Relationship between surface tension of upper airway lining liquid and upper airway collapsibility during sleep in obstructive sleep apnea hypopnea syndrome

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Submitted 9 May 2003; accepted in final form 8 July 2003

Kirkness, Jason P., Melanie Madronio, Rosie Stavrinou, John R. Wheatley, and Terence C. Amis. Relationship between surface tension of upper airway lining liquid and upper airway collapsibility during sleep in obstructive sleep apnea hypopnea syndrome. J Appl Physiol 95: 1761–1766, 2003.—Lowering surface tension (γ) of upper airway lining liquid (UAL) reduces upper airway opening (anesthetized humans) and closing (anesthetized rabbits) pressures. We now hypothesize that in sleeping obstructive sleep apnea hypopnea syndrome (OSAHS) patients lowering γ of UAL will enhance upper airway stability and decrease the severity of sleep-disordered breathing. Nine OSAHS patients (respiratory disturbance index [RDI]: 49 ± 8 [SE] events/h, diagnostic night) participated in a two-part, one-night, polysomnography study. In the first part, upper airway closing pressures (during non-rapid eye movement sleep, Pcrit) were measured and samples of UAL (awake) were obtained before and after 2.5 ml of surfactant (Exosurf, Glaxo Smith Kline) was instilled into the posterior pharynx. The γ of UAL was determined with the use of the “pull-off” force technique. In the second part, subjects received a second application of 2.5 ml of surfactant and then slept the remainder of the night (205 ± 30 min). Instillation of surfactant decreased the γ of UAL from 60.9 ± 3.1 mN/m (control) to 45.2 ± 2.5 mN/m (surfactant group) (n = 9, P < 0.001). Pcrit decreased from 1.19 ± 1.41 cmH2O (control) to −0.56 ± 1.15 cmH2O (surfactant group) (n = 7, P < 0.02). Compared with the second half of diagnostic night, surfactant decreased RDI from 51 ± 8 to 35 ± 8 events/h (n = 9, P < 0.03). The fall in RDI (ΔRDI) correlated with the fall in γ of UAL (Δγ) (ΔRDI = 1.8 × Δγ, r = 0.68, P = 0.04). Hypopneas decreased ~50% from 42 ± 8 to 20 ± 5 events/h (n = 9, P < 0.03, paired t-test). The γ of UAL measured the next morning remained low at 49.5 ± 2.7 mN/m (n = 9, P < 0.001, ANOVA, compared with control). In conclusion, instillation of surfactant reduced the γ of UAL in OSAHS patients and decreased Pcrit and the occurrence of hypopneas. Therapeutic manipulation of γ of UAL may be beneficial in reducing the severity of sleep-disordered breathing in OSAHS patients.

Upper airway mechanics

OBSTRUCTIVE SLEEP APNEA HYPOPNEA SYNDROME (OSAHS) is a sleep-related breathing disorder characterized by frequent episodes of upper airway obstruction during sleep. The pathophysiological mechanisms associated with upper airway narrowing, collapse, and reopening during sleep have been extensively investigated over the past two decades. Although the pivotal interactive role of upper airway size and sleep-related decrements in upper airway dilator muscle activity is widely recognized (9, 17), other contributing factors have received less attention. One such factor is the role of surface tension (γ) forces associated with the liquid lining layer that coats the upper airway mucosa [upper airway liquid (UAL)]. The idea that the γ of UAL may play a role in determining upper airway luminal patency is now supported by studies that demonstrate that the topical instillation of an exogenous surfactant into the upper airway decreases the intraluminal pressure required to reopen a closed pharyngeal airway in both awake (26) and anesthetized healthy humans (14). Moreover, in anesthetized rabbits, the extent to which exogenous surfactant lowers both pressure required to reopen a pharyngeal airway and the intraluminal pressure at which the upper airway closes is strongly correlated with the magnitude of the associated change in γ of UAL (13). In addition, there are now published studies demonstrating that instillation of exogenous surfactant into the upper airway of OSAHS patients reduces the severity of their sleep-disordered breathing (10, 18). These latter studies, however, did not assess the change in γ of UAL associated with exogenous surfactant administration and has not established any relationship between γ of UAL and measures of upper airway collapsibility for OSAHS patients during sleep.

Recently, Boudevyns and colleagues (4) developed a standardized protocol for assessment of upper airway collapsibility in sleeping human subjects via measurement of the critical upper airway luminal pressure at which airway closure occurs (Perit). We have now combined this approach with methodology that we have previously developed to measure γ (12) to examine the influence of exogenous surfactant instillation on the γ

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of UAL and upper airway mechanics in sleeping OSAHS patients. Furthermore, using a split-night study design involving the same patients, we have also explored the quantitative relationship between the γ of UAL and the severity of sleep-disordered breathing.

**METHODS**

**Subjects.** We studied nine adult patients (7 men, 2 women; age: 47 ± 16 yr; body-mass index: 32.1 ± 5.3 kg/m²), all of whom were referred to a sleep laboratory with a presumptive diagnosis of OSAHS. Written, informed consent was obtained, and the protocol was approved by the Western Sydney Area Health Service Human Ethics Committee.

**Study design.** Subjects underwent two overnight polysomnography studies. The first (diagnostic night) involved no interventions or test-related sleep disruption and was used to confirm the diagnosis of OSAHS [respiratory disturbance index (RDI) as measured by number of apneas plus hypopneas per hour of > 10 events/h], as well as providing a baseline value for sleep-disordered breathing severity for later comparison with the test night results. On the test night, subjects underwent a split-night study design: aimed at examining 1) the effect of instillation of exogenous surfactant on the γ of UAL and the collapsibility of the upper airway during sleep and 2) the influence of a low γ of UAL on the severity of sleep-disordered breathing.

**Polysomnography.** Polysomnography signals recorded included left and right electrooculogram (EOG), submental electromyogram, electroencephalogram (EEG), arterial oxygen saturation, nasal pressure (Salter Adult Nasal Cannulas, Salter Labs, Arvin, CA), chest and abdominal wall movement (impedance plethysmography), and body position. All monitored parameters were recorded directly on a computer software system (S Series, Compumedics, Melbourne, Australia). Sleep staging, based on the EEG and EOG signals, was performed manually according to Rechtschaffen and Kales (19). Arousals were identified according to American Academy of Sleep Medicine criteria (2) and respiratory events by using the “Chicago” criteria (1).

**Upper airway mucosal lining liquid.** All UAL samples were obtained during periods of wakefulness by advancing polyethylene tubing (internal diameter = 0.5 mm; external diameter = 0.8 mm) attached to a 1-ml syringe (Terumo Medical, Elkerton, MD) via the mouth to the posterior pharyngeal wall and drawing a small quantity (5–10 μl) of UAL into the tubing. The γ of UAL was measured via the “pull-off” technique (12). This approach uses the force required to separate two silica surfaces bridged by a droplet (~0.2 μl) of the test liquid to estimate γ. We have previously described the application of this methodology for the measurement of γ of UAL (14). The γ of UAL was measured before sleep, before the commencement of the study (PM sample group), during the night before (control group), after administration of exogenous surfactant (surfactant group), and in the morning immediately on awakening (AM sample group).

**Exogenous surfactant.** A nasopharyngeal introducing catheter was advanced via the nares until the tip of the catheter reached the posterior wall of the nasopharynx. The oropharynx was then inspected to ensure that the tip of the catheter was above the level of the soft palate, and the catheter was then taped in place. The γ of UAL was altered by instilling an exogenous surfactant into the upper airway (Exosurf neonatal, GSK) via a polyethylene catheter (external diameter = 0.8 mm; internal diameter = 0.5 mm) advanced through the introducing catheter. Two and a half milliliters of exogenous surfactant were instilled through this catheter into the nasopharynx over a 1-min period. The installation catheter was then withdrawn; however, the introducing catheter was maintained in place until the commencement of the second part of the study. The γ of Exosurf neonatal has been reported to be between 38 and 44 mN/m (3, 20) [compared with γ values for human saliva of –53 mN/m (5, 8)].

**Measurement of upper airway collapsibility during sleep.** The collapsibility of the upper airway during sleep was assessed by measuring the intraluminal pressure associated with the cessation of airflow (Perit as described by Boudeyns and coworkers (4) and recently modified by Eastwood and colleagues (7) for application in subjects under general anesthesia. We have also recently used this approach to examine the relationship between the γ of UAL and airflow closure in anesthetized subjects (14).

Briefly, after initial UAL sampling, subjects were fitted with a nasal mask (Mirage, ResMed, North Ryde, Australia) connected to a BiPAP system (BiPAP S/T-D ventilatory support system, Respironics, Murrysville, PA) capable of applying different levels of continuous positive airway pressure (CPAP) or of delivering subatmospheric pressure via connection to a vacuum source. Nasal mask pressure was measured with the use of a pressure transducer (±100 cmH₂O, Celecox, IDM Instruments, Dandenong, Australia). Airflow was monitored with a pneumotachograph (H7400 Accutach, Hamilton, Reno, Nevada) connected to the nasal mask. Subjects were then permitted to fall asleep, and the level of CPAP was adjusted to a value (maintenance level, mask pressure ranged from 8 to 18 cmH₂O) sufficient to eliminate inspiratory airflow limitation (defined as the presence of abdominal and thoracic movements associated with a plateau on the airflow trace), as well as apneas and hypopneas during sleep. All signals were digitally recorded with a sampling frequency of 1,000 Hz on a PowerLab data-acquisition and analysis system (model 16s; ADInstruments, Sydney, Australia) and stored on a Macintosh computer for later analysis.

During stable supine stage II non-rapid eye movement sleep, mask pressure was rapidly decreased from the maintenance level (in ~2 cmH₂O steps) until the appearance of inspiratory airflow limitation and then maintained for five successive breaths before being returned to the maintenance level. This procedure was repeated (3–5 times) to obtain a range of mask pressure and airflow values during airflow limitation. As previously described by Boudeyns and coworkers (4), Perit was then calculated from the relationship between mask pressure and airflow as the mask pressure at which airflow became zero. In addition, the resistance of the upper airway segment upstream of the collapse site (RUS) was calculated as described by Smith et al. (24).

**Protocol.** On the diagnostic night, subjects underwent standard polysomnography as described above. On the test night, all measurements of upper airway collapsibility were performed during the first half of the night (10:00 PM to 2:00 AM; Fig. 1). After an initial measurement of Perit, subjects were woken and a sample of UAL was obtained. After this, 2.5 ml of an exogenous surfactant (Exosurf neonatal, GSK) were instilled into the nasopharynx, and the subjects were allowed to return to sleep. Once stable non-rapid eye movement sleep was reestablished (~10–30 min), the measurement of Perit was repeated. Each subject was then woken again, and a UAL sample was obtained followed by a second administration of 2.5 ml of exogenous surfactant. The nasal mask and in situ nasal catheter were removed, and the subject was allowed to return to sleep without CPAP administration for the remainder of the night (~40–297 min) before being woken for the morning UAL sample.
For the purposes of comparison with the second half of the test night, the second half of the diagnostic night was defined (for each subject) as that period of the diagnostic night study occurring during the same time period (time of night) as was recorded on the test night. Test night studies were performed between 1 and 4 wk after the diagnostic study.

Data analysis. Data are expressed as means ± SE. Single comparisons were made with a paired Student’s t-test. Multiple comparisons were performed with repeated-measures ANOVA. Linear regression analysis was used to examine relationships between the changes in γ of UAL, Perit, and RUS achieved with surfactant (control – AM sample) on the test night and the difference between the second half of night RDI values obtained on the test and diagnostic nights (ΔRDI = test night RDI – diagnostic night RDI). P < 0.05 was considered significant.

RESULTS

γ of UAL. For the group, the γ of UAL was 58.5 ± 1.6 mN/m for the PM sample, unchanged at 60.9 ± 3.1 mN/m for the control sample (P = 0.5, compared with PM sample), significantly reduced at 45.2 ± 2.5 mN/m for the surfactant sample (P < 0.008, compared with PM and control), and remained significantly reduced at 49.5 ± 2.7 mN/m for the AM sample (P = 0.02, compared with PM and control, P = 0.24 compared with surfactant).

Perit and RUS. Perit values decreased from 1.19 ± 1.14 cmH2O during control to −0.56 ± 1.15 cmH2O with surfactant (n = 7, P < 0.02; Fig. 2A). RUS values, however, were not significantly different between the control and surfactant conditions (9.0 ± 0.9 vs. 9.3 ± 1.1 cmH2O·1−1·s, respectively; P > 0.05, Fig. 2B).

Table 1. Sleep study parameters

<table>
<thead>
<tr>
<th>Stage</th>
<th>Diagnostic</th>
<th>Test</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 NREM, %SPT</td>
<td>7.9 ± 1.7</td>
<td>13.6 ± 2.7</td>
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<tr>
<td>Stage 2 NREM, %SPT</td>
<td>65.2 ± 4.7</td>
<td>56.9 ± 4.6</td>
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<tr>
<td>Stage 3 NREM, %SPT</td>
<td>4.7 ± 1.3</td>
<td>5.5 ± 1.8</td>
<td>0.70</td>
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<tr>
<td>Stage 4 NREM, %SPT</td>
<td>4.6 ± 2.1</td>
<td>2.0 ± 1.2</td>
<td>0.25</td>
</tr>
<tr>
<td>REM, %SPT</td>
<td>17.6 ± 3.1</td>
<td>22.0 ± 3.8</td>
<td>0.41</td>
</tr>
<tr>
<td>Minimum SaO2, %</td>
<td>81.6 ± 1.8</td>
<td>82.7 ± 2.1</td>
<td>0.47</td>
</tr>
<tr>
<td>SPT, min</td>
<td>182.4 ± 8.6</td>
<td>205.1 ± 30.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Values are means ± SE. Diagnostic, second half of the diagnostic polysomnographic recording; Test, second half of polysomnographic recording with surfactant administration. Stages 1, 2, 3, and 4 non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep are expressed as percent of the sleep period time (SPT).
night (both $P < 0.04$). No significant relationships ($n = 7, P > 0.2$) were detected between the control values for $P_{\text{crit}}$, RUS or \Delta $P_{\text{crit}}$ and \Delta RUS, and RDI or \Delta RDI.

**DISCUSSION**

The major finding in this study was that instillation of exogenous surfactant into the upper airway of patients with OSAHS resulted in a fall in $\gamma$ of UAL accompanied by decreased upper airway collapsibility and reduced sleep-disordered breathing. Surfactant delivered into the pharyngeal airway resulted in a group mean reduction of $\sim16$ mN/m in the $\gamma$ of UAL. This was associated with a fall in $P_{\text{crit}}$ of $\sim1.8$ cmH$_2$O and group mean RDI values that were $\sim30\%$ lower than those obtained during the previous diagnostic study night (no surfactant).

This is the first study to provide data on the effect of exogenous surfactant on $\gamma$ of UAL in sleeping OSAHS patients and to quantitatively link this effect with a measure of upper airway collapsibility during sleep. We have previously described and evaluated the “pull-off” force technique for the measurement of $\gamma$ (12). Values obtained in the present study for $\gamma$ of UAL of PM and control samples in OSAHS patients are similar to those reported for human saliva (5, 8).

In the present study, administration of surfactant and sampling of UAL were performed during wakefulness. We used this approach, rather than attempting these procedures via in situ catheters during sleep, because preliminary pilot studies demonstrated that instillation of surfactant during sleep triggered a cough reflex resulting in an arousal. Also sampling via the mouth with a separate catheter allowed us to avoid contamination of the UAL sample with exogenous surfactant contained within the administration catheter or pooled at the catheter tip. After administration of exogenous surfactant, $\gamma$ of UAL decreased by $\sim25\%$ compared with control values. This decrease is of the same magnitude as we previously demonstrated (14) in anesthetized humans but with half the volume of surfactant.

We measured upper airway collapsibility during sleep using established methodology (4). Control $P_{\text{crit}}$ values in our subjects varied substantially (range of $-4.9$ to $5.8$ cmH$_2$O). In healthy subjects, $P_{\text{crit}}$ values during sleep are usually subatmospheric (23), whereas reported values in OSAHS patients range from $-0.1$ to $10$ cmH$_2$O (4, 24). In our OSAHS patients, instillation of surfactant into the pharyngeal airway decreased $P_{\text{crit}}$ during sleep such that the postsurfactant group mean value was subatmospheric (approximately $-0.6$ cmH$_2$O).

For determination of $P_{\text{crit}}$, subjects were studied in the supine position. Boudevyns et al. (4) showed that there is a decrease in $P_{\text{crit}}$ when OSAHS patients are positioned in the lateral recumbent position. Therefore, each subject was visually monitored to ensure that both body and head and neck positions remained constant throughout the determination of $P_{\text{crit}}$. We were unable to demonstrate an effect of low $\gamma$ of UAL on RUS. Because RUS is a measure of resistance upstream from the site of collapse, it may be that in OSAHS patients this resistance is structurally determined (e.g., nasal resistance) and so less influenced by $\gamma$ or it may be that surfactant was not delivered to this segment of the airway.

At the beginning of the second half of the night, a second dose of surfactant was instilled, and subjects returned to sleep. After a further $\sim3.5$ h of sleep, the $\gamma$ of the UAL AM sample was still significantly lower than the PM and control sample values obtained the previous evening. Exosurf neonatal (GSK) consists of a mixture of dipalmitoylphosphotidyl choline (a surfactant), colfosceril palmitate (an adhering agent), and the spreading agents cetyl alcohol and tyloxapol. The presence of these adjunctive agents contributes to persistence of the surfactant component at the target site. Indeed, in neonates, aspirates of tracheal liquid show a decreased $\gamma$ up to 12 h after tracheal instillation of Exosurf (16). Reduced saliva production (6) and swallowing frequency (25) during sleep also likely contributed to the persistence of exogenous surfactant in the pharynx.

When the severity of sleep-disordered breathing was assessed during the low $\gamma$ of UAL sleep period and the results were compared with the second half of the prior diagnostic study night (performed 1–4 wk previously), RDI fell in seven of nine patients by $\sim34$–$69\%$. Such falls in RDI occurred in both supine and lateral body positions, and there was no significant group mean differences in sleep architecture between the two nights. However, conclusions should be drawn cautiously from this part of our study since sleep-disordered breathing was assessed only over the second half of the night. Also, data were gathered after instrumentation and sleep disruption associated with the measurements of $P_{\text{crit}}$, and subsequently treatment RDI values were compared with a baseline value from the second half of a previous study night. However, despite these limitations, the group mean reduction in RDI of

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**Fig. 3.** Decrease in respiratory disturbance index (RDI) correlates with a reduction in the $\gamma$ of the UAL. Regression line shows the correlation between $\Delta$RDI ($\Delta = \text{diagnostic night} - \text{surfactant night}$) and $\Delta\gamma$ of UAL for individual patients ($n = 9$). $\Delta$RDI $= 1.8 \times \Delta\gamma$ of UAL ($P = 0.04, r = 0.68$).
RDI between the surfactant and diagnostic nights correlates strongly with the fall in $\gamma$ of UAL achieved with surfactant on the surfactant night. This comparison also assumes that $\gamma$ of UAL control values on the surfactant night are representative of the diagnostic night value.

In contrast, no such relationships were detected between control or change values for measures of upper airway mechanics (Pcrit and RUS) and the RDI values. This may indicate that the effect of surfactant on RDI is mediated via pathways other than Pcrit and RUS. However, because changes in Pcrit achieved via other interventions (e.g., weight loss) have been linked to changes in RDI (22), it would seem more likely that this is a reflection of the small number of subjects studied ($n = 7$) and the small (but significant) changes in Pcrit achieved. In any case, because the part of our study dealing with the effects of $\gamma$ of UAL on RDI is limited by small numbers, as well as variable and lengthy periods between the diagnostic and surfactant nights, potential effects of interventions occurring in the first half of the night, no $\gamma$ of UAL measurements on the diagnostic night, and short sleep periods, a larger more comprehensive study of the effect of changing the $\gamma$ of UAL on RDI appears warranted.

The nature of the disease process in our patient group was such that their sleep-disordered breathing was characterized by a large number of hypopneas. Thus it was a reduction in the number of hypopneas that was primarily responsible for the change in RDI in the study group. Because the upper airway in OSAHS patients is structurally narrow and has increased mucosal folds (15, 21), a low $\gamma$ of UAL may reduce the tendency for further functional narrowing by inhibiting $\gamma$-mediated mucosal fold apposition. Because the major effect on RDI in the present study was a reduction in the number of hypopneas, it appears that lowering the $\gamma$ of UAL may be sufficient to prevent milder degrees of airway narrowing (i.e., hypopneas) but not sufficient to prevent the occurrence of complete closure (i.e., apneas) when large intraluminal negative pressures are generated.

In one of the less severely affected patients in the present study, the RDI on the surfactant night was reduced to levels encountered in healthy subjects (i.e., <10 events/h). This raises the possibility that surfactant administration may be useful as an adjunctive therapy for controlling sleep-disordered breathing in more mildly affected individuals. We conclude that lowering the $\gamma$ of UAL decreases both upper airway collapsibility and the severity of sleep-disordered breathing in OSAHS patients.

DISCLOSURES

This work was supported by the Garnett Passe and Rodney Williams Memorial Foundation, Westmead Millennium Foundation, and National Health and Medical Research Council of Australia.

REFERENCES


