Effect of surface tension of mucosal lining liquid on upper airway mechanics in anesthetized humans

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Effect of surface tension of mucosal lining liquid on upper airway mechanics in anesthetized humans. J Appl Physiol 95: 357–363, 2003. First published March 7, 2003; 10.1152/japplphysiol.01198.2002.—Upper airway (UA) patency may be influenced by surface tension (γ) operating within the (UAL). We examined the role of γ of UAL in the maintenance of UA patency in eight isoflurane-anesthetized supine human subjects breathing via a nasal mask connected to a pneumotachograph attached to a pressure delivery system. We evaluated 1) mask pressure at which the UA closed (Pc), 2) UA resistance upstream from the site of UA collapse (RUS), and 3) mask pressure at which the UA reopened (Po). A multiple pressure-transducer catheter was used to identify the site of airway closure (velopharyngeal in all subjects). UAL samples (0.2 ml) were collected, and the γ of UAL was determined by using the “pull-off force” technique. Studies were performed before and after the intralaryngeal instillation of 5 ml of exogenous surfactant (Exosurf, Glaxo Smith Kline). The γ of UAL decreased from 61.9 ± 4.1 (control) to 50.3 ± 5.0 mN/m (surfactant; P < 0.02). Changes in Po, RUS, and Pc – Po (change = control – surfactant) were positively correlated with changes in γ (r² > 0.6; P < 0.02) but not with changes in Perit (r² = 0.4; P > 0.8). In addition, mean peak inspiratory airflow (no flow limitation) significantly increased (P < 0.04) from 0.31 ± 0.06 (control) to 0.36 ± 0.06 l/s (surfactant). These findings suggest that γ of UAL exerts a force on the UA wall that hinders airway opening. Instillation of exogenous surfactant into the UA decreases both pharyngeal airflow resistance and the rate of occurrence of apneas and hypopneas during sleep. Although these studies give some insight into the mechanisms of UA collapse, none provide any direct measurement of UA surface forces. Consequently, the precise nature of these surface forces, the magnitude of their contribution to airway collapse and reopening, and their potential for therapeutic modification remain undefined.

Recently, our laboratory (13) demonstrated in anesthetized rabbits that there was a significant positive relationship between the surface tension (γ) of the UAL and UA closing and opening pressures, but there are no comparable data in humans. However, Eastwood et al. (7, 8) have also recently shown that state-related inhibition of motoneuron activity during general anesthesia in humans allows UA mechanics to be studied in the absence of UA muscle activity. This approach allows assessment of UA collapsibility without the confounding influence of reflex neurogenic activity. In the present study, we utilize this anesthetized human model to examine the effect of modifying γ of UAL on the mechanical properties of the UA in adult human subjects.

METHODS

Subject selection. Eight participants (2 men, 6 women; see Table 1 for anthropometric data) were selected from patients...
undergoing general anesthesia for minor surgery not involving the head or neck. There was no a priori determination of the propensity for subjects to have sleep-disordered breathing or respiratory disease. The study was approved by the Sir Charles Gairdner Hospital Ethics Committee, and informed consent was obtained from each participant.

Subject preparation. The methodology used in the present study is based on the approach described by Eastwood et al. (7). Briefly, anesthesia was induced with intravenous propofol (1.5–2 mg/kg) and maintained during surgery with isoflurane and nitrous oxide in oxygen, which were administered via a laryngeal mask. A four-sensor pressure transducer catheter (Gaeltec CTO-4; Dunvegan, Isle of Skye, Scotland) was passed via the nares into the UA and esophagus to simultaneously measure esophageal (Pes), hypopharyngeal, oropharyngeal, and nasopharyngeal pressures. A catheter (outer diameter 2 mm; inner diameter 1 mm) was attached to a 1-ml syringe and advanced via the nares into the posterior pharyngeal lumen. Samples were taken from the mucosal lining liquid in the UA at the site of UA collapse (see Data analysis below).

Measurement of airway closure. The collapsibility of the UA was assessed by measuring the Pmask associated with the cessation of respiratory airflow (Pcrit), as described by Smith et al. (22). Intermittently, Pmask was rapidly decreased from a maintenance level (Fig. 1) that was sufficient to prevent inspiratory airflow limitation. Inspiratory airflow limitation was identified by the presence of an inspiratory flow plateau associated with continuing fluctuations in Pes. This lower Pmask level was determined by the appearance of inspiratory airflow limitation and maintained for five successive breaths before being returned to the maintenance level. This procedure was repeated (3–5 runs) to obtain a range of Pmask and peak inspiratory airflow (Vimax) values during airflow limitation (Fig. 2). For the runs where there was airflow limitation, only breaths 3, 4, and 5 of the five successive breaths were used for further analysis (7) (see also Data analysis). As previously described by Smith et al. (22), Pcrit was calculated from the relationship between Pmask and Vimax as the Pmask at which Vimax became zero.

Subject anthropometric data

<table>
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<th>Subject No.</th>
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<th>Weight, kg</th>
<th>BMI, kg/m²</th>
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<td>8</td>
<td>50</td>
<td>F</td>
<td>165</td>
<td>89</td>
<td>32</td>
</tr>
</tbody>
</table>

| Mean ± SE  | 45.2 ± 2.0 | 167 ± 5 | 88 ± 7 | 31 ± 2 |

BMI, body mass index; F, female; M, male.

This lower Pmask level was determined by the appearance of inspiratory airflow limitation and maintained for five successive breaths before being returned to the maintenance level. This procedure was repeated (3–5 runs) to obtain a range of Pmask and peak inspiratory airflow (Vimax) values during airflow limitation (Fig. 2). For the runs where there was airflow limitation, only breaths 3, 4, and 5 of the five successive breaths were used for further analysis (7) (see also Data analysis). As previously described by Smith et al. (22), Pcrit was calculated from the relationship between Pmask and Vimax as the Pmask at which Vimax became zero.
Measurement of airway reopening. Airway opening pressure (Po) was measured by decreasing Pmask to 1 cmH₂O below Pcrit for two inspiratory efforts (monitored by Pes) before Pmask was increased for the third inspiratory effort. Pmask was then returned to the maintenance pressure immediately after the third inspiratory effort. This cycle was repeated with the pressure level for the third inspiratory effort being incremented by 0.5 cmH₂O for each successive cycle until a Pmask was reached where respiratory airflow was reestablished (Fig. 3). Po was taken as the average third-breath Pmask for the last two cycles in the series.

Genioglossus muscle activity. At the conclusion of the data-gathering phase of the study, a square-wave negative pressure of −30 cmH₂O was applied to the airway for a single inspiratory effort to determine whether a reflex response could be obtained from the genioglossus muscles (i.e., an increase in EMGgg).

Measurements of γ. Measurements of γ were made by using the “pull-off force” technique described by Kirkness et al. (12). In this method, the force required to separate two silica surfaces bridged by the test liquid sample is used to measure the γ of the sample. This method permits measurements of γ to be performed with sample volumes as small as ~0.2 μl.

Exogenous surfactant. The γ of UAL was altered by instilling an exogenous surfactant into the UA. Five milliliters of Exosurf Neonatal (Exosurf Neonatal, Glaxo Smith Kline, Greenville, NC) was instilled via a polyethylene catheter (outer diameter = 2 mm; inner diameter = 1 mm) advanced through the nares to the posterior pharynx. Exosurf Neona-
tal is stored as a sterile white lyophilized powder in vacuum vials. Each vial contains 108 mg of colfosceril palmitate formulated with 12 mg of cetyl alcohol, 8 mg of tyloxapol, and 47 mg of sodium chloride. When reconstituted with 8 ml of sterile water, Exosurf neonatal suspension contains 13.5 mg/ml colfosceril palmitate, 1.5 mg/ml cetyl alcohol, and 1 mg/ml tyloxapol in 0.1 M NaCl, and it has an osmolality of 185 mosm/kg H2O. The γ of Exosurf Neonatal has been reported to be between 38 and 44 mN/m (1, 20).

Protocol. With the subject instrumented and PETiso maintained at 0.8%, a maintenance Pmask (6–17 cmH2O) was applied at a level sufficient to ensure no inspiratory airflow limitation. Once a stable baseline was established, a measurement of Perit was obtained followed by a measurement of Po. UAL samples were then obtained prior to instillation of 5 ml of Exosurf into the nasopharynx. Measurements of Perit, Po, and γ of UAL were then repeated.

After completion of the measurements of UA mechanics, a square-wave negative pressure of −30 cmH2O was applied to the airway. Inspired isoflurane was then discontinued, and the subject recovered from anesthesia while breathing 100% oxygen via the nasal mask at the maintenance CPAP level. Inspired iso

RESULTS

Depth of anesthesia. Control and surfactant data were obtained under similar levels of anesthesia, as determined by the level of PETiso (control: 0.84 ± 0.04%; surfactant: 0.85 ± 0.03%; P = 0.6).

Genioglossus muscle activity. No phasic respiratory-related EMGgg activity was detected in any subject for any condition throughout the study, including during the inspiratory efforts that occurred with the application of −30 cmH2O to the mask. In all subjects, phasic respiratory EMGgg signals were obtained within 5 min of removal of the anesthetic gas. During the recovery period, either swallowing and/or tongue protrusion generated a substantial EMGgg signal in all subjects. γ of UAL. After administration of exogenous surfactant, the γ of UAL decreased in seven of the eight subjects (Fig. 5). For the group, γ of UAL decreased from 61.9 ± 4.1 (control) to 50.3 ± 5.0 mN/m (surfactant; P < 0.02).

UA mechanics. Typical responses to decreasing Pmask during general anesthesia in one subject are shown in Fig. 1. In all subjects, inspiratory flow limitation was apparent when Pmask was reduced sufficiently below the maintenance pressure. On each occasion that Pmask was reduced to a level sufficient to cause inspiratory airflow limitation for five successive breaths, Vi,max progressively decreased over the first two breaths before stabilizing between breaths 3 and 5 (see Fig. 2). This pattern of change of Vi,max was seen in all subjects during all sequences of flow-limited breaths. In each subject, Vi,max was linearly related to Pmask for flow-limited breaths both before and after the administration of surfactant (see Fig. 4; all r² > 0.91; all P < 0.05). Control Perit values for subjects 4–6 were also included in data previously reported by Eastwood et al. (7).

In all subjects, the site of obstruction was located in the velopharynx. Figure 1 demonstrates a typical example where a period of zero flow was accompanied by similar changes in Pes, hypopharyngeal pressure, and oropharyngeal pressure during inspiratory efforts together with failure of these pressure changes to be transmitted to the nasopharynx, thus indicating retropalatal airway obstruction. The site of obstruction was not altered by administration of surfactant in any subject.

In four subjects, Perit decreased with the instillation of surfactant into the UA. Similarly, Po decreased in four subjects, RUS decreased in six subjects, and Po – Perit decreased in six subjects. However, despite these tendencies toward a change with surfactant, there were no significant group mean differences between control and surfactant conditions for Perit (3.3 ± 0.8 vs. 3.0 ± 0.8 cmH2O, respectively; P = 0.3), Po (0.4 ± 1.3 vs. 0.2 ± 1.2 cmH2O; P = 0.5), or RUS (17.4 ± 2.3 vs. 15.3 ± 1.5 cmH2O · l−1 · s; P = 0.3).
Changes in UA mechanics vs. changes in $\gamma$ of UAL. The change in Po (control – surfactant) after the administration of surfactant was strongly and positively correlated ($r = 0.89; P < 0.003$; Fig. 6) with the change in $\gamma$ of UAL. Similarly, the change in RUS also strongly correlated with the change in $\gamma$ (change in RUS: $r = 0.93; P < 0.001$; Fig. 6). However, changes in Pcrit with surfactant were not significantly correlated with the change in $\gamma$ ($r = 0.4; P > 0.9$), although the change in Po – Pcrit was positively correlated with the change in $\gamma$ ($r = 0.8; P < 0.02$).

CPAP related $V_{\text{Imax}}$. Although there was no significant difference ($P = 0.9$) between the mean $V_{\text{Imax}}$ during control (11.2 ± 1.3 cmH2O) and surfactant (11.0 ± 1.2 cmH2O) conditions, mean $V_{\text{Imax}}$ (no airflow limitation) significantly increased ($P < 0.04$) from 0.31 ± 0.06 l/s during control to 0.36 ± 0.06 l/s during surfactant. Such an increase occurred in all but one of the subjects and is consistent with a fall in UA resistance associated with instillation of surfactant into the UA. The magnitudes of the changes in mean $V_{\text{Imax}}$ with surfactant, however, were not significantly correlated with changes in $\gamma$ ($r = 0.3; P > 0.4$).

DISCUSSION

The major findings in this study of anesthetized humans were 1) topical instillation of an exogenous surfactant into the UA decreased the $\gamma$ of the UAL from ~62 to ~50 mN/m; 2) these changes in $\gamma$ were correlated with decreases in Po, Po – Pcrit, and RUS; and 3) the $V_{\text{Imax}}$ achieved at the same level of CPAP increased after the instillation of exogenous surfactant into the UA.

The values for $\gamma$ measured in the present study are the first measurements reported in the literature for UAL in humans. At ~62 mN/m, the $\gamma$ of human UAL is substantially less than that for saline [71.2 mN/m (14)], which reflects the presence of endogenous surfac-
HUMAN UPPER AIRWAY LINING LIQUID SURFACE TENSION

ported by other investigators using different surfac-
to the change in the possibility that effects on UA mechanics were not due

Values for Pcrit obtained in the present study ranged from −4.3 to +7.3 cmH2O under control conditions. These values are similar to those we have obtained previously (8) but are substantially greater than the value of approximately −12 cmH2O that was reported in awake subjects by Van der Touw and colleagues. This difference most likely reflects different levels of neuromuscular activity between the awake and anesthetized state. The wide range of Pcrit values encountered suggests that we were probably dealing with a heterogeneous group in terms of their UA mechanical properties.

Although Pcrit decreased with surfactant in four of eight subjects, this effect did not reach statistical significance for the group, nor was the change in Pcrit significantly correlated with the change in γ of UAL. This result contrasts with our laboratory’s previous finding in rabbits (13), where a range of changes in γ of UAL was achieved by administering both surfactant and saline, which tends to increase γ of UAL. Furthermore, UA closing pressure has been shown to decrease with gargling of exogenous surfactant in awake humans (23). Differences in the delivery and uniformity of distribution of the surfactant within the UA may explain these different findings. Although we studied only eight subjects, they conferred sufficient power (~85%) to detect a difference of ~1 cmH2O. Hence, although we cannot exclude the possibility that instillation of surfactant decreases Pcrit, we believe that any such change is likely to have been small.

Our findings suggest that changing γ of the UAL has less impact on airway closure than airway reopening. Previous studies have consistently demonstrated a difference between UA opening and closing pressure in both animal (5) and human studies (23, 27). As our laboratory has previously demonstrated in rabbits (13), change in Po – Pcrit was positively correlated with change in γ of UAL. Moreover, this relationship explained ~60% of the variance in Po – Pcrit, indicating that γ of UAL has a major influence on the difference between UA closure and reopening pressures.

A further finding in the present study was the relationship between change in RUS and change in γ of UAL. This is consistent with previous findings in dogs (26) and sleeping OSAHS patients (16) and also with the work of Ward et al. (25), who showed that application of a topical lubricant into the UA decreased the CPAP pressure requirement of patients with severe OSAHS. It would appear that the γ of UAL influences UA mechanics not only at the point of closure and reopening but also when the airway is patent. Our finding that airflow increased after surfactant administration, at the same level of CPAP, is supportive of this concept.

The major effect of lowering the γ of UAL in anesthesitized human subjects was to decrease Po. This finding is consistent with that of Van der Touw et al. (23), who found a substantial decrease in Po after instillation of exogenous surfactant into the UA of awake human subjects, and of our laboratory’s previous study in rabbits (13). Pcrit is a measure of UA collapsibility that has been used widely to assess UA mechanical properties in animals (17, 19) and humans (2, 21, 22).
In summary, we have demonstrated that decreasing the γ of UAL in anesthetized humans reduces UA airflow resistance and augments reopening of the collapsed UA. We conclude that, at least in states associated with depression of neuromuscular activity, such as general anesthesia and sleep, forces associated with the UAL act to reduce UA patency. This influence on UA mechanics, however, is modifiable through the instillation of exogenous surfactant into the UA.

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REFERENCES