Effect of surface tension and surfactant administration on Eustachian tube mechanics

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Ghadiali, Samir N., Julie Banks, and J. Douglas Swarts. Effect of surface tension and surfactant administration on Eustachian tube mechanics. J Appl Physiol 93: 1007–1014, 2002. First published June 7, 2002; 10.1152/japplphysiol.01123.2001.—Development of otitis media has been related to abnormal Eustachian tube (ET) mechanics. ET is a collapsible tube that is periodically opened to regulate middle ear pressure and to clear middle ear fluid into the nasopharynx. The ability to perform these physiological functions depends on several mechanical properties, including the ET’s opening pressure (P_open), compliance (ETC), and hysteresis (η). In this study, a previously developed modified force-response protocol was used to determine ET mechanical properties after experimental manipulation of the mucosal surface condition. Specifically, these properties were measured in the right ear of six cynomologous monkeys under baseline conditions after “washing out” the normal ET mucous layer and after instillation of a pulmonary surfactant, Infasur. Removal of the normal mucosa did not significantly alter P_open but did result in a decrease in ETC and η (P < 0.05). Treatment of the mucosa with Infasur was effective in reducing P_open and increasing both ETC and η to baseline values (P < 0.05). These results indicate that the mucosa-air surface tension can affect the overall ETC and η properties of the ET. In addition, this study indicates that surfactant therapy may only be beneficial in patients with rigid or inelastic ETs (large P_open and low ETC and η).

Otitis media (OM) is a common childhood disease that includes inflammation of the middle ear (ME) mucosa and an accumulation of fluid within the ME. By age 3, a significant number of children (33%) experience more than three episodes of OM (32). The persistence of OM often results in hearing loss, with possible effects on language acquisition, speech production, and social and educational development (31). The cost of treating persistent OM by medical and surgical procedures approaches $3 billion annually in the US (1). Although antibiotic treatment has proven effective in treating acute OM, the overuse of antibiotics has resulted in an increase in the prevalence of antibiotic resistance pathogens (5). In addition, surgical treatments, which include the placement of ventilating tubes in the tympanic membrane, require general anesthesia and are thus costly and distressing to children and their parents. The development of alternative treatment therapies for OM is, therefore, one of the most important, unresolved clinical problems in otology.

Although bacterial or viral infections and nasal allergies contribute to the onset of OM, the development of persistent OM is associated with a functional impairment of the Eustachian tube (ET) (2). The structure of the ET, which connects the ME with the nasal cavity, is similar to other respiratory airways in that the lumen of the tube is bounded by a fluid layer (the mucosa) and is surrounded by cartilaginous and muscular elements (2). Under normal conditions, the ET exists in a collapsed “closed” configuration that protects the ME from nasopharyngeal secretions. However, the ET is also responsible for maintaining ambient ME pressures and clearing ME fluid into the nasopharynx (2). These pressure-regulating and clearance functions require an open ET in which the resistance to air and fluid flow is minimal. ET dysfunction and the resulting disease complications can, therefore, develop when the tube is excessively patent or cannot be readily opened.

Flisberg et al. (6) were the first to suggest that the presence of surface tension-lowering substances (surfactants) might influence the function of the ET. Although the role of surfactant in ET has not been entirely determined, the presence and importance of these surface active substances in the lung have been well documented (33). The components of pulmonary surfactant, which include surface-active phospholipids and surfactant-associated proteins, are synthesized in the type II epithelial cells that line the alveolar walls (33). The presence of these surfactant components has been shown to influence the function and mechanics of the lung (19). Specifically, phospholipid surfactant molecules adsorb to the mucosal air-liquid interface and reduce the interfacial surface tension. This reduction in surface tension reduces the pressure required to inflate the lung, increases the compliance or flexibility of the lung, and stabilizes the mucosa to prevent air-...
way collapse (3). In addition to these mechanical effects, hydrophilic surfactant proteins have been shown to enhance immunological functions in the lung (20). Premature infants suffering from respiratory distress syndrome (RDS) have not developed a mature surfactant system and must, therefore, be treated with exogenous surfactant to restore lung function. Several different surfactant systems, including a natural calf lung extract (Infasurf, ONY) as well as synthetically modified surfactants, have been developed and used to improve lung function and airway compliance in RDS infants (13).

Several studies have used a variety of biochemical techniques to document the presence of surfactant components in the ME-ET system of both animals and humans (21). Karchev et al. (16) found surfactant-producing cells in the dorsal section of the ET that are morphologically similar to the type II epithelial cells found in the lung. Recently, Paananen et al. (26) measured gene expression for several surfactant proteins in the porcine ET. In addition, Svane-Knudsen et al. (30) demonstrated that the quantity and composition of surfactant components in ontologically healthy children are significantly different than the quantity and composition in children with OM. The presence of a sufficient quantity and quality of ET surfactant may therefore be an important determinant of ET function and mechanics.

**ET mechanics.** The forces required to open the ET and maintain its patency will be a function of several mechanical properties, including the elasticity of the surrounding tissue and the surface tension of the fluid mucosa layer. When collapsed, the ET is generally considered to be a liquid-lined slit-like structure with a noncircular cross-sectional shape (Fig. 1). However, histological studies (28) have also demonstrated that this slit-like structure can be buckled into several nearly circular lobes. Once this structure is opened to airflow, increases in lumen pressure may result in an opening of the slit-like structure and/or an opening of the circular lobes. To account for either situation, we have depicted a generalized cross-sectional shape in Fig. 1 that can be used to represent opening in a slit-like structure when the length-to-width ratio is large or opening in a circular lobe when the length-to-width ratio is 1. In either case, the surface tension of the liquid layer is directed toward collapse of the ET lumen. The force required to increase the lumen area [i.e., the translumenal pressure (∆P)], must therefore overcome both surface tension and tissue elastic forces (9). For a static system, the surface tension forces can be related to the pressure drop across the air-liquid interface by using a LaPlace’s Law relationship, Pf − Pfext = γk, where P is the internal lumen pressure, Pf is the fluid pressure within the mucosa, γ is the air-liquid surface tension, and k is curvature of the mucosa-air interface. The tissue elastic forces can be accounted for with a linear tube-law or pressure-area relationship, Pf − Pfext = EtissueA, where Pfext is the external pressure, Etissue is the elastic modulus of the tissue, and A is the cross-sectional lumen area (9). The translumenal pressure [∆P = P − Pfext = (P − P0) + (Pf − Pfext) = γk + EtissueA] will therefore be a function of interfacial and tissue elastic properties [∆P = f(γ, Etissue)].

Although ∆P is related to the inflation of an opened ET, the initial opening process is considerably more complicated. For example, as the ME pressure is increased, a finger of air will penetrate into the ET, separating its walls. At a critical pressure [i.e., the opening pressure (Popen)], the liquid meniscus contained within the lumen will rupture, and air will pass freely through an open ET. Although the factors that determine this critical level are complicated, the ∆P at the point of opening can be used to approximate Popen = γk + EtissueA’. Here, k’ and A’ are specific values at the instant of opening and can only be determined from a detailed analysis of this opening phenomenon (9). Nonetheless, Popen will be a function of both interfacial and tissue properties (γ, Etissue). In this study, we focus on identifying the importance of interfacial mechanics by introducing surface active agents that reduce γ and should therefore reduce the passive Popen of the ET.

In addition to Popen, the function of the ET has also been associated with other mechanical properties, including ET compliance (ETC) or flexibility (15). ETC is defined in engineering terms as the change in the cross-sectional area of the ET lumen for a given change in pressure (ETC = dA/dP). Rigid or inelastic ETs (low ETC) are difficult to open and thus might impair ventilation and clearance functions. Conversely, ETs with high ETC, often described as “floppy” ETs (2), may have impaired protective functions. This lack of stiffness may also affect the ability of the surrounding musculature to actively open the tube during swallowing. ETC magnitude will be determined by the intrinsic stiffness of the surrounding cartilage and muscular elements and the surface tension forces at the air-liquid interface. Specifically, the applied ∆P must overcome surface tension and tissue elastic forces to produce a given change in A. An increase in γ or Etissue will result in a larger ∆P and, therefore, a more rigid ET (small ETC). Conversely, a reduction in Etissue or a reduction in γ due to the presence of surfactants will result in a smaller ∆P and a more compliant/flexible ET (large ETC). Therefore, ETC will also be a function of both interfacial and tissue elastic properties [ETC = f(γ, Etissue)].
Another mechanical property that may influence ET function, but has not previously been considered, is the ET’s hysteretic nature. Hysteresis occurs when the forces acting on the ET (i.e., pressure) are dissipated such that they do not produce the same deformation (or cross-sectional area) during inflation and deflation. Fredberg and Stamenovic (8) have quantified hysteretic phenomena in lung tissue by using a hysteretic modulus (\(\eta\)). Furthermore, these authors described how surface tension hysteresis at the air-liquid interface caused by the presence of pulmonary surfactants (\(\gamma_n\)) and the viscoelasticity of the surrounding tissue (\(\mu_{\text{tissue}}\)) can both influence global hysteretic phenomena. Therefore, \(\eta\) will also be a function of both interfacial and tissue mechanical properties (\(\eta = f(\gamma_n, \mu_{\text{tissue}})\)).

The goal of the present study is to selectively alter the mucosal surface condition to determine whether interfacial properties can significantly affect global ET mechanical properties. Specifically, we will quantitatively determine how removal of the normal ET mucosal surfactant and the subsequent instillation of a naturally pulmonary surfactant extract (Infasurf) affects P_{\text{open}}, ETC, and \(\eta\). Although a study by Miura et al. (22) attempted to determine the ability of surfactant to modify ETC, that study used a nonphysiological surfactant and was based on a summary parameter that is not consistent with the engineering definition of compliance. In addition, ET \(\eta\) has not been specifically investigated. Therefore, the present study uses a physiological surfactant (Infasurf) and measures ET mechanical properties with a modified forced-response test previously developed by our research group (10). This testing protocol is unique in that ET mechanical properties (ETC and \(\eta\)) are determined by correlating pressure-flow (P-Q) measurements with a mathematical model of flow in a collapsible tube. ETC determined by this protocol is therefore consistent with the engineering definition. An accurate determination of how the mucosa-air surface tension and surfactant administration affect ET mechanics may lead to a better understanding of how surfactant therapy may be used clinically to treat OM patients.

**MATERIALS AND METHODS**

For this study, data were obtained from the right ears of six cynomologous monkeys (Macaca fascicularis, 2–4 kg). The monkey was chosen as the animal model since previous investigators demonstrated that the operational biomechanics of monkey and human ETs are nearly identical (4). All protocols used in this study were approved by the Children’s Hospital of Pittsburgh Animal Research and Care Committee. For each experiment, the monkey was sedated with 30 mg of ketamine and anesthetized with “monkey mix” (10 mg/kg ketamine, 2 mg/kg xylazine, and 0.3 mg/kg acepromazine). The external auditory canal was cleaned, and normal ME status was verified by using tympanometry. Once a myringotomy was performed in the right tympanic membrane, a probe with an integrated flow sensor and micropressure transducer was hermetically sealed in the right external auditory canal. All pressures were measured relative to the ambient atmospheric pressure. As shown in Fig. 2, the probe was connected to a syringe pump that delivered air at specific flow rates. Continuous outputs from the flow and pressure sensors were routed to a microcomputer for visual display in real time data storage and data processing using a HP VEE data acquisition routine (Agilent Technologies) (10).

After each experimental manipulation described below, data were obtained and analyzed in each animal according to the modified forced-response protocol previously developed in our laboratory (10). In this protocol, the syringe pump was used to inflate the ME with ambient air at a flow rate of 5 ml/min until ET was forced open at P_{\text{open}}, as shown in Fig. 3A. After ET was opened, the syringe pump was programmed to produce a sinusoidal flow rate between 5.0 and 23 ml/min with a period of 72 s. The pressure and flow rate were measured simultaneously as a function of time until a steady state, defined as a <5% change in the maximum and minimum pressure between two successive oscillations, was obtained (Fig. 3A). The magnitude of this oscillation cycle is based on steady-state flow rates used in previous investigations (4), whereas the oscillation frequency is small enough to ensure that the test could be conducted in a reasonable amount of time (12). Data for analysis consisted of the pressure and flow rate during the final oscillation period, which was plotted as a P-Q hysteresis loop (see Fig. 3B). This P-Q loop was then correlated with a mathematical model of airflow in a collapsible tube (solid line in Fig. 3B) to obtain ETC and \(\eta\) (12). This correlation technique, which is described in the APPENDIX, is based on a least-square analysis and resulted in correlation coefficients (\(r^2\)) that were consistently >0.95. Note that ETC and \(\eta\) are global parameters and may therefore depend on both interfacial as well as tissue mechanical properties. In general, the average slope of the P-Q loop is inversely related to ETC (i.e., larger slope results in lower ETC), whereas the area enclosed by the loop is directly related to \(\eta\) (i.e., larger area results in larger \(\eta\)). Execution of this protocol, therefore, results in three primary parameters that describe the mechanics of ET (P_{\text{open}}, ETC, and \(\eta\)).

These mechanical parameters were determined by performing this modified forced-response protocol after various experimental manipulations. First, baseline mechanical parameters were determined in freshly perforated ears before any manipulation (Normal conditions). Second, the ME-ET system was rinsed with 37°C isotonic saline at 1 ml/min for 5 min. For this procedure, animals were placed in a prone position, and the ET lumen was washed by injecting saline into the ME via the hermetically sealed probe and collecting the washed fluid at the nasal orifice. Once the ET was rinsed, any residual fluid in the ME was cleared by subsequently introducing airflow at 5 ml/min for 2–3 min. After the normal ET mucosa had been disrupted in this manner, the mechanical parameters were measured via the testing protocol (Sa-
line conditions). Finally, the ET lumen was treated with a calf lung surfactant extract, Infasurf, currently used to treat RDS infants. The surfactant solution was injected into the ME-ET system at 1 ml/min for 2 min, and the residue was collected at the nasal ori

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ce. After this surfactant installation, residual ME fluid was again cleared with air at 5 ml/min for 2–3 min. Mechanical properties of the surfactant-treated ET were then measured with the testing protocol (Surfactant conditions). After these experimental manipulations, the probe was removed, and the external ear canal was cleaned with an alcohol solution to reduce the possibility of infection.

Mechanical parameters ($P_{\text{open}}$, ETC, $\eta$) were determined for six animals under three treatment conditions: normal, saline, and surfactant. A within-subjects ANOVA was performed to document statistically significant differences among all treatment groups, whereas post hoc planned comparisons were used to document statistically significant differences between individual treatment groups. Significance for these tests was set at $P < 0.05$.

**RESULTS**

$P_{\text{open}}$ measured in each animal after a given experimental manipulation is presented in Fig. 4. Mean $P_{\text{open}}$ values measured under each experimental condition are reported in Table 1. These mean $P_{\text{open}}$ values were significantly different ($F = 27.8$, $P < 0.01$). Post hoc between treatment comparisons indicated that mean $P_{\text{open}}$ measured under normal conditions was not significantly different from mean $P_{\text{open}}$ measured after the ET mucosa had been rinsed in saline ($P = 0.80$). Mean $P_{\text{open}}$ measured after surfactant instillation, however, was significantly lower than mean $P_{\text{open}}$ measured under both normal and saline conditions ($P < 0.01$).

$P\cdotQ$ loops measured in a typical subject during each experimental condition are presented in Fig. 5. Only the mathematical correlations are displayed for clarity. The $P\cdotQ$ loop measured after the ET was rinsed with saline had a larger slope and less loop area than the $P\cdotQ$ loop measured under normal conditions. Subsequent administration of surfactant resulted in a slight decrease in the slope of the $P\cdotQ$ loop and an increase in the loop area. These qualitative observations were quantified by analyzing each loop with the mathematical model presented in the APPENDIX and described in detail by Ghadiali et al. (12). This analysis resulted in a quantitative measurement of the ETC and $\eta$ parameters in each animal for a given experimental manipulation. Mean values for these parameters under each experimental condition are reported in Table 1. The variation of ETC between treatment groups is presented in Fig. 6A. Mean ETC values were significantly different ($F = 4.11$, $P < 0.05$). Between-treatment comparisons indicated that mean ETC under saline conditions was significantly lower than mean ETC measured under

![Fig. 3. Typical experimental data obtained during a modified force-response test. A: pressure and flow rate as a function of time. B: pressure-flow hysteresis loop and the mathematical correlation used to obtain ET compliance (ETC) and hysteresis ($\eta$) parameters. $P_{\text{open}}$, opening pressure.](https://example.com/fig3.png)

![Fig. 4. Changes in ET $P_{\text{open}}$ after saline washout of the mucosa and after the application of the pulmonary surfactant (Infasurf).](https://example.com/fig4.png)

**Table 1. Mechanical properties measured under various experimental conditions**

<table>
<thead>
<tr>
<th>Mechanical Property</th>
<th>Normal Conditions</th>
<th>Saline Conditions</th>
<th>Surfactant Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{\text{open}}$, mmH$_2$O</td>
<td>471 ± 72</td>
<td>476 ± 91</td>
<td>356 ± 82</td>
</tr>
<tr>
<td>ETC, $\times 10^{-3}$ cm$^2$/mmH$_2$O</td>
<td>4.12 ± 0.76</td>
<td>2.73 ± 1.00</td>
<td>3.64 ± 1.49</td>
</tr>
<tr>
<td>$\eta$, $\times 10^6$ Poise/cm$^2$</td>
<td>9.72 ± 3.78</td>
<td>3.62 ± 2.92</td>
<td>8.92 ± 1.93</td>
</tr>
</tbody>
</table>

Values are means ± SD. $P_{\text{open}}$, opening pressure; ETC, Eustachian tube compliance; $\eta$, hysteresis.
both normal and surfactant conditions ($P < 0.05$). In addition, ETC measured under surfactant conditions was not significantly different from ETC measured under normal conditions ($P = 0.58$). The variation of $\eta$ between treatment groups is presented in Fig. 6B. Mean $\eta$ values were also significantly different ($F = 8.55$, $P < 0.01$). Between-treatment comparisons indicate that mean $\eta$ measured under saline conditions was significantly lower than mean $\eta$ measured under normal and surfactant conditions ($P < 0.05$). In addition, mean $\eta$ measured under surfactant conditions was not significantly different from mean $\eta$ measured under normal conditions ($P = 0.57$).

DISCUSSION

We measured several ET mechanical properties after flushing the ET mucosa with saline and after the subsequent administration of a natural pulmonary surfactant, Infasurf. These mechanical properties include $P_{\text{open}}$, ETC, and $\eta$. These parameters were measured in six cynomolgous monkeys with the previously developed modified force-response technique. This technique, which is based on an engineering model of airflow in the ET, results in an accurate determination of global ET mechanical properties. Although both interfacial and tissue mechanical properties could affect these global mechanical properties, our goal was to obtain a better understanding of how disruption of the normal mucosal surface condition and treatment of the mucosa with a pulmonary surfactant influences global ET mechanics. Therefore, these experiments were designed to alter interfacial properties without affecting the tissue mechanical properties.

Although washing of the ET mucosa with saline did not result in a significant change in $P_{\text{open}}$, the instillation of Infasurf into the ET resulted in a reduction in $P_{\text{open}}$ consistent with a reduction in the mucosa-air surface tension. To interpret these results, which are consistent with similar measurements obtained in ger-
Although $P_{open}$ may be an important factor, several other mechanical properties, such as ETC and $\eta$, will also be important determinates of ET function. However, the influence of $\gamma$ and surfactant on these properties has not been adequately studied. The current study was therefore designed to provide new information with respect to how surfactants influence ETC and $\eta$. Figure 6A demonstrates that $\gamma$ can significantly affect ETC. Washing the ET lumen with saline, which potentially removes native surfactant and thus increases $\gamma$, resulted in a decrease in ETC and thus a more rigid ET. Note that, although this increase in $\gamma$ is large enough to alter ETC, it is apparently not large enough to alter $P_{open}$ (see Fig. 4). In contrast, application of a pulmonary surfactant to the ET lumen, which decreases $\gamma$, resulted in an increase in ETC to prewash values and thus a more flexible ET. This inverse relationship between $\gamma$ and ETC can be understood by recalling the definition of ETC as the change in cross-sectional area for a given change in $\Delta P$ (ETC = d$A$/d$\Delta P$). As discussed in the introduction, $\Delta P$ will be a function of interfacial and tissue mechanical properties: $\Delta P = \gamma k + E_{tissue}A$. By assuming constant tissue properties (d$E_{tissue}$/d$A = 0$) and negligible surface tension hysteresis (d$\gamma$/d$A = 0$), we can express ETC = $(\gamma k d\gamma/dA + E_{tissue})^{-1}$. Therefore, ETC is inversely related to $\gamma$ when $d\gamma$/d$A > 0$ (see Fig. 1). This inverse relationship is consistent with surface-tension forces directed toward collapse of the ET. Specifically, as $\gamma$ increases, surface tension collapsing forces increase, requiring a larger applied pressure to maintain lumen area, which results in a more rigid ET (lower ETC). This inverse relationship is also consistent with previous studies in the pulmonary system. Specifically, Buchanan et al. (3) demonstrated that airway compliance increases on surfactant administration (i.e., decrease in $\gamma$).

In contrast to this inverse relationship, Miura et al. (22) reported an opposite behavior in which an index of compliance, known as the tubal compliance index (TCI), decreased when $\gamma$ decreased due to the application of a nonphysiological surfactant. TCI was defined as the ratio of the flow resistance ($R_s$) at two different flow rates. Specifically, constant flow in an open ET was established, and resistance was calculated as $R_s = P_s/Q_s$, where $P_s$ is the steady-state pressure and $Q_s$ is the applied flow rate. TCI was then calculated as the resistance at a low flow rate ($Q_s$, of $\sim$10 cm/min) over the resistance at a high flow rate ($Q_s$, of $\sim$40 ml/min). Because the resistance to airflow in the ET is an inverse function of the lumen area, this parameter essentially measures the relative change in lumen area for a given change in flow rate. However, the elastic nature of the ET (i.e., ETC) is related to how much force must be applied to produce a given deformation or change in lumen area. The relevant force in this system is the applied pressure ($\Delta P$), not the flow rate. TCI, therefore, may not be an accurate measure of compliance since it does not relate changes in lumen area (i.e., resistance) to changes in the applied pressure. We believe that the results of the current study, which utilizes an engineering definition of compliance (i.e., ETC = d$A$/d$\Delta P$) and successfully predicts an increase in compliance with a reduction in surface tension, are a more accurate representation of the influence of surfactant on ET mechanics.

Another potentially important mechanical parameter that can be influenced by the presence of surfactants is the hysteretic nature of the ET. As demonstrated by the arrows in Fig. 3B, pressures obtained during inflation (i.e., increasing flow rate) may be slightly larger than the pressure obtain during deflation, resulting in a P-Q loop. These loops are similar to the pressure-volume (P-V) loops observed in the lung. In this study, the area of the P-Q loop was quantified with a global hysteretic parameter ($\eta$). Fredberg and Stamenovic (8) demonstrated that $\eta$ may be a function of surfactant-induced surface tension hysteresis ($\gamma_h$) and viscoelastic tissue properties. In this study, we have focused on the influence of $\gamma_h$ by altering interfacial properties by using a pulmonary replacement surfactant. Pulmonary surfactant’s ability to generate a significant loop area depends on several complex physical properties, including differences in adsorption and desorption rates (25) and the development of multiple surfactant layers on the air-liquid interface (18). We have demonstrated that the P-Q loop area observed in normal ETs can be eliminated by removing the native ET mucosal surfactant (see Fig. 6B). This behavior is consistent with observations in the lung where significant P-V loop area is observed in lungs with a functional surfactant system, whereas the P-V loop area in lungs without a functional surfactant system is negligible (19). Therefore, chemical components of ET surfactant likely contain the complex physical properties known to exist in native pulmonary surfactant and are required to produce significant loop area. In addition, the instillation of a pulmonary surfactant into the ET resulted in an increase in loop area, as measured by $\eta$, to normal values. Krueger and Gaver (18) demonstrated that the pulmonary surfactant used in the current study, Infasurf, was also capable of producing these hysteresis loops in an in vitro model of lung alveoli. Therefore, Infasurf contains the requisite physical properties to maintain P-Q hysteresis in the ET and P-V hysteresis in the lung.

Several recent studies investigated the efficacy of surfactant therapy on the resolution of OM (17). These studies were conducted by inducing acute OM experimentally with a bacterial agent, administering surfactant on a periodic basis, and observing the resolution time. For this experimental model, surfactants were found to be effective in reducing the resolution time. Bacterial infections of the ME cause mucosal inflammation, which likely results in increased $P_{open}$, decreased ETC, and thus a dysfunctional ET. The current study demonstrates that treatment with surfactant restores ET function by reducing the mucosa-air surface tension and thus reducing the $P_{open}$ and increasing the ETC or flexibility of the ET. Although surface-active substances may be helpful in resolving acute OM due to infection and inflammation, persistent OM
can develop due to a variety of pathological conditions related to the structure of the ET. For example, Blue stone and Klein (2) demonstrated that persistent OM is consistent with a reduction in ET and reduces the mechanical properties. Knowledge of how surfactant affects these mechanical properties has led to a better understanding of which patients may benefit from surfactant therapy, i.e., patients with large $P_{open}$ and rigid ETs. With the development of noninvasive testing protocols, effective surfactant delivery methods, and cheaper synthetic surfactants, the use of surfactant therapy may become a practical alternative to standard antibiotic and surgical treatments of OM.

**APPENDIX**

The mechanical parameters (ETC and $\eta$) were determined by analyzing experimental P-Q measurements with the fluid-structure model of airflow in a collapsible tube shown in Fig. 7 (12). In this model, the Poiseuille-type relationship is used to describe the pressure drop along the ET in terms of the cross-sectional area $A(t)$, and the flow rate $Q(t)$

$$P(t) - P_d = \frac{\mu L Q(t)}{A(t)^2} \Gamma_S Q(t) = q_m + q_m \sin [\omega t] \quad (1)$$

where $Q(t)$ is fixed by protocol ($q_m = 14$ ml/min, $q_d = 9$ ml/min, and $\omega = 2\pi/72$ s), $P(t)$ is the ME pressure, $P_d$ is the downstream pressure, $\mu$ is the viscosity of air, $L$ is the length of the collapsed segment, and $\Gamma_S$ is a hydraulic-geometric shape factor, which is only a function of the cross-sectional shape. The solid mechanics are described by a potentially nonlinear pressure-area relationship

$$P_{mean} - P_{ext} = A_2(t) + \eta \frac{dA_2(t)}{dt} \quad (2)$$

Here, $P_{mean}$ is the mean pressure in the tube, $E_{tube}$ and $\eta$ represent the global stiffness and hysteretic properties of the ET, respectively, and $A_2(t)$ is the shape-independent area defined as $A_2(t) = A(t)/\Gamma_S$. Note that the mechanical parameters ($E_{tube}$ and $\eta$) are independent of the cross-sectional shape such that the correlation technique described below does not require a specific $\Gamma_S$ value. This model also assumes no variations in cross-sectional area along the length of the ET, i.e., $A = A(t)$ only, as suggested by histological measurements (29).

We seek solutions to these equations for $P(t)$ as a function of $E_{tube}$, $\eta$, and $P_{ext}$. These solutions, however, require an assumption regarding $P_d$ and the coefficient $n$. As described in detail by Ghadiali et al. (12), setting $P_d = 0$ and allowing $n > 1$ results in a numerical solution scheme. A simpler analytical solution can also be obtained by setting $P_d = P_{ext}$ and $n = 1$. Note that these assumptions were only made to obtain an analytical solution and may not have any physiological significance. As demonstrated by Ghadiali et al. (12),

![Diagram](image-url)

**Fig. 7.** Engineering model of a collapsible ET where the global parameters [$\eta$ and tube elastance ($E_{tube}$)] will depend on interfacial and tissue mechanical properties.
the choice of models (i.e., numerical or analytical) does not substantially affect the magnitudes of the $E_{\text{tube}}$ and $\eta$ obtained when these models are correlated with experimental data. Therefore, the current study has utilized the simpler analytical solution.

Given the $P_d = P_{\text{ext}}$ and $n = 1$ assumptions, Eqs. 1 and 2 can be solved analytically for $A_d(t)$. With this expression for $A_d(t)$, Eq. 1 can be used to generate a predicted pressure that will be a function of $E_{\text{tube}}, \eta$, and $P_{\text{ext}}$. For each experimental condition, a least-squares regression analysis is performed by varying the three free parameters to obtain the best fit between predicted pressure and the experimentally measured $P(t)$. This regression technique is able to capture the experimentally observed P-Q hysteresis (see Fig. 3B) and consistently results in a correlation coefficient of $r^2 > 0.95$. As a result, we can quantitatively estimate the ET’s global elastic and hysteretic properties, $E_{\text{tube}}$, and $\eta$. Because compliance is defined as $dA/dP(t) - P_{\text{ext}}$, we utilize Eq. 2 to specify ETC = $1/E_{\text{tube}}$. Note that this “lumped-parameter” model utilizes global parameters ETC and $\eta$, which may depend on both interfacial and tissue mechanical properties. Therefore, this model is not able to specifically identify the functional form of these relationships, $E_{\text{tube}} = 1/ETC = f(E_{\text{tissue}}, \gamma)$ and $\eta = f(\mu_{\text{tissue}}/\gamma)$. We thank Dr. Edmund Egan and ONY for providing Infasurf samples for use in this study and William Karanavas for assistance in developing and maintaining the forced-response system.

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