folds in subjects with obstructive sleep apnea. J Appl Physiol 118: 707–715, 2015. First published January 29, 2015; doi:10.1152/japplphysiol.00691.2014.—Mechanical processes underlying pharyngeal closure have not been examined. We hypothesized that the pharyngeal mucosal surface would fold during closure, and lowering the upper airway lining liquid surface tension would unfold areas of mucosal apposition, i.e., folds. We compared baseline pharyngeal fold numbers and response to reduction in upper airway liquid surface tension in healthy and obstructive sleep apnea (OSA) subjects. Awake, gated magnetic resonance pharyngeal airway images of 10 healthy and 11 OSA subjects were acquired before and after exogenous surfactant administration (beractant). Upper airway liquid surface tension was measured at the beginning and end of image acquisition and averaged. Velopharyngeal and oropharyngeal images were segmented and analyzed separately for average cross-sectional area, circumference, and fold number. Compared with healthy subjects, at baseline, velopharynx for OSA subjects had a smaller cross-sectional area (98.3 ± 32.5 mm² healthy, 52.3 ± 23.6 mm² OSA) and circumference (46.5 ± 8.1 mm healthy, 30.8 ± 6.1 mm OSA; both P < 0.05, unpaired t-test), and fewer folds (4.9 ± 1.6 healthy, 3.1 ± 1.8 OSA, P < 0.03). There were no differences in oropharynx for cross-sectional area, circumference, or folds. Reduction in upper airway liquid surface tension from 61.3 ± 1.2 to 55.3 ± 1.5 mN/m (P < 0.0001) did not change cross-sectional area or circumference for velopharynx or oropharynx in either group; however, in OSA subjects, oropharyngeal folds fell from 6.3 ± 3.1 to 4.7 ± 1.2 (n = 8, P < 0.05), and velopharyngeal folds from 3.3 ± 1.9 to 2.3 ± 1.2 (P = 0.08), and were unchanged in healthy subjects. Subjects with OSA have fewer velopharyngeal wall folds, which decrease further when surface tension falls. We speculate that reduced pharyngeal wall folds contribute to an increase in pharyngeal collapsibility.

Pharyngeal collapse; upper airway; surface tension

UPPER AIRWAY NARROWING AND closure during sleep is the defining pathophysiological characteristic of obstructive sleep apnea (OSA); however, the underlying mechanical processes and susceptibilities are incompletely understood. The pharyngeal airway is often modeled as a floppy-walled tube that collapses when exposed to critical levels of inspiratory negative intraluminal pressure (9). The individual and integrated roles of upper airway lumen size and shape (1, 47), dilatory muscle recruitment levels (31), wall stiffness (1, 15, 19, 42, 44), and surrounding tissue pressures (2, 15–18, 20) have all been explored in previously published analyses. Recently, our laboratory hypothesized that susceptibility to upper airway closure may also be influenced by an additional factor: the presence of mucosal wall folds (14).

It is a well-known feature of thin-walled collapsible tube mechanics that wall folds alter tube collapsibility by modifying wall stiffness (48). In its lowest energy state, a thin-walled tube collapses by folding in two places (48). However, the more folds that form, the less collapsible the tube (48). The influence of wall folds on the collapsibility of a thin-walled tube was first quantified 100 years ago by von Mises (46). In his analysis, the relationship between wall fold numbers and collapsibility is expressed as the critical transmural pressure at which wall buckling commences [P_B (46)]. For any particular thin-walled tube, the value for P_B is given by:

\[
P_B = \frac{-Eh^3(n^2 - 1)}{12r^3(1 - v^2)}
\]

where P_B is the transmural pressure at which the tube wall commences to buckle (i.e., begins to collapse), E is the Young’s modulus, h is the wall thickness, n is the number of wall folds, r is the initial radius of the tube, and v is Poisson’s ratio (7, 46). It should be noted that the Von Mises critical pressure (Perit) differs from the Perit concept associated with the widely used Starling resistor model of the upper airway (10), i.e., Perit at which the airway closes under dynamic flow conditions.

The principles under which wall folds influence tube function have been extensively applied to the mechanics of bronchial airway narrowing in asthmatic subjects (48). Recently, our laboratory demonstrated prevention of flow limitation in a bench model of the pharyngeal airway when tube wall folding was trifold rather than bifold (1). In these studies, there was an interaction between applied longitudinal strain and wall fold formation, such that the onset of trifold collapse occurred at a strain level associated with optimal tube function (1). Our laboratory has also previously suggested that, as a consequence of chronic inflammatory changes and remodeling in the pharyngeal mucosal surface (37, 43), fold numbers may be reduced in OSA patients via a process similar to the effects of remodeling in the lower airways of asthmatic subjects (14, 35, 36, 48). However, an alternative hypothesis is that nonuniform, patchy, chronic inflammatory changes and edema, combined with repetitive collapse events over many years, may increase fold numbers. Since no previous studies have examined pharyngeal wall fold anatomy in humans, either with or without OSA, it is not known which of these two alternatives applies. However, as subjects with OSA have an increase in pharyngeal collapsibility (9), we hypothesized that subjects with OSA would have a reduction in upper airway mucosal wall folds.

The primary aim of the present study was to develop a method of detecting and quantifying pharyngeal mucosal folds in human...
respiratory disturbance index

METHODS

complete. Partially separated, or decrease if surface separation is more

apposed surfaces (and therefore not detectable as folds) are only

tion, baseline fold numbers might increase if previously tightly

Lowering the surface tension of the upper airway lining liquid may alter fold numbers

this part of our study, we reasoned that lowering the surface tension of the upper airway lining liquid may alter fold numbers by reducing surface forces acting between already apposed (folded) mucosal surfaces. Lowering the surface tension of the upper airway lining liquid decreases the collapsibility of the pharynx in anesthetized animals and humans (21, 23, 24, 29) and reduces the severity of sleep-disordered breathing in OSA patients (25). However, depending on the effectiveness of this intervention, baseline fold numbers might increase if previously tightly apposed surfaces (and therefore not detectable as folds) are only partially separated, or decrease if surface separation is more complete.

METHODS

Subjects

We recruited 10 healthy subjects (6 men) with either no documented sleep-disordered breathing on laboratory polysomnography (Respiratory Disturbance Index < 5 events/h, n = 6) or a low likelihood of sleep-disordered breathing using the Multivariable Apnea Prediction Index (30) questionnaire (all Multivariable Apnea Prediction Index < 0.5). We also recruited 11 subjects with documented severe OSA (Respiratory Disturbance Index > 30 events/h). Anthropometric data are shown in Table 1. All subjects gave informed consent, and the protocol was approved by the Western Sydney Area Health Services Human Ethics Committee.

Magnetic Resonance Imaging

Subject positioning. Subjects were studied awake, supine, mouth closed, with the head and neck positioned with the naso-meatal line at 90° to the table-top. Earplugs were inserted, and a pneumatic belt was positioned around the lower chest to detect respiratory movement of the chest wall, thus allowing for respiratory gating of the magnetic resonance imaging (MRI) images.

Upper airway image acquisition. MRI studies were performed using a 3.0 Tesla GE Signa HDxt magnet system with an eight-channel HD neurovascular array coil in conjunction with version 15M4 software (GE Medical Systems, Milwaukee, WI). A three-plane localizer was performed, followed by three to four sets of respiratory-triggered (end-expiratory) axial T2-weighted fast spin echo images, covering the anatomy from nasal choanae to larynx. The following sequence parameters were used: 2-mm slice thickness, 0-mm interslice gap, 230-mm field of view with a 512 x 384 matrix, culminating in a pixel size of 0.27 mm². Repetition times varied according to individual pulse rates and were typically in the range of 3,500–6,500 ms. The selected echo time was 85 ms, echo train length = 18, number of excitations = 4, and bandwidth = 31.25 kHz.

Upper airway image processing. From the axial magnetic resonance (MR) images, the upper airway lumen was segmented from the level of the nasal choanae to the tip of the epiglottis (Fig. 1, Amira version 5.2; Visage Imaging). Luminal contours for each slice were extracted using Hounsfield numbers for air. These were then exported into an analysis package and smoothed (Rhinoceros version 4; Robert McNeil and Associates).

Upper airway image geometry analysis. Cross-sectional area, circumference, anteroposterior and lateral diameters, and shape index (anteroposterior/lateral) were measured for each of the luminal contours for each slice of the airway.

Upper airway fold analysis. To analyze upper airway folds, data were exported from the analysis program into MATLAB (version R2011b), and the presence or absence of folds was determined using a custom-written MATLAB script. This program calculated curvature (1/R) at 0.1-mm intervals around the luminal contours. Curvature is defined as the inverse of the radius of the circle that most tightly approaches the curve at a point. Folds that were defined as convex to the lumen were quantified using a two-part criteria consisting of the following: 1) minimum curvature threshold; and 2) minimum angular change in the curve tangent (see Figs. 2 and 3). A neural network was initialized with these two parameters set to 40 mm⁻¹ (curvature threshold) and 45° (minimal angular change), respectively, and then further trained by the same user (KK) to recognize those features deemed to classify as a fold (see Fig. 2). A fold was classified if there was a clear deviation from baseline curvature that could be detected visually and that returned to baseline curvature within 5% of the total luminal circumference. Using these criteria, the neural network was initially trained to recognize folds using four different upper airway images (two healthy subjects and two subjects with OSA) and then applied across the data set.

Validation of folding measurement. To validate the reproducibility of our folding metric, we performed the following studies:

1) Phantom images: Two Perspex phantoms immersed in water were imaged, segmented, and analyzed for folds as described.

2) Repeated analysis: Software analysis for folds was performed twice on the same data.

3) Repeated imaging: Five healthy subjects had gated MR images of the velopharynx performed 1 wk apart. The images were segmented, and fold numbers were analyzed as described above.

Fig. 1. Axial magnetic resonance (MR) images at the level of the velopharynx (VP) from a healthy 35-yr-old man (A) and a 47-yr-old man with obstructive sleep apnea (OSA; B). The white lines represent the upper airway luminal contours at each level.
Experimental Protocol

Upper airway images were acquired as described above. After the initial baseline image was acquired, 2.5 ml of a commercially available surface tension-lowering agent (beractant, Abbott, Australia) was administered onto the pharyngeal mucosa surface via a spray into the mouth, and further images obtained.

Surface tension measurements. A small sample of the upper airway lining liquid was obtained from the posterior pharyngeal wall at the beginning and end of each of the upper airway imaging acquisitions using a 2-ml syringe and a fine-bore polyethylene tube, as previously described (23, 24). The surface tension of the upper airway lining liquid was analyzed using the “pull off” force technique, as previously described (22).

Power Calculation

A post hoc power calculation was performed. A sample size of 11 in each group provides 80% power to detect, with a probability of at least 0.85, that the velopharyngeal mucosal fold number measured in a randomly selected OSA subject is significantly less than that observed in a randomly selected healthy subject.
Table 1. Anthropometric data from healthy and OSA subjects

<table>
<thead>
<tr>
<th></th>
<th>Healthy Subjects</th>
<th>OSA Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Men, n</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Age, yr</td>
<td>33.7 ± 8.6</td>
<td>50.6 ± 10.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.2 ± 3.1</td>
<td>32.9 ± 6.7</td>
</tr>
<tr>
<td>Neck circumference, cm</td>
<td>37.4 ± 4.4</td>
<td>41.6 ± 2.9</td>
</tr>
<tr>
<td>Respiratory disturbance index, events/h</td>
<td>1.7 ± 1.4 (n = 6)</td>
<td>48.7 ± 16.5</td>
</tr>
<tr>
<td>Apnea hypopnea index, events/h</td>
<td>1.7 ± 1.4 (n = 4)</td>
<td>35.1 ± 15.1</td>
</tr>
<tr>
<td>Oxygen desaturation index, events/h</td>
<td>1.7 ± 1.4 (n = 4)</td>
<td>14.1 ± 11.2</td>
</tr>
<tr>
<td>MAP</td>
<td>0.2 ± 0.2 (n = 6)</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of subjects. Note that polysomnography data were available from only 4 of the healthy subjects. The remaining subjects had a low likelihood of obstructive sleep apnea (OSA) multivariable apnea prediction index (MAP) < 1.

Data Analysis

From the upper airway axial MRI images, the velopharyngeal airway (nasal choanae to base of uvula) and oropharyngeal airway (base of uvula to tip of the epiglottis) were defined. For each condition and subject, for each slice, fold numbers, together with upper airway geometry metrics, were separately averaged for the velopharyngeal and oropharyngeal airway. Data were expressed as group mean values and compared using an unpaired t-test. Correlations were examined with Spearman’s correlation coefficient. P < 0.05 was considered significant.

RESULTS

Anthropometric Data

The OSA subject group was predominantly male, older, and more obese with a larger neck circumference than the healthy subject group (Table 1).

Pharyngeal Lumen Geometry

Compared with the healthy group, OSA subjects had smaller velopharyngeal cross-sectional areas, circumferences, and lateral diameters, with a more circular lumen shape (all P < 0.05; Table 2). There were no significant differences between the two groups for oropharyngeal cross-sectional area or circumference; however, the OSA group had smaller lateral diameters and a more circular lumen shape (both P < 0.05; Table 2).

Folding Validation

Phantom images. Two measurable folds were detected for the crescent shape (circumference = 64.2 mm; cross-sectional area = 185.5 mm²; average peak curvature for each identified fold = 59.7 mm⁻¹), while no folds were detected for the cylindrical shape (circumference = 58.1 mm; cross-sectional area = 264.0 mm²).

Repeated analysis. In five subjects (2 healthy, 3 OSA), repeated fold analysis in the same dataset resulted in identical results, with the same number of folds detected in the same place in every image (mean fold numbers run 1: 5.9 ± 2.8; run 2: 5.9 ± 2.8; means ± SD, P > 0.99, paired t-test).

Repeated imaging and analysis. The mean difference between velopharyngeal folds measured 1 wk apart in a group of five subjects was 0.13 ± 0.3. In week 1 for the group, fold numbers were 3.0 ± 0.9, and in week 2 fold numbers were 3.1 ± 0.7. There was no significant difference between fold numbers measured at the two time points (paired t-test, P = 0.4).

Fold Numbers

The average number of velopharyngeal mucosal folds was significantly less for the OSA (3.1 ± 1.8) vs. healthy subject groups (4.9 ± 1.6; P < 0.03; Fig. 4), whereas the number of oropharyngeal folds did not differ between the groups (6.3 ± 2.7 vs. 6.9 ± 3.0, P > 0.05).

Correlational Analyses

For both groups, average velopharyngeal fold numbers correlated with average lateral velopharyngeal diameter [r = 0.83, P < 0.005 (healthy); r = 0.6, P < 0.05 (OSA); Fig. 5].

Effects of Reduced Surface Tension

In the OSA group, technically acceptable images were obtained for only eight subjects after administration of beractant. Administration of beractant lowered surface tension of the upper airway lining liquid from 61.5 ± 1.5 to 55.7 ± 1.2 mN/m in OSA subjects and from 61.25 ± 1.0 to 54.7 ± 1.5 mN/m in healthy subject (both P < 0.0001 compared with baseline).

There was no significant effect of lowering the surface tension of the upper airway lining liquid on pharyngeal airway geometry in either group (P > 0.05, all comparisons). In the healthy group, fold numbers in both the velopharynx and oropharynx were also unaffected by surfactant administration (Fig. 6). However, in the OSA group, surfactant administration resulted in a significant fall in oropharyngeal fold numbers from 6.8 ± 3.1 to 4.7 ± 1.2 (Fig. 6D, P < 0.05). Fold numbers also tended to fall in the velopharynx from 3.3 ± 1.9 to 2.3 ± 1.2; however, this change failed to reach significance (P = 0.08).

Correlational Analyses

In OSA subjects, there was a significant correlation between change in upper airway lining liquid surface tension and change in velopharyngeal folds (r = 0.86, P < 0.01). In the

Table 2. Velopharyngeal and oropharyngeal data for the healthy and OSA subject groups

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>OSA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Velopharynx</td>
<td>Oropharynx</td>
</tr>
<tr>
<td>Cross-sectional area, mm²</td>
<td>98.3 ± 32.5</td>
<td>160.0 ± 64.4</td>
</tr>
<tr>
<td>Circumference, mm</td>
<td>46.5 ± 8.1</td>
<td>60.0 ± 16.6</td>
</tr>
<tr>
<td>AP diameter, mm</td>
<td>6.2 ± 1.7</td>
<td>9.9 ± 2.9</td>
</tr>
<tr>
<td>Lat diameter, mm</td>
<td>17.0 ± 3.6</td>
<td>19.0 ± 4.1</td>
</tr>
<tr>
<td>Shape index (AP/Lat)</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>Velopharynx</td>
<td>Oropharynx</td>
</tr>
<tr>
<td></td>
<td>52.3 ± 23.6*</td>
<td>114.7 ± 46.6</td>
</tr>
<tr>
<td></td>
<td>30.8 ± 6.1*</td>
<td>50.8 ± 11.2</td>
</tr>
<tr>
<td></td>
<td>6.6 ± 2.7</td>
<td>10.5 ± 4.7</td>
</tr>
<tr>
<td></td>
<td>8.7 ± 3.0*</td>
<td>12.2 ± 1.9*</td>
</tr>
<tr>
<td></td>
<td>0.9 ± 0.5*</td>
<td>1.1 ± 0.7*</td>
</tr>
</tbody>
</table>

Values are means ± SD. AP, anteroposterior; Lat, lateral. *P < 0.05 compared with corresponding data for healthy group.
healthy subjects, there was a significant correlation between the change in surface tension and the change in oropharyngeal folds ($r = 0.68, P < 0.04$).

**DISCUSSION**

We have developed and applied a new methodology for determining the number of folds present in the upper airway mucosal surface of healthy subjects and OSA patients. Our data suggest that, at baseline, OSA patients have significantly less total velopharyngeal folds than healthy subjects. When the surface tension of the upper airway lining liquid was reduced, fold numbers fell only in OSA patients, particularly in the oropharynx, suggesting that reduction of surface tension unfolds the mucosal surface, and that surface forces play a role in mucosal apposition.

However, since velopharyngeal cross-sectional area was significantly smaller in OSA patients, the overall effect of fold numbers on the collapsibility of the upper airway, as expressed by the transmural pressure associated with the onset of tube wall buckling, will depend on the offsetting interactions between fold numbers and initial tube lumen radius (see above Eq. 1) (1). Reduced fold numbers for OSA patients promote increased buckling pressure (von Mises Pcrit less negative); however, opposing this, a smaller lumen radius promotes decreased buckling pressure (more negative von Mises Pcrit).

**Critique of Methods**

For the purposes of this study, a fold was defined on the basis of curvature and angular threshold, as described in Fig. 2. In addition, our methodology included the development of a neural network, thus allowing an operator to further refine the fold definition, and then to apply this neural network uniformly to the experimental data. Clearly our definition is arbitrary. However, we could find no workable existing definition in the literature and faced several difficulties in developing a mucosal fold definition and detection algorithm. In the geological literature, a topographical fold is defined in terms of curvature, with a fold defined by measuring a curvature “crest” subtended by two curvature “inflection points” (38), similar to our definition of folds. Very recently, a similar analysis has been used to characterize cortical folding patterns in fetal brains, also based on surface curvature measurements (49).

However, unlike geological formations or the fetal cortex, mucosal folds can exist in several states. If mucosal surfaces are in complete apposition, then it may not be possible, using our methodology, to detect the presence of a fold. Alternatively, if there is only a site for a potential fold, then again we will not be able to detect this until the mucosal surface begins to fold. Our methodology measures the baseline state and may overestimate or underestimate the actual fold number formed during collapse.

However, we have demonstrated that our methodology can measure folds in fixed structures such as a Perspex phantom, and our software measures the same number of folds reproducibly in the same images. In addition to this, we have demonstrated that there is no significant difference in folds measured in the same group of healthy subjects at a weekly interval.

In addition to this evidence of reproducibility, we have demonstrated both a difference in number of folds at baseline between healthy and OSA subjects and, in addition, dynamic behavior in OSA subjects, i.e., unfolding with a reduction in surface tension of the upper airway lining liquid. Consequently, our methodology is capable of detecting differences in fold numbers.

Upper airway MR images were acquired to measure mucosal fold numbers. These images were gated to end expiration, as this represents the baseline state before the onset of negative (collapsing) intraluminal pressures during inspiration (32, 33, 39, 47). Surface tension was lowered via administration of an oral spray, and changes were small compared with those reported previously in anesthetized and sleeping human subjects (24, 26). In addition, surface tension changes were only

---

**Fig. 4.** Average fold numbers for the VP (A) and oropharynx (OP; B) in healthy subjects (●) and subjects with OSA (○). Individual subjects are represented by individual data points; lines are means ± SD. *$P < 0.05$. Note that, for the group, there were significantly less folds in the VP of subjects with OSA.

**Fig. 5.** Relationship between average fold number measured in the VP and the average lateral velopharyngeal diameter for healthy subjects (●) and subjects with OSA (○). For each group, there were significant correlations between velopharyngeal fold number and lateral diameter ($r = 0.83, P < 0.005$, healthy; $r = 0.6, P < 0.05$, OSA). Individual subjects are represented by individual symbols.
measured in the oropharynx and may not be reflective of those in the velopharynx. These smaller reductions may be a consequence of using a different surface tension-lowering agent (24, 26), but more likely because subjects were awake and swallowing, and thus the applied surfactant was quickly dissipated. In addition, oral administration, rather than via the nasopharynx, as in previous studies (24, 26), may have resulted in delivery of less surfactant to the velopharynx, which may explain why the changes following reduction of surface tension occurred in the oropharynx rather than the velopharynx.

Subjects were studied awake, and the findings may not be representative of those found during sleep. Nevertheless, we have demonstrated a significant difference in anatomy between subjects with OSA and healthy subjects, as have a number of other investigators (4, 5, 34, 41). Subjects were not matched for age and body mass index. Both obesity and age may themselves result in a reduction in pharyngeal fold numbers; however, this study was not designed to examine this hypothesis but only whether there is a difference between healthy and OSA subject. In particular, age has been shown to result in changes in the epithelial surface (37) that may, in turn, influence fold numbers. We acknowledge that the lack of matching is a limitation, and other factors may have influenced fold numbers and explain the observed differences between healthy and OSA subjects.

Significance of Findings: Static Pharyngeal Mechanics

The passive pharyngeal mechanics of subjects with OSA and healthy subjects have been studied under paralyzed conditions (13). These studies have shown that, in the absence of muscle activity, maximal velopharyngeal cross-sectional area for OSA subjects is significantly less than for healthy subjects, and, furthermore, that the OSA airway closes at a greater transmural pressure (13). These workers also demonstrated that pressure-area relationships of the passive pharynx are curvilinear, with a steeper slope in subjects with sleep-disordered breathing (13). Overall, these findings support the concept that static pharyngeal mechanics can be understood using “tube law” (12). One of the properties of tubes is that, during the process of closing, the wall will buckle or develop folds (1, 3, 48).

The influence of wall folds on the collapsibility of a thin-walled floppy tube is quantified as the critical Pₐ and is described in the above Eq. 1. Inspection of this relationship reveals that, for a tube of constant wall thickness, Young’s modulus, and Poisson’s ratio, the von Mises Pcrit value depends on the relationship between fold number and lumen radius:

\[ P_{\text{crit}} = -K \frac{(n^2 - 1)}{r^3} \]

where \( K \) is a constant:

\[ K = \frac{Eh^3}{12(1-\nu^2)} \]

Our data suggest that, at least in the velopharynx, fold numbers are reduced in OSA patients, thus increasing the \( P_{\text{B}} \) (less negative). However, as the equation above reveals, cross-sectional area, or radius, of the airway will increase the \( P_{\text{B}} \) value.

To explore the impact of these competing factors on the onset of upper airway collapse in OSA patients vs. healthy subjects, we modeled our data using the following assumptions for both OSA and healthy subjects: Young’s modulus (\( E \)), as measured for the tongue, is 0.008 N/mm² (6); Poisson’s ratio (\( \nu \)), for soft biological tissue, is 0.5 (8); wall thickness (\( h \)) is 1 mm; and lumen shape is circular. The assumed wall thickness value of 1 mm was made since it resulted in buckling pressure estimates that fitted with published data arising from pharyngeal tube law analyses of the upper airway in healthy and OSA subjects (12, 13). The major limitation of this application is that tube law describes the behavior of thin-walled tubes, and different assumptions are required for thick-walled tubes (27). In addition, we assume that baseline fold numbers measured

---

**Fig. 6.** Folds before and after administration of surface tension-lowering agent (beractant) in the healthy (\( A \) and \( C \)) and OSA (\( B \) and \( D \)) subjects in the VP (\( A \) and \( B \)) and OP (\( C \) and \( D \)). Individual subjects are represented by individual points; bars represent group mean. *\( P < 0.05 \). Note that there was a significant fall in folds in the OP of OSA subjects when the surface tension was lowered. The fall in velopharyngeal folds approached significance in OSA subjects (\( P = 0.08 \)).
are the fold numbers that will form during collapse, and again 
this may not be a correct assumption.

Using these parameter values in the Von Mises Perit equa-
tion, we developed iso-fold number plots for Von Mises Perit 
vs. lumen radius (Fig. 7). We then plotted the average values 
from our data for fold numbers and lumen radius for both the 
velopharynx and oropharynx in healthy subjects and OSA 
groups.

From inspection of Fig. 7, it is clear that, for circular tubes 
with a radius of <6 mm, assuming that all else is unchanged, 
the number of folds formed in the tube will significantly 
influence the transmural pressure required to buckle the tube 
wall, and that this influence is even greater at smaller radii, as 
is present with the subjects with OSA. We speculate some of 
the demonstrated heterogeneity in pressure-area relationships 
demonstrated by Isono et al. (13) may be a consequence of 
variations in the fold numbers formed during pharyngeal col-
apse.

From Fig. 7, it is also apparent that the predicted average 
buckling pressures are not different in healthy and OSA sub-
jects at baseline, as each X mark falls at similar transmural 
pressure values. Given that the radii of both the velopharynx 
and oropharynx of OSA subjects are less than those of healthy 
subjects, it would be expected that the estimated buckling 
pressure would be more negative and the airway less collaps-
able. However, due to the reduced fold numbers in the OSA 
subjects, the estimated buckling pressure is very similar to that 
of healthy subjects, despite the smaller cross-sectional area.

Surface Tension Effects on Fold Numbers

At baseline, the cross-sectional areas of both the velopha-
ryn and the oropharynx of OSA subjects were significantly 
smaller, with a smaller circumference, as has been previously 
shown (41, 47). Possible explanations for these differences in 
baseline dimensions are that the airways of subjects with OSA 
are inherently smaller, or alternatively, that the mucosal sur-
faces are apposed (i.e., folded). An already partially collapsed 
opharynx in subject with OSA at baseline may explain why 
we were unable to demonstrate a difference in fold numbers 
from healthy subjects. Previous investigators have demon-
strated that application of positive intraluminal pressures via 
nasal mask results in an increase in upper airway size (11, 28, 
40). The processes by which this increase in upper airway size 
occurs have been considered as “thinning” of the lateral pha-
ryngeal walls (40). However, an alternate hypothesis is that the 
upper airway mucosal surface is folded at baseline. Reduction 
in the surface tension of the upper airway lining liquid resulted 
in a reduction in numbers of folds in OSA subjects, but did not 
significantly change the numbers of folds in healthy subjects.

In OSA subjects, surface tension falls correlated with changes 
in velopharyngeal folds. This supports the concept that the 
mucosal surfaces of pharyngeal wall folds are apposed in 
subjects with OSA, i.e., at baseline there are folds in the upper 
airway mucosal wall. This suggests that subjects with OSA 
may have already exceeded buckling pressure (Von Mises Perit), as the mucosa was already folded.

There were moderate correlations between lateral velopha-
ryngeal wall diameter and number of folds in the velopharynx 
for both groups. Previously, MR studies of the upper airway 
wall have shown that the pharynx of subjects with OSA is 
narrowed in the lateral direction, with an increase in thickness 
and volume of the lateral pharyngeal walls (41). It has also 
been demonstrated that the lateral walls become thinner with 
the application of positive airway pressure (40) and become 
thicker with sleep onset (45). We now propose the hypothesis 
that this previously described lateral pharyngeal wall volume 
reduction in lateral diameter may be a consequence of 
folding and mucosal apposition, particularly in the lateral 
walls.

Conclusion

In conclusion, we have developed a methodology for mea-
suring folds in the pharyngeal wall. We have demonstrated 
that, in awake subjects at atmospheric pressure, there are fewer 
folds in the pharyngeal mucosal surface of OSA subjects, 
particularly in the velopharynx, compared with healthy sub-
jects. Moreover, reduction in the surface tension of the upper 
airway lining liquid results in a reduction in folds in OSA 
subjects compared with healthy subjects, suggesting that there 
is mucosal apposition present at baseline in OSA subjects, and
that the pharynx of subjects with OSA are folded at atmospheric pressure. We speculate that a reduction in upper airway folding during upper airway collapse may contribute to the collapsibility of the pharynx. These original findings describe a new anatomical variation in OSA subjects that may increase pharyngeal wall collapsibility and hence contribute to the pathogenesis of OSA.

ACKNOWLEDGMENTS

The authors thank Josh Martin for assistance with folding analysis, and Sharon Lee for assistance with ethics.

GRANT SUPPORT

K. Kairaitis is supported by National Health and Medical Research Council of Australia (NHMRC) Health Professional Fellowship 1013234, and J. R. Wheatley by NHMRC Clinical Practitioner Fellowship 632910. This study was also supported by NHMRC Grant Project 402654.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


