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Multi-scale Modeling of an Upper Respiratory Airway: Effect of Mucosal Adhesion on Eustachian Tube Function in Young Children

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Abstract

Background—The Eustachian tube is a collapsible upper respiratory airway that is periodically opened to maintain a healthy middle ear. Young children, <10 years old, exhibit reduced Eustachian tube opening efficiency and are at risk for developing middle ear infections. Although these infections increase mucosal adhesion, it is not known how adhesion forces alters the biomechanics of Eustachian tube opening in young children. This study uses computational techniques to investigate how increased mucosal adhesion alters Eustachian tube function in young children.

Methods—Multi-scale finite element models were used to simulate the muscle-assisted opening of the Eustachian tube in healthy adults and young children. Airflow during opening was quantified as a function of adhesion strength, muscle forces and tissue mechanics.

Findings—Although Eustachian tube function was sensitive to increased mucosal adhesion in both adults and children, young children developed Eustachian tube dysfunction at significantly lower values of mucosal adhesion. Specifically, the critical adhesion value was 2 orders of magnitude lower in young children as compared to healthy adults. Although increased adhesion did not alter the sensitivity of Eustachian tube function to tensor and levator veli palatini muscles forces, increased adhesion in young children did reduced the sensitivity of Eustachian tube function to changes in cartilage and mucosal tissue stiffness.

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Interpretations—These results indicate that increased mucosal adhesion can significantly alter the biomechanical mechanisms of Eustachian tube function in young children and that clinical assessment of adhesion levels may be important in therapy selection.

Keywords

otitis media; airway mechanics; finite element modeling; tissue mechanics; fluid mechanics

1. Introduction

Otitis Media (OM) is the most commonly diagnosed clinical condition in young children¹ and involves inflammation of the middle ear (ME) and Eustachian tube (ET) dysfunction^{2, 3}. Although bacterial/viral infections often cause of disease onset, the persistence of ME inflammation, a.k.a. chronic OM, is due to ET dysfunction (ETD)⁴. The ET is an upper respiratory airway that connects the nasopharynx (NP) with the ME and is normally closed to protect the ME from nasopharyngeal pathogens. The ET must be periodically opened to clear ME fluids, maintain ambient ME pressures and a sterile ME cavity³. The ET is a complex 3D structure comprising of cartilage and periluminal mucosal tissue (PMT), an embedded epithelial-lined lumen and several craniofacial muscles with insertions or associations with ET tissues^{5, 6}. Contraction of the two primary muscles associated with ET function, the tensor and levator veli palatini muscles (mTVP and mLVP), during swallowing are responsible for ET opening. mTVP has direct insertions into ET tissues and is known to be the main dilator of the ET lumen^{7, 8}. Although mLVP does not have direct insertions into ET tissues, mLVP contraction leads to elevation and rotation of the ET's NP orifice which has been hypothesized to facilitate ET opening⁹. In addition to muscle forces, experimental and computational studies indicate that changes in tissue mechanics can alter ET function in animal models^{7, 10}, healthy adults^{11, 12} and several OM prone populations^{5, 13}.

Several anatomical factors, including a shorter/smaller ET and horizontal orientations reduces ET opening efficiency in young children and this clinical population experiences a high rate of OM due to ETD³. In addition, infection of the ET-ME system results in the over-expression of muco-adhesive glycoproteins and the secretion of viscous mucus fluid into the lumen^{14–17} which may further exacerbate ETD by increasing luminal adhesion forces. Previously, our laboratory incorporated mucosal adhesion dynamics into 3D finite element models of the adult ET¹⁸. Although those computational models indicate that increased mucosal adhesion can significantly alter the biomechanics of ET function in normal adults, they did not account for the pathologic anatomy found in young children and did not simulate airflow dynamics during ET opening. As a result, the influence of adhesion dynamics on ET function in OM-prone pediatric populations is not well understood.

The primary goal of this study is to use computational techniques to investigate how elevated adhesion forces in young children alters the biomechanical mechanisms of ET function/dysfunction. We develop sophisticated multi-scale computational models of the ET that account for adhesion dynamics, the tissue anatomy observed in young children and airflow rate during ET opening. We use these models to test the hypothesis that young children are

more susceptible than normal adults to increased mucosal adhesion and that increased mucosal adhesion alters the biomechanical mechanisms of ETD in young children.

2. Methods

2.1 Finite Element Modeling

Histological data from $n=4$ young children (age 4–10yrs, 3 male, 1 female) and $n=6$ normal adults (age 19–76yrs, 3 male, 3 female) were used to develop anatomically accurate 3D finite element models of the ET. All histological data was obtained from the Elizabeth McCullough Knowles Otopathology Laboratory at the University of Pittsburgh where fixed extended temporal bone specimens were recovered after autopsy and cut into 30-micron sections perpendicular to the long axis of the ET. Sections were stained with hemotoxylin and eosin and previous described techniques⁵ were used to create models of the cartilaginous portion of the ET (see Figure 1) which included cartilage and periluminal mucosa tissue (PMT) and mTVP and mLVP. Free form meshing techniques were used to generate four-node tetrahedral elements within the cartilage and PMT volumes (red and green volumes in Figure 2A). Mesh size was based on a mesh independence analysis as described in the results and a non-linear, large displacement finite element solver in the ADINA software package (Watertown, MA) was used to solve the 3D tissue deformation equations.

$$\frac{\partial \sigma_{ij}}{\partial x_j} = \rho \frac{\partial^2 d_j}{\partial t^2} \text{ where } \sigma_{ij} = \frac{\partial W}{\partial \varepsilon_{ij}} \text{ and } \varepsilon_{ij} = \frac{1}{2} \left(\frac{\partial d_i}{\partial x_j} + \frac{\partial d_j}{\partial x_i} + \frac{\partial d_k}{\partial x_i} \frac{\partial d_k}{\partial x_j} \right) \quad (1)$$

Here $i=1,2,3$ represents the medial-lateral(x), inferior-superior(y), distal-proximal(z) directions, σ is the Cauchy stress tensor, d_j is displacement, ρ is tissue density (1100 kg/m³ and 1200 kg/m³ for PMT and cartilage respectively)⁵, W is the strain energy density function and ε_{ij} is the strain.

Several boundary conditions and loads were used to solve equation (1) and simulate tissue deformation and lumen opening during swallowing. Zero displacements were applied at the distal ME end model attachment to the non-deformable bony portion of the ET and the NP ends of the cartilage and PMT were constrained against deformation in the distal direction. To allow for tissue rotations consistent with clinical observations⁹ and simulate attachment to the cranial base, grounded linear springs were specified at the superior portion of the ET cartilage (see insert Fig. 2A). mTVP contraction was simulated by applying nodal forces on lateral aspects of the cartilage and PMT with force vectors directed towards the pytergoid hamulus¹⁹. To account for clinically observed medial rotations⁹, mLVP contraction was simulated by applying nodal forces onto the inferior surface of the cartilage at a 45° angle (Figure 2A). The mTVP and mLVP forces, F_{TVP} and F_{LVP} , were uniformly distributed over their site of action and followed a time-dependent sequence described in our previous study²⁰. Although baseline values of muscle forces in adults, $F_{TVP}=0.2\text{N}$ and $F_{LVP}=0.05\text{N}$, are based on measurements of velopharyngeal closure force²¹, as shown in Table 1, these forces were varied over a wide range to capture the potential range of these forces. In

addition, lower baseline force values ($F_{TVP}=0.04N$ and $F_{LYP}=0.01N$) were used in children given the ~5:1 ratio of muscle cross-sectional areas between adults to children⁵.

The cartilage was modeled as a hyperelastic neo-Hookean material defined as

$$W = \frac{G}{2}(J_1 - 3) + \frac{\kappa}{2}(J_3 - 1)^2 \quad (2)$$

where, J_1 and J_3 are reduced strain invariants and G and K are the shear and bulk moduli defined by the Young's modulus (E) and Poisson's ratio (ν)

$$G = \frac{E}{2(1 + \nu)} \text{ and } \kappa = \frac{E}{3(1 - 2\nu)} \quad (3)$$

Similar hyperelastic constitutive models have been used to model both ET mechanics and other soft-biological tissues^{5, 18, 22}. The PMT was modeled as a Maxwell viscoelastic material defined as.

$$E(t) = E_{PMT}e^{-t/\tau_{PMT}}, \quad G(t) = \frac{E(t)}{2(1 + \nu)} \text{ and } \kappa(t) = \frac{E(t)}{3(1 - 2\nu)} \quad (4)$$

E_{PMT} and τ_{PMT} are the PMT's Young's modulus and relaxation time and $G(t)$ and $K(t)$ were specified using convolution integrals in ADINA³

$$s_{ij}(t) = 2G(0)e_{ij}(t) + 2 \int_0^t e_{ij}(t - \tau) \frac{dG(\tau)}{d\tau} d\tau \quad (5)$$

$$\sigma_{ij}(t) = 3\kappa(0)\varepsilon_{kk}(t) + 3 \int_0^t \varepsilon_{ij}(t - \tau) \frac{d\kappa(\tau)}{d\tau} d\tau \quad (6)$$

where s_{ij} and e_{ij} are the deviatoric stress and strain and δ_{ij} is the Kronecker delta. We set a constant $\tau_{PMT}=0.25s$ and modeled the cartilage and PMT as nearly incompressible, $\nu_{cart}=\nu_{PMT}=0.49$. For adults, literature values^{23, 24} were used to specify baseline values of $E_{cart}=300kPa$ and $E_{PMT}=50kPa$. Since ET tissue compliance can be 2x greater in young children²⁵, we specified baseline values of $E_{cart}=150kPa$ and $E_{PMT}=25kPa$ in young children. These material properties were varied over a wide range to capture possible *in-vivo* conditions (Table 1).

2.3 Adhesion Modeling

Following our previous study¹⁸, mucosal adhesion was simulated by incorporating non-linear, rupturable spring elements that connected nodes on the medial and lateral surfaces of

lumen (see Figure 2A and orange elements in 2C). Springs were specified using a linear force-displacement relationship with spring constant K_a and rupture distance x_r . For total spring displacements larger than x_r the spring force was set to zero and the total adhesion energy density was quantified by

$$E_{adh} = \frac{1}{2} K_a x_r^2 N_s / A_s \quad (7)$$

where A_s is the lumen surface area and N_s is the number of spring elements. To account for inflamed and non-inflamed conditions, E_{adh} was varied over a large range (10^{-7} to 1.0 N/m) by varying K_a and assuming a constant rupture force per spring of $F_r = K_a * x_r = 1.56 * 10^{-4}$ N.

2.4 Computational Fluid Dynamics

Although we previously quantified the amount of ET opening via the number of ruptured springs¹⁸, in young children the % spring rupture did not accurately represent ET function. For example, Figure 2B shows the location of ruptured (green) and non-ruptured (black) springs in representative young children (P519) and adult (R55) models at maximum mTVP force application. Although both models exhibit ~50% spring rupture, from a clinical perspective the young children model is 100% closed since there is no path for airflow. Therefore, in this study we used the COMSOL Multiphysics software (Burlington, MA) to quantify the airflow rate in the lumen at maximum mTVP force application. First, the medial and lateral surfaces at maximum mTVP force application were exported into the Rhino-3D CAD software package (Seattle, WA) which was used to cap these surfaces and create a lumen volume. The lumen volume was then imported into COMSOL (Figure 2C) and meshed with quadratic elements with a mesh size determined by a mesh-independence study (see section 3.1). Finally, a non-linear, iterative solver was used to solve the incompressible, Stokes and continuity equations governing.

$$\nabla \cdot [-p\mathbf{I} + \mu(\nabla \mathbf{u} + (\nabla \mathbf{u})^T)] = 0 \text{ and } \rho \nabla \cdot (\mathbf{u}) = 0 \quad (8)$$

Where μ and ρ are the viscosity and density of air ($1.8 * 10^{-5}$ kg/m*s and 1.299 kg/m³), p is the pressure and $\mathbf{u}$ is the velocity field. Stokes flow is assumed since our previous study¹⁰ demonstrated that the Reynolds number for this systems is ~0.1 and that viscous flow models (that neglect inertial terms) accurately reproduce experimental airflow measurements. Pressure boundary conditions were imposed on the middle ear orifice (980 Pa) and the nasopharyngeal opening (0 Pa) and a no slip boundary condition was specified on the medial and lateral lumen surfaces. Note the pressure drop of 980 Pa is consistent with the magnitude used during clinical tests of ET function²⁰. Solution of equation (8) leads to velocity profiles within the lumen that vary along the length of the ET (Fig 2C) and the airflow rate, Q , was obtained by integrating the velocity profile at one cross-section. Since model construction results in a small but non-zero lumen volume, we quantified the degree of lumen opening due to muscle force application by

$$Q_{rel} = \frac{Q - Q_o}{Q_o} \quad (9)$$

Where Q is the flow rate through the lumen at maximum mTVP force application, Q_o is the flow through the undeformed lumen and increasing Q_{rel} corresponds to the relative increase in ET opening.

2.5 Data and Statistical Analysis

Data related to ET opening as a function of controllable biomechanical parameters within the study (E_{adh} , F_{TVP} , F_{LVP} , E_{cart} , and E_{PMT}) were analyzed with a two-way Analysis of Variance (ANOVA) to determine statistical significance between groups. ET opening as a function of adhesion energy was found to follow a sigmoidal relationship on a semi-log scale and the following equation was used to analyze data from each subject.

$$Q_{rel} = \frac{Q_{rel,max}}{1 + e^{- (\chi - \chi_c)/b}} \quad (10)$$

where $Q_{rel,max}$ is the maximum value of Q_{rel} , χ is the logarithm of E_{adh} and χ_c is the logarithm of a critical point where Q_{rel} is 50% of $Q_{rel,max}$. We also report the slope at the critical point as a measure of sensitivity of ET opening to E_{adh} . The critical adhesion values and slopes were compared using one-way repeated measures ANOVA or non-parametric tests if the data were not normally distributed. To investigate the sensitivity of ET opening to F_{TVP} , F_{LVP} , E_{cart} , and E_{PMT} , we calculated the normalize slope of the Q_{rel} vs parameter curves as

$$S = \frac{d(Q_{rel})}{d\Omega} \Omega_b \quad (11)$$

where Ω is the parameter of interest and Ω_b is the baseline value of the that parameter. A two-way repeated measures ANOVA was used to compare sensitivity values at different adhesion levels. Fisher's least significant difference was used for all post-hoc analysis.

3. Results

3.1 Mesh Independence Studies

A mesh independence study was conducted for each subject both in ADINA (structural mechanics) and COMSOL Multiphysics (fluid dynamics) by reducing the mesh density and calculating Q_{rel} as a function of degrees of freedom. For structural mechanics study, the relative change in Q_{rel} compared to the finest mesh was <0.01% for all mesh selections. For the CFD study, there was also <0.01% relative difference in Q_{rel} between meshes. Furthermore, both quadratic and linear elements were analyzed and there was <1%

difference between Q_{rel} for linear and quadratic elements. The final maximum element length used for mesh construction was 0.1mm in ADINA and 0.4mm in COMSOL.

3.2 Influence of Adhesion Energy Density on ET function in Adults and Young Children

Figure 3 shows how changing adhesion energy density, E_{adh} , altered the degree of ET opening as assessed by the relative change in flow rate, Q_{rel} . This parameter variation was conducted for baseline F_{TVP} and larger/smaller F_{TVP} values in both children and adults. For all F_{TVP} values and both patient populations, Q_{rel} exhibited an inverse sigmoidal pattern with respect to E_{adh} on a semi-log scale (Figure 3A and Figure 3B). Statistical analysis (two-way ANOVA) indicates that for both adults and young children, E_{adh} and F_{TVP} are both statistically significant factors ($p < 0.001$). Post-hoc analysis indicates that for both young children and adults, the Q_{rel} vs E_{adh} relationship at the higher F_{TVP} value was statistically different from the Q_{rel} vs E_{adh} relationships at baseline and low F_{TVP} values ($p < 0.05$).

Regardless of mTVP force, F_{TVP} , we observed a critical adhesion energy value at which ET function (measured by Q_{rel}) drastically declines resulting in ET dysfunction. As shown in Figure 3C, in young children, the mean critical adhesion value at the high F_{TVP} was significantly higher than the critical adhesion at low and baseline F_{TVP} ($p < 0.05$, one-way repeated measures ANOVA). Similarly, in adults, the mean critical adhesion value at high F_{TVP} was significantly higher than the critical adhesion value at low F_{TVP} ($p < 0.05$). The critical adhesion at baseline F_{TVP} also trended higher than critical adhesion at low F_{TVP} . Comparing between patient populations, at low and baseline mTVP forces the critical adhesion value in adults is significantly higher than the critical adhesion values in young children ($p < 0.05$, Mann-Whitney Rank Sum Test). Importantly, the critical adhesion values in children are ~2 orders of magnitude lower than in adults. Sensitivity of ET function to changes in adhesion was quantified via the slope at the critical point and as shown in Figure 3D, in young children the critical point slope at low F_{TVP} is significantly higher than the slope at higher F_{TVP} ($p < 0.05$, one-way ANOVA). Conversely, in adults there was no statistically significant difference in critical point slope at the different mTVP force levels. Comparing between patient populations, at baseline and lower F_{TVP} , the critical point slope was significantly higher in young children as compared to adults ($p < 0.05$, one-way ANOVA). Together, the data in Figure 3 indicate that at low and baseline mTVP forces, the critical adhesion values in young children are dramatically lower than in adults and that young children are highly susceptible to small increases in adhesion.

3.2 Role of Muscle Forces on ET Function in Adults and Young Children

As shown in Figures 4A and 4B, we next investigated how changes in F_{TVP} alters the degree of ET opening at different adhesion values. For both adults and children, Q_{rel} followed a sigmoidal relationship with mTVP force on a semi-log scale. Two-way ANOVA indicated that F_{TVP} was a statistically significant factor ($p < 0.001$) for both adults and children, where increasing F_{TVP} results in a statistically significant increase in Q_{rel} . Figure 3A and 3B also indicate the F_{TVP} below which Q_{rel} is statistically lower than the Q_{rel} value at maximum F_{TVP} ($p < 0.05$, one-way ANOVA). Interestingly, for both adults and young children, adhesion energy density was not found to be a statistically significant factor. This data

indicates that increasing F_{TVP} is an effective way to restore ET function regardless of the mucosal adhesion status in both young children and adults.

We next investigated how mLVP forces influenced ET function at different adhesion levels and found that increasing F_{LVP} in young children resulted in statistically significant increases in ET opening and Q_{rel} (Figure 4A). However, increasing LVP forces in adults only resulted in minor, non-statistically significant changes in Q_{rel} . Two-way ANOVA indicates that in young children both F_{LVP} and E_{adh} are significant factors and that Q_{rel} vs F_{LVP} relationships at all adhesion energy levels are statistically different ($p < 0.05$). At all levels of adhesion, increasing F_{LVP} resulted in statistically significant increases in Q_{rel} ($p < 0.05$). Interestingly, at the highest adhesion condition, Q_{rel} values were ~ 0 for $F_{LVP} < 0.015\text{N}$ which indicates complete ET dysfunction. Increasing F_{LVP} above $\sim 0.02\text{N}$ lead to a statistically significant increase in Q_{rel} and therefore increasing LVP forces was found to improved ET function under these conditions. By contrast, in adults, only adhesion energy density was found to be a statistically significant factor ($P < 0.001$) with the Q_{rel} vs F_{LVP} relationships at all adhesion energy density levels showing statistical difference ($p < 0.05$). This data indicates that in young children, but not adults, increasing F_{LVP} can aid in ET function during conditions of elevated adhesion (i.e. inflammation).

3.3 Increasing Tissue Stiffness and its Effects on ET Function for Different Levels of Adhesion

We next investigated how cartilage stiffness, E_{cart} , alters ET function at different adhesion levels and found that decreasing E_{cart} in both young children and adults resulted in statistically significant increases in ET opening and Q_{rel} (Figure 5AB). Two-way ANOVA indicates that in both young children and adults, E_{cart} and E_{adh} are significant factors ($p < 0.05$) and that the Q_{rel} vs E_{cart} relationship at high adhesion was statistically different than the relationship at low adhesion. Interestingly, in young children at high adhesion there was a significant range (i.e. 60kPa to 1500kPa) over which changes in E_{cart} did not significantly increase the Q_{rel} from ~ 0 . By contrast, in adults, decreasing E_{cart} at high adhesion levels lead to a more uniform increase in ET opening. This data indicates that although decreases in E_{cart} can improve ET function in adults at different adhesion levels, large reductions in E_{cart} may be necessary to restore ET function in young children under elevated adhesion conditions.

Finally, we investigated how changes in the periluminal mucosa tissues stiffness, E_{PMT} , alters ET function at different mucosal adhesion levels and found that decreasing E_{PMT} resulted in a statistically significant increase in ET opening and Q_{rel} . (Figures 4CD). Two-way ANOVA indicates that in both young children and adults, E_{PMT} and E_{adh} are significant factors ($p < 0.01$). In young children, the Q_{rel} vs E_{PMT} relationships at different levels of adhesion were all statistically different ($p < 0.05$) while in adults, only the Q_{rel} vs E_{PMT} relationship at high adhesion levels was statistically different than the relationships at baseline and low adhesion conditions. Interestingly, for young children, decreasing E_{PMT} resulted a dramatic and statistically significant increase in Q_{rel} under baseline and low adhesion conditions. However, under high adhesion conditions, decreasing E_{PMT} did not have a statistically significant effect on Q_{rel} . By contrast, in adults, decreasing E_{PMT} resulted

in a statistically significant increase in ET opening at all adhesion levels. In addition, for both young children and adults, decreasing E_{PMT} below a threshold value (10kPa for children and 20kPa for adults) did not result in any further increase in ET opening. This data indicates that although decreasing mucosal tissue stiffness can improve ET function in adults at all adhesion levels, decreasing E_{PMT} in young children results in increased ET opening only under moderate/low adhesion.

3.4 Sensitivity Analysis

We evaluated the relative importance of the different biomechanical parameters by conducting a sensitivity analysis where the data presented in Figures 2–4 were used to calculate a normalized slope, S , via equation (11). S was calculated for each subject for the four parameters of interest (F_{TVP} , F_{LVP} , E_{cart} and E_{PMT}) under moderate and high adhesion conditions and mean values in both young children and adults are shown in Figure 6AB. Two-way repeated measures ANOVA indicates that there is a statistically significant interaction between parameter type and adhesion level ($p < 0.05$) in both young children and adults. In young children, increasing adhesion led to a statistically significant decrease in cartilage stiffness sensitivity ($p < 0.01$) and a trend towards decreasing PMT stiffness sensitivity ($p = 0.066$). However, increasing adhesion did not alter the sensitivity of ET function to mTVP or mLVP forces. Further, the sensitivities to mTVP force was larger than the sensitivity to mLVP force. This data indicates that the most efficient way to restore ET function in young children during inflammation is by altering mTVP of mLVP forces. By contrast, in adults, although we observed a statistically significant decrease in cartilage stiffness sensitivity ($p < 0.01$) and a trend towards lower PMT stiffness sensitivity ($p = 0.059$) under elevated adhesion conditions, the magnitude of this change was much smaller than that observed in young children. As a result, the relative importance of muscle forces and tissue stiffness on ET function is not dramatically altered by increased adhesion in adults. This data indicates that increased adhesion dramatically alters the mechanisms of ET function in young children but not in adults.

4. Discussion

It is well documented that an inability to open the Eustachian tube (ET), aka ET dysfunction (ETD), results in chronic otitis media (COM) and that several clinical populations are at higher risk for developing ETD and COM^{3, 4}. Several anatomical and biomechanical properties, including muscle forces and tissue stiffness, can influence the degree of the ET opening and previous computational studies have investigated how the anatomy in at-risk populations influences ET function⁵. However, these previous models did not account for the increased mucosal adhesion that occurs during ME infections. Therefore, this study used multi-scale computational models to investigate how increased mucosal adhesion alters ET function in young children who are at higher risk for developing ETD and COM.

In addition to mucosal adhesion, we incorporated several enhancements to allow for more accurate simulation of ET function. First, enhanced boundary conditions in the current models resulted in medial rotation of the ET cartilage during mLVP contraction (see Figure 2A) and is therefore more consistent with experimental observations⁹. Second, since

quantifying the percentage of spring rupture did not accurately characterize the degree of ET opening (Figure 2B), the current models use computational fluid dynamics techniques to calculate relative changes in airflow during ET opening.

Our first hypothesis was that young children would be more sensitive to increases in mucosal adhesion as compared to adults. As shown in Figure 3, increasing mucosal adhesion results in a rapid decline in ET opening and the rate of this decline (i.e. slope at the critical point) was larger in young children as compared to adults (Figure 3D). Furthermore, the adhesion value at which significant ETD occurs, i.e. the critical adhesion, is 2 orders of magnitudes lower in young children as compared to adults (Figure 3C). Therefore, these models clearly indicate that young children are highly susceptible to ETD where small increases in mucosal adhesion can significantly hinder ET opening. This data is consistent with the higher rates of COM in young children and suggests that therapies which seek to reduce mucosal adhesion may be an effective way to restore ET function.

Figure 3 also indicates that the critical adhesion value depends on the mTVP force generated and that children who are able to generate larger muscle forces are less susceptible to ETD. This critical role of mTVP force is further supported by data in Figures 4 and 6 where increasing F_{TVP} improved ET function at all levels of adhesion. In addition, the sensitivity of ET function to F_{TVP} was not affected by increasing adhesion (Figure 6). Together, this data indicates that although young children are highly susceptible to ETD due to increased adhesion during inflammatory OM, treatment strategies that increase mTVP forces might be effective. In fact, previous studies indicates that ET rehabilitation therapy (ETRT), which involves muscle strengthening exercises, can improve outcomes in both adults and young children^{26, 27}. However, strict adherence and compliance with ETRT may limit the clinical applicability of muscle based therapies in young children.

Adequate mLVP function has recently been suggested to be an important component of ET function. Although previous computational studies which did not account for medial rotation of the ET cartilage indicate that mLVP forces are not a major determinant of ET function, we found that increasing F_{LVP} in young children can significantly improve ET function at all adhesion levels. One potential explanation for this data is that in the current models, increased F_{LVP} rotates the ET into a configuration that changes that direction of mTVP forces, which are always directed towards the fixed pytergoid hamulus, and that this change in vector relationships results in increased ET opening. In fact, previous studies indicate that mLVP contraction rotates the ET into a more favorable configuration^{9, 28} and proper mTVP vector relationships are an important determinant of ET function²⁹. Interestingly, in adults the effect of increased mLVP forces on ET opening was minor and this may be due to the fact that the adult anatomy is already in a favorable configuration such that additional rotation does not dramatically alter mTVP vector relationships. Clearly, additional computational models that can control the amount of ET cartilage rotation are needed to test these hypotheses.

In addition to altering muscle forces, several therapeutic modalities involve alterations in cartilage/PMT tissue mechanics. For example, laser ablation of mucosal/cartilage tissue, aka laser ET tuboplasty³⁰, involves the removal of hypertrophic mucosa and cartilage and

therefore likely involves changes/reductions in cartilage and PMT stiffness. Balloon dilation/tuboplasty is another emerging treatment for ETD that involves catheterization and balloon dilation of the ET lumen which may result in cartilage microfractures and thus altered tissue mechanics^{31, 32}. Laser/balloon ET tuboplasty has been used to improve otologic outcomes in adults³³ and this is consistent with data in Figure 4 where decreased cartilage/PMT stiffness in adults at all adhesion levels resulted in increased ET opening. However, in children, ET function was not found to be sensitive to changes in cartilage or PMT stiffness at high adhesion values (Figure 5 and 6). In fact, data in Figure 5AC indicate that under elevated adhesion conditions, very large reductions in cartilage stiffness are required for improved ET function and that reductions in PMT stiffness do not significantly affect ET opening. Therefore, the tissue mechanical changes associated with laser/balloon tuboplasty may not be effective in young children during conditions of inflammatory OM. However, these treatments may also alter surface adhesion properties in the lumen which as discussed above may significantly improve ET function.

Although the current computational models have incorporated several features to better simulate ET function, future studies could incorporate additional enhancements. In this study, rupturable springs was used to efficiently model the multi-scale aspects of ET function during inflammation. However, this model does not account for fluid adhesion parameters, such as mucus viscosity and/or surface tension, which are the targets of several therapeutics, i.e. mucolytics and surfactants. Therefore, future studies could use advanced fluid-structure interaction (FSI) and free-surface CFD techniques³⁴ to directly simulate the dynamics of air-liquid interface movement during ET opening. In addition, molecular scale interactions between muco-adhesive glycoproteins may involve non-linear force-displacement relationships and plastic deformation. Therefore, future studies could use either numerical (i.e. molecular dynamic simulations) or experimental (atomic force microscopy) techniques to quantify these non-linear relationships and integrate them into finite element models of ET function. Although the current models simulate the dynamics of tissue deformation during swallowing, they do not account for dynamic airflow patterns. Future studies could use two-way FSI techniques^{35, 36} to obtained these dynamic airflow patterns. Finally, the current models cannot simulate common delivery mechanisms for ET therapies and future studies could develop anatomically accurate models of the nasal cavity that are linked to multi-scale models of the ET to evaluate several intranasal delivery routes.

In summary, we have developed a novel set of multi-scale computational models of ET function in an OM prone population (i.e. young children) and compared results with models in a healthy adult population. Results indicate that ET function in young children is more sensitive to changes in mucosal adhesion and that small increases in adhesion can lead to rapid ET dysfunction. Therapies that reduce mucosal adhesion or increase mTVP and/or mLVP forces were predicted to be effective in restoring ET function while therapies that alter cartilage and PMT tissue stiffness were not predicted to have a significant effect on ET in young children under elevated adhesion conditions. Continued development of multiscale models of ET function may be useful in identifying the most effective therapies and delivery routes in a given OM prone population.

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Highlights

- The influence of mucosal adhesion on Eustachian Tube function was modeled
- Eustachian tube function in young children was highly sensitive to mucosal adhesion
- Eustachian tube dysfunction occurred at lower values of adhesion in young children
- Mucosal adhesion altered the biomechanical mechanisms of Eustachian tube function
- Increased muscle forces can restore Eustachian tube function during inflammation

Figure 1.
Schematic representation of the ME-ET-NP system indicating the region of finite element analysis in this study.

Figure 2.

(A) Representative 3D computational model of the ET: cartilage (green), periluminal mucosal tissue (red) with a lumen containing adhesion elements (orange), and superior adhesion springs (teal). Deformation is shown at different time points and pink arrows indicate mTVP and mLVP forces. (B) Illustration of the functional differences for 50% spring rupture profiles (green) in representative young child and adult models (C) Creation of lumen volume by extraction of ET lumen surfaces and finite element mesh used to solve for velocity profiles in the lumen. Color map indicates velocity magnitude.

Figure 3.

Relative flow rate (Q_{rel}) as a function of adhesion energy density (E_{adh}) in young children (A) and adults (B) for low, baseline and high mTVP force (F_{TVP}). Data represents mean $\pm$ standard error for $n=4$ young children and $n=6$ adults. E_{adh} and F_{TVP} were statistically significant factors ($p < 0.001$) and * and ^ indicate statistically different Q_{rel} vs E_{adh} relationships ($p < 0.05$). (C) Critical E_{adh} at different F_{TVP} for young children and adults. (D) Slope about the critical point for different F_{TVP} for young children and adults. For C) and D) data represents mean $\pm$ standard error and * indicates statistically significant differences between populations at a given F_{TVP} and – indicates statistically significant differences within a population ($p < 0.05$).

Figure 4.

Relative flowrate, Q_{rel} , as a function of F_{TVP} (A – young children and B – adults) and F_{LVP} (C – young children and D – adults). (A & B) F_{TVP} is a statistically significant factor in both young children and adults ($p < 0.001$). For low, baseline and high adhesion conditions respectively *, o, and ^ indicate the F_{TVP} value below which Q_{rel} is statistically lower than the Q_{rel} at maximum mTVP force ($p < 0.05$). In young children both F_{LVP} and E_{adh} were statistically significant factors ($p < 0.001$) and $\times$ indicates statistically significant differences in the Q_{rel} vs F_{LVP} relationships ($p < 0.05$). For low, baseline and high adhesion conditions respectively *, o and ^ indicate the F_{LVP} force value below which Q_{rel} is statistically lower than the Q_{rel} at maximum mLVP force ($p < 0.05$). D) In adults, only E_{adh} was a statistically significant factor ($p < 0.001$) and * indicates statistically significant differences in the Q_{rel} vs F_{LVP} relationships ($p < 0.05$).

Figure 5.

Relative flowrate, Q_{rel} , as a function of E_{cart} (A – young children and B – adults) and E_{pMT} (C – young children and D – adults). (A & B) E_{cart} and E_{adh} were statistically significant factors in both young children (A) and adults (B) ($p < 0.001$ for E_{cart} and $p < 0.05$ for adhesion) and x and $^{\#}$ indicates statistically significant differences in the Q_{rel} vs E_{cart} relationships ($p < 0.05$). For low, baseline and high adhesion conditions respectively * , o , and $^{\wedge}$ indicate the E_{cart} value above which the mean Q_{rel} is statistically lower than the mean Q_{rel} at minimum E_{cart} ($p < 0.05$). (C & D) E_{pMT} and E_{adh} were statistically significant factors in both young children (C) and adults (D) ($p < 0.01$) and x and $^{\#}$ indicate statistically significant differences in the Q_{rel} vs E_{pMT} relationships ($p < 0.05$). For low, baseline and high adhesion conditions respectively * , o , and $^{\wedge}$ indicate the E_{pMT} value above which the mean Q_{rel} is statistically lower than the mean Q_{rel} at minimum E_{pMT} ($p < 0.05$).

Figure 6.

Sensitivity of ET opening, S , to different biomechanical parameters (F_{TVP} , F_{LVP} , E_{cart} and E_{pMT}) at moderate and high adhesion levels. Two-way repeated measures ANOVA indicate statistically significant interaction between parameter type and adhesion level in both young children (A) and adults (B) ($p < 0.05$). Data is mean $\pm$ standard error and * indicates statistically lower mean S values with respect to mean S value at moderate adhesion within a given parameter ($p < 0.01$). ~ indicates a trend towards lower mean S values with respect to mean S value at moderate adhesion within a given parameter. $n=4$ young children and $n=6$ adults.

Table 1

Parameter values used in the finite element models for both young children and adults. Data includes baseline values as well as range of parameter values tested for young children and adults.

Parameter	Baseline Value	Range of Values Tested
Adhesion Energy	N/A	$1e^{-7} - 1$ N/m
F_{TVP}	0.2 N (adults) 0.04 N (children)	0.02 – 2 N (adults) 0.004 – 0.4 N (children)
F_{LVP}	0.05 N (adults) 0.01 N (children)	0.005 – 0.5 N (adults) 0.002 – 0.05 N (children)
E_{Cart}	300 kPa (adults) 150 kPa (children)	30 – 3000 kPa (adults) 15 – 1500 kPa (children)
E_{PMT}	50 kPa (adults) 25 kPa (children)	5 – 500 kPa (adults) 2.5 – 250 kPa (children)