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Three-dimensional Finite Element Analysis of Eustachian Tube Function under Normal and Pathological Conditions

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Abstract

A primary etiological factor underlying chronic middle ear disease is an inability to open the collapsible Eustachian tube (ET). However, the structure-function relationships responsible for ET dysfunction in patient populations at risk for developing otitis media (OM) are not known. In this study, three-dimensional (3D) finite element (FE) modeling techniques were used to investigate how changes in biomechanical and anatomical properties influence opening phenomena in three populations: normal adults, young children and infants with cleft palate. Histological data was used to create anatomically accurate models and FE techniques were used to simulate tissue deformation and ET opening. Lumen dilation was quantified using a computational fluid dynamic (CFD) technique and a sensitivity analysis was performed to ascertain the relative importance of the different anatomical and tissue mechanical properties. Results for adults suggest that ET function is highly sensitive to tensor veli palatini muscle (TVPM) forces and to periluminal mucosal tissue (PMT) elasticity. Young children and cleft palate subjects exhibited reduced sensitivity to TVPM forces while changes in PMT stiffness continued to have a significant impact on ET function. These results suggest that reducing PMT stiffness might be an effective way to restore ET function in these populations. Varying TVPM force vector relationships via changes in hamulus location had no effect on ET opening in young children and cleft palate subjects but did alter force transmission to the ET lumen during conditions of elevated adhesion. These models have therefore provided important new insights into the biomechanical mechanisms responsible for ET dysfunction.

Key terms

biomechanics; airway opening; tissue mechanics; tissue morphology; otitis media; fluid-structure interactions; respiratory airway; mathematical modeling; mucosal adhesion

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1.0 Introduction

Otitis media (OM), inflammation of the middle ear mucosa, is the most frequent reason children take antibiotics¹ and the cost of treating OM in United States has been estimated at ~\$4 billion annually². Although bacterial/viral infections are responsible for the acute phase of OM, the persistence of OM is primarily due to a dysfunctional Eustachian tube (ET). The ET is a collapsible airway which connects the nasopharynx (NP) with the middle ear (ME). Although the ET is normally closed to protect the ME from nasopharyngeal pathogens, it can open periodically to maintain ambient ME pressures and to clear ME fluids and contaminants³. In healthy subjects, these openings occur during swallowing where the contraction of craniofacial muscles results in the deformation of the ET's soft tissue structure and an opening of the ET lumen. Unfortunately, abnormal anatomical and tissue mechanical properties may compromise this opening process in several OM prone patient populations. The inability to dilate the ET during swallowing results in sub-ambient ME pressures, the transudation of fluid into the ME space and the persistence of the ME mucosal inflammation (i.e. otitis media)⁴. Although ET openings provide rapid equilibration of ME pressures, several other structures, including the mastoid⁵ and eardrum⁶, can also play important roles in ME pressure regulation. Nonetheless, an inability to open the ET is a major cause of OM³ and standard treatment therapies (e.g. antibiotics and the insertion of ventilation tubes into the eardrum) do not address the pathological mechanisms responsible for ET dysfunction. A better understanding of the anatomical and biomechanical mechanisms underlying ET opening phenomena could lead to more effective treatment options for OM.

The ET is a complex 3D structure which contains a lumen that is lined with epithelial cells and coated with a viscous fluid. This lumen, which is normally closed, is surrounded by cartilage and periluminal mucosal tissue (see Figure 1). Several craniofacial muscles, including the tensor veli palatini and levator veli palatini muscles (TVPM and LVPM), are attached to these soft tissue elements. Although it is well established that the contraction of the TVPM during swallowing is required for normal ET function⁷⁻⁸, several other tissue mechanical properties may also play a role in dilating the collapsed ET lumen. For example, experiments indicate that the elastic and/or viscoelastic properties of the cartilage and mucosal tissue may be important determinants of ET function⁹⁻¹⁰. In addition, *in-vivo* studies indicate that the surface tension¹¹⁻¹² and inflammatory¹³ properties of the ET mucosa may influence the degree of opening. Although these tissue mechanical properties have been implicated in ET dysfunction, the relative importance of different mechanical parameters on ET function in different patient populations is not well established.

Previous studies¹⁴⁻¹⁸ have used histological techniques to investigate how anatomical properties such as the size and shape (i.e. morphology) of cartilage and mucosal tissues may contribute to ET function. These studies found that the three-dimensional (3D) anatomy of the ET is complex and that morphological variations may play an important role in opening phenomena¹⁴⁻¹⁶. For example, displacement of the hamulus of the pterygoid bone during reconstructive surgery in patients with craniofacial disorders (i.e. cleft palate), may alter the 3D vector relationships of TVPM forces and thus compromise ET function¹⁹⁻²⁰. In addition, the abnormal morphology of the cartilage, TVPM and LVPM may contribute to ET dysfunction in cleft palate infants and young children¹⁷⁻¹⁸. However, these observational studies are limited since they could not quantify how the measured morphological relationships impact the tissue deformation processes responsible for ET opening. In addition, these previous studies could not account for the interaction between tissue anatomy and tissue mechanics. As a result, a detailed understanding of the anatomical and tissue mechanical mechanisms responsible for ET opening phenomena in different patient populations is not currently available.

Previously, our laboratory developed two-dimensional (2D) finite element models of ET function to investigate the relative importance of muscle forces, contraction timing sequences and tissue elastance on opening phenomena^{21–22}. Although these 2D models provided valuable information regarding the biomechanical mechanisms responsible for normal ET function, a significant limitation of these models is that they did not account for the complex 3D anatomy of the ET. Specifically, the 2D models did not account for variations in tissue size/morphology along the length of the ET and could not investigate 3D relationships between the TVPM and the soft tissue structures. Since these 3D relationships could significantly influence ET function, the first goal of this study is to develop and analyze anatomically realistic 3D finite element (FE) models of ET opening phenomena.

Our previous studies^{21–22} focused on the mechanisms of “normal” ET function and therefore only utilized histological data from adult subjects with no history of middle ear disease. Although understanding the mechanisms of normal ET function is important, from a clinical perspective it is essential to also identify the mechanisms responsible for ET “dysfunction” in different OM prone patient populations. For example, infants and young children are known to have a “shorter” ET which may impair ET function and lead to increased OM susceptibility²³. In addition, patients with craniofacial abnormalities such as a cleft palate exhibit nearly 100% incidence rates of OM²⁴. However, the precise structure-function relationships responsible for ET dysfunction in these populations are not known. Therefore, the second goal of this study is to develop 3D FE models of ET function in two OM prone patient populations (young children and infants with cleft palate) and use these models to investigate the biomechanical mechanisms responsible for ET dysfunction. In addition to creating “normal” and pathological models of ET function that account for complex tissue deformation and airflow dynamics, we have conducted an extensive sensitivity analysis to identify which biomechanical properties have the greatest impact on ET function in the different populations. We specifically hypothesize that anatomical differences between normal adults, young children and cleft palate infants result in differential sensitivity of ET function to various tissue biomechanical parameters. Knowledge of these sensitivities may be useful in designing specific treatment strategies for the different populations.

2.0 Methods

2.1 Histological Imaging

Temporal bone specimens that included the ME, cranial base, ET cartilage, TVPM, LVPM and periluminal mucosal tissue (PMT), were obtained from six adults, four young children, and five infants with cleft palate. All adult subjects (specimen numbers E32, E37, E41, E63, E82, and R55) were negative for a history of ME disease or ET dysfunction and ranged in age range from 19 years to 76 years with equal number of male and female subjects. The young children group (specimen numbers P519, P573, P622, and P809) had an age range of 4 years to 10 years and an equal number of male and female patients. The cleft palate infant group (specimen numbers P506, P578, P598, P847, and P849) had an age range of 1 month to 2.5 years with 3 female and 2 male subjects. All specimens were processed according to the technique developed by Sando et. al²⁵. Briefly, each specimen was fixed in formalin, decalcified with trichloroacetic acid and dehydrated in ethanol. Serial 30 μ m sections were cut vertically in a plane perpendicular to the long axis of the ET and every 20th section was stained with hematoxylin and eosin. The sections located distal to the hamulus bone which contained all four soft tissue elements (cartilage, TVPM, LVPM, and PMT), were analyzed for model construction (see below for details). These sections represented the deformable “cartilaginous” portion of the ET as defined by previous investigators²⁶. In addition to ensuring that the selected cross sections are comparable among subjects, the use of the cartilaginous portion for model construction is physiologically valid since the other “bony”

portions of the ET would have no influence on opening phenomena²⁷. All histological specimens were generously provided by the Elizabeth McCullough Knowles Otopathology Laboratory at the University of Pittsburgh.

All histological images were visualized with a Diaphot inverted microscope (Nikon Instruments) and a high resolution CCD camera (Carl Zeiss) and analyzed according to the procedure described by Ghadiali et al.²¹. Images were acquired at an average resolution of 0.039 ± 0.011 mm/pixel. The Metamorph image analysis package (Universal Imaging) was used to obtain high quality contours of the soft tissue elements and to identify important surface locations for application of muscle forces and boundary conditions (see Figure 1). Surface locations include attachment of the cartilage to the cranial base (section A in Figure 1), TVPM insertion onto lateral portions of the cartilage and PMT (sections B and C), and contact surfaces between the LVPM and inferior portions of the PMT and cartilage (sections D and E). Although histological processing resulted in an “artificial” opening of the lumen due to tissue dehydration (see Figure 1), all models were created with an initially closed lumen in order to simulate *in-vivo* conditions. For consistency, the closed lumen “line” was always drawn on the medial edge of the PMT. For each subject, a cubic spline algorithm was used to generate smooth lofted-surfaces between the cross-sectional contours. The ProEngineer solid modeling package (Needham, MA) was then used to convert lofted surfaces into 3D solid models of both the cartilage and PMT tissues. Note that this 3D model generation procedure converts sections A–E into easily identifiable 3D surfaces for boundary condition application and attaches the PMT to the cartilage tissue at appropriate locations.

2.1 Finite Element Analysis

The 3D solid models were imported into the ADINA finite element program (Watertown, MA) for meshing and analysis. First, free-form meshing techniques were used to generate four-node tetrahedral elements within the cartilage and PMT volumes. Two element groups with different material properties were used to model the cartilage and PMT. Typical finite element meshes used for the cartilage and PMT domains for an adult subject are shown in Figure 2A. A non-linear, large-displacement finite element routine²⁸ was then used to solve the following 3D tissue deformation equations.

$$\frac{\partial \sigma_{ij}}{\partial x_j} = 0 \text{ where } \sigma_{ij} = \frac{\partial W}{\partial \varepsilon_{ij}} \text{ and } \varepsilon_{ij} = \frac{1}{2} \left(\frac{\partial d_i}{\partial x_j} + \frac{\partial d_j}{\partial x_i} + \frac{\partial d_k}{\partial x_i} \frac{\partial d_k}{\partial x_j} \right) \quad (1)$$

Here σ is the Cauchy stress tensor, W is the strain energy density and ε is the strain. Note that all equations are written in standard tensor notation for a Cartesian coordinate system where $i=1,2,3$ represents the x, y and z directions. Equation (1) specifies stress-equilibrium and the primary solution variable is the displacement of each mesh node, d_i .

The solution of equation (1) requires specification of appropriate boundary conditions. Fixed boundary conditions, i.e. zero displacements, were applied to surface A (see Figure 1) to simulate the cartilage's attachment to the non-deformable cranial base. The nasopharyngeal and middle ear ends of the ET cartilage and PMT were constrained against deformation in the distal, or z direction, to simulate the tension applied by adjacent sections of the ET. Contraction of the TVPM and LVPM muscles were simulated by applying forces on the load-bearing surfaces (sections B–E in Figure 1). The LVPM, which has origins in the inferior aspect of the bony portion of the ET and the soft palate, runs inferior to the ET lumen and along its distal axis^{29–31}. Contraction of the LVPM results in the application of superiorly directed forces onto the inferior surfaces of the membranous wall and cartilage³². LVPM contraction was therefore simulated by applying a normally directed pressure load P

$= F_{LVP}/(A_D + A_E)$ where A_D and A_E are the areas of surfaces D and E and F_{LVP} is the force magnitude generated by the LVPM. The TVPM is a flat, ribbon-like muscle that attaches to the cranial base and lateral portions of the cartilage and PMT, descends inferiorly and proximally, and ends in a tendon that winds around the pytergoid hamulus³³. As a result, contraction of the TVPM results in the application of forces onto the lateral aspect of the tubal cartilage and PMT that are directed toward the pterygoid hamulus. TVPM contraction was therefore simulated by applying a series of nodal forces on surfaces B and C which were directed towards the pytergoid hamulus (see Figure 2B). Note that these forces were defined as “follower loads” such that the direction of each force vector changes during tissue deformation such that the force vector always points towards the fixed hamulus location. The magnitude of each TVPM force vector was constant, $F_v = F_{TVPM}/n$, where F_v is the magnitude of each force vector, F_{TVPM} is the total force applied by the TVPM and n is the number of nodes on surfaces B and C. Note that the baseline position of the hamulus near the NP orifice is based on the observed location in adult patients³⁴.

The magnitude of force generated by craniofacial muscles during jaw opening in adults has been estimated to be ~20–50N³⁵. Therefore, in this study we assumed a baseline TVPM force magnitude of $F_{TVPM}=20N$ in the adult group and simulated ET opening phenomena for values of F_{TVPM} up to 50N. The LVPM contracts primarily in the proximal-distal direction and does not directly insert into ET tissues. However, expansion of the LVPM cross-sectional area during contraction will exert forces on inferior surfaces of ET tissues. Since the forces generated by cross-sectional area expansion are expected to be lower than the primary forces generated by the muscle, the baseline magnitude for LVPM force on ET tissues was set at $F_{LVP}=5N$. Since the isometric force generated by a muscle is linearly proportional to its cross-sectional area³⁶, young children and infants with cleft palate would be expected to have a lower muscle force magnitude than the adults. Therefore, measurements of LVPM cross-sectional area were used to specify baseline muscle force magnitudes in the young children and cleft palate groups. The average cross-sectional area of the LVPM in the adult, young child and cleft palate groups were measured using the MetaMorph image analysis package (Universal Imaging) and results indicate that the average ratio of cross-sectional area from adults to young children is 1:0.75 while the average ratio from adults to cleft palate infants is 1:0.5. Therefore, we specified baseline muscle force values of $F_{TVPM}=15N$ and $F_{LVP}=3.75N$ in the young children group and $F_{TVPM}=10N$ and $F_{LVP}=2.5N$ in the cleft palate infant group. Note that in this study the entire muscle contracts simultaneously and peristaltic movement is therefore not considered. In addition, our models assume stress free initial conditions and we therefore do not simulate passive tissue forces.

Although linear constitutive relationships can be used to describe the mechanical properties of simple materials, these relationships can only be used to describe the deformation of biological tissue when the amount of deformation or strain is very small³⁷. Since the deformation of ET tissues during swallowing may be relatively large (i.e. strains of ~35%)²¹, we utilized a non-linear, hyper-elastic constitutive relationship to describe the mechanical properties of ET tissues. This neo-Hookean relationship is defined by a shear modulus (G) and a bulk modulus (κ), which depend on the Young's modulus (E) and the Poisson's ratio (ν).

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

These moduli are then used to define the strain energy density function,

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

Where J_1 and J_3 are the reduced strain invariants as defined by Bathe²⁸. We note that several investigators have used similar Neo-Hookean material models to simulate the deformation of soft biological tissues^{38–39} including breast tissue⁴⁰ and cartilage in the ear canal⁴¹. Both the cartilage and PMT are modeled as nearly incompressible, i.e., $\nu_{\text{cart}} = \nu_{\text{PMT}} = 0.49$. For adult subjects, the cartilage's baseline Young's modulus ($E_{\text{cart}} = 300$ kPa) was based on literature values⁴² and the baseline PMT stiffness ($E_{\text{PMT}} = 50$ kPa) was based on previous measurements in glandular breast tissue⁴³. However, *in vivo* studies indicate that ET compliance in infants and young children may be 2 fold greater than that of adults⁴⁴. Therefore, in the young children and cleft palate groups the baseline elastic moduli for the cartilage and PMT were $E_{\text{cart}} = 150$ kPa and $E_{\text{PMT}} = 25$ kPa.

2.3 Computational Fluid Dynamics

The application of the appropriate boundary conditions, muscle loads, and tissue mechanical properties results in different amounts of lumen opening (see column i, Figure 3) and the degree of opening was quantified by calculating a viscous flow resistance parameter, R_v , according to the following procedure. After simulating ET deformation, the volume defining the opened lumen was imported into the ADINA FE package (Watertown, MA) and meshed with fluid elements (see column ii, Figure 3). These elements were used to solve the standard, incompressible continuity and Navier-Stokes equations for the velocity of air inside the lumen.

$$\frac{\partial v_i}{\partial x_j} = 0 \text{ and } \rho \frac{\partial v_i}{\partial t} + \rho v_j \frac{\partial v_i}{\partial x_j} = - \frac{\partial p}{\partial x_i} + \mu \frac{\partial^2 v_i}{\partial x_i \partial x_j} \quad (4)$$

where ρ is the density and μ is the viscosity. For this model, we assume the viscosity and density of air (0.018 cP and 0.001229 g/cm³), prescribe a pressure drop of 200 mm H₂O from the NP to ME, and assign no slip boundary conditions on the walls of the lumen. The primary outcome variable from these models was the 3D velocity field and example flow fields for each population can be seen in Figure 3, column iii. This velocity profile was integrated in the mid-cartilaginous section to determine the flowrate of air through the lumen, Q . Finally, the viscous flow resistance parameter was calculated as

$$R_v = \frac{\Delta P}{Q} \quad (5)$$

where ΔP is the prescribed pressure drop from the NP to the ME (i.e. 200 mm H₂O). Note that R_v is inversely proportional to the degree of opening, i.e. larger lumen openings result in larger flow rates, thus smaller R_v values. R_v was calculated as a function of several biomechanical and anatomical parameters for each subject (see Figure 6 or Figure 7) and this data was used to calculate a sensitivity ratio defined as the ratio of R_v at a reference parameter value to R_v at a 4x the reference parameter value. For example, in adults this sensitivity ratio for F_{TVP} was defined as $R_{v|F_{\text{TVP}}=10\text{N}}/R_{v|F_{\text{TVP}}=40\text{N}}$. In general,

$$\text{Sensitivity} = \frac{R_v|_{\text{Reference Parameter Value}}}{R_v|_{4 \times \text{Reference Parameter Value}}} \quad (6)$$

These sensitivity parameters represent the relative importance of a given biomechanical parameter on ET function where sensitivity equal to unity indicates that the parameter has no effect on ET function and larger values indicate larger effects on ET function. For clarity, the “reference parameter value” and “4x reference parameter value” are indicated by dashed lines in Figures 6, 7 and S1–S4. Note that all sensitivity parameters were calculated to be greater than unity. Both repeated measures within groups analysis of variance (ANOVA) and between groups ANOVA were used to document statistical difference in sensitivity values ($p < 0.05$).

3.0 Results

3.1 Meshing and Convergence

Histological data from all fifteen subjects in this study were successfully analyzed and converted into 3D solid models of the ET cartilage and PMT. Furthermore, all models were successfully analyzed for tissue deformation and lumen opening. Figure 4A shows all of the 3D models generated in this study and clearly depicts anatomical variations between the normal adult group ($n=6$, top row), young child group ($n=4$, middle row) and cleft palate infant group ($n=5$, bottom row). All solid models shown in Figure 4A were meshed with 4-node tetrahedral elements and the average number of elements used to model the cartilage and PMT domains in adults was 41016 ± 9885 and 27261 ± 6976 respectively. The average number of elements used to model the cartilage and PMT domain in the young children group was 26369 ± 11369 and 23058 ± 17619 while the average number of cartilage and PMT elements in the cleft palate infant group was 30603 ± 33427 and 23230 ± 18461 . We also measured the maximum medial-lateral, inferior-superior and proximal-distal dimension of the ET in each model and report this data in Figure 4B. ANOVA indicates that all three dimensions in the adult population were larger than the corresponding dimension in the children and cleft palate infant groups ($p < 0.05$). In addition, the proximal-distal and inferior-superior dimensions in the children are larger than corresponding dimension in the cleft palate infants ($p < 0.05$). However there was no statistical difference between the medial-lateral dimensions in the children and cleft palate infants ($p > 0.8$).

For all populations, tissue deformation resulted in an opened lumen which was analyzed with a finite-element mesh to solve equation (4) for the velocity field within the lumen (Figure 3). This velocity field was used to calculate the air flowrate (Q) and the flow resistance parameter, R_v , for each simulation. Due to the complex geometry of the fluid domain, an adequate mesh size is required for accurate calculation of R_v and a mesh-independence study was conducted to determine the appropriate mesh density. Specifically, the fluid domain in one adult subject was meshed with different numbers of finite elements and R_v was calculated for each case under baseline conditions. Figure 5A shows how the calculated value of R_v varies as a function of the number of fluid elements. This data indicates that using ~95,000 fluid elements results in a mesh independent solution. This convergence check was performed with an adult subject since that patient population has the largest lumen openings. The same number of elements was then used to mesh the smaller fluid domains in young children and cleft palate infants. Note that a similar mesh convergence study was performed to set the number of elements used in the solid tissue domain (data not shown).

In addition to mesh-independence, we also confirmed that the calculation of R_v does not depend on the method used to reconstruct the 3D geometry. First, recall that histological processing creates an “artificially” opened lumen and that the *in-vivo* condition of a closed lumen was simulated by drawing a “lumen line” on the medial side of the artificially opened lumen. To verify that this medial location does not influence the calculation of R_v , a 3D model from one adult subject was reconstructed with a “lumen line” drawn in the center of

the artificial opening. Comparison of R_v data obtained from these models (Figure 5B) indicates that the choice of initial lumen location (medial vs. central) does not affect the shape or magnitude of the R_v vs F_{TVP} curve. We also confirmed that the calculation of R_v does not depend on the selected 3D reconstruction algorithm. For this analysis, histology data from one adult subject was analyzed and in addition to using the cubic spline algorithm in the Pro-Engineering software package, quadratic, cubic and quartic non-uniform rational b-splines (NURBS) were used to construct 3D models of this subject. The NURBS technique was implemented using the Rhino3D CAD software package (Seattle, WA). As shown in Figure 5C, the choice of 3D reconstruction algorithm did not affect the magnitude or shape of the R_v vs F_{TVP} curve. Therefore, all reconstructions were performed using the cubic spline algorithm in the Pro-Engineering software package.

3.2 Parameter Variation Results

For all three groups (adult, young children and cleft palate infants), the finite element models were used to determine the sensitivity of ET opening to four biomechanical parameters (F_{TVP} , F_{LVP} , E_{cart} and E_{PMT}) and three anatomical parameters (the X, Y and Z location of the pytergoid hamulus). First, R_v was calculated as a function of the given parameter and equation (6) was then used to calculate the sensitivity for this parameter in each group. In this manuscript we present the raw R_v as a function of biomechanical/anatomical parameters for the adult group in Figures 6 and 7 and provide the raw R_v vs. parameter data for the young children and cleft palate infants as online supplemental figures (S1–S4). Legends in these figures refer to specimen labels as described in the beginning of the Methods section.

The effect of varying TVPM and LVPM forces on R_v in the six normal adult models is presented in Figure 6AB. As expected, increasing the TVPM force from 5 to 50 N resulted in a decrease flow resistance, i.e. a greater luminal opening and increased airflow. In contrast, varying the LVPM force from 0.2 to 8 N had little effect on R_v , while increasing the LVPM force to ~20N resulted in an increase in R_v , i.e. lumen closure, in one subject. Visualization of lumen opening indicated that this increase in R_v was due to lumen constriction at the higher (i.e. ~20N) LVPM force. The effect of varying cartilage and PMT elastic moduli on flow resistance in the six adult models is shown in Figure 6CD. Increasing the cartilage elastic modulus from 75 to 3000 kPa resulted in a moderate increase in luminal resistance, i.e. lumen closure. Increasing the PMT elastic modulus from 20 to 500 kPa also resulted in an increase in luminal resistance. The relative increase in luminal resistance as a function of elastic modulus was larger for the PMT and this effect is quantitatively captured in our sensitivity analysis (see Figure 8A).

In the present study, variations in the hamulus' X (lateral-medial), Y (superior-inferior) and Z (distal-proximal) position were accomplished by displacing the hamulus from its original location up to 100% of the lateral, superior or distal span of the ET as measured in each subject. For example, if the subject's ET measured 18 mm in the distal direction then the Z coordinate of the hamulus was allowed to vary up to 18 mm in that direction. Note that although our computational models are able to simulate these very large changes in hamulus position, our sensitivity analysis was conducted over a more physiological range (i.e. 0 to 20%). As shown in Figure 7A, lateral displacement of the hamulus resulted in a minor decrease in R_v (i.e. increase in ET opening) for all adult subjects. Conversely, superior displacement of the hamulus resulted in a variable response (Figure 7B) where both minor increases and minor decreases in R_v were observed. Distal displacements of the hamulus up to ~60% resulted in a minor decrease in R_v while displacements >~60% resulted in a minor increase in R_v .

3.3 Sensitivity Analysis

Figures 6 and 7 clearly demonstrate that changes in tissue mechanics and anatomical structure can significantly impact ET function in adults. Similar data presented in figures S1–S4 in the online supplement indicate that muscle forces, cartilage/PMT stiffness and hamulus location can also impact ET function in the young children and cleft palate populations. However, equivalent changes in a given parameter (e.g. PMT stiffness) produce different magnitude changes in ET opening/resistance in different populations. For example, a four-fold (4x) change in LVP force causes very little change in resistance in adults while a 4x change in TVP force causes large changes in resistance. We therefore quantified the relative importance of the tissue mechanical parameters F_{TVP} , F_{LVP} , E_{cart} and E_{PMT} in each group by calculating sensitivity ratios according to equation (6). Sensitivity ratios were calculated for each subject and we report mean and the 95% confidence intervals in Figure 8A. We also calculated sensitivity ratios based on changes in R_v as a function of hamulus position (Figure 8B). Note that these sensitivity ratios were calculated as a ratio of R_v at 0% to R_v at 20% displacement since 20% displacement represents significant but not physiologically unrealistic movement of the hamulus.

For the adult population, repeated measures ANOVA documented that the sensitivity of ET function to TVPM forces is larger than its sensitivity to LVPM forces ($p < 0.03$) and that ET function is more sensitive to changes in mucosal and cartilage tissue elasticity than LVPM forces ($p < 0.03$). In addition, there was no statistically significant difference between unity and the sensitivity values for LVPM force ($p = 0.56$). ANOVA also indicated that ET opening phenomena is more sensitive to PMT stiffness compared with cartilage stiffness ($p < 0.01$) and that the mean sensitivity values for TVPM forces and PMT stiffness were not statistically different ($p = 0.52$). Although all sensitivity parameters for hamulus movement were close to unity, the mean sensitivity to lateral and distal movement was statistically greater than unity ($p < 0.01$).

As with the adult population, ANOVA indicated that in young children, the sensitivity of ET function to TVPM forces, cartilage elasticity and mucosal elasticity were all greater than the sensitivity to LVPM forces ($p < 0.03$). In addition, there was no statistically significant difference between unity and the sensitivity values for LVPM force ($p = 0.18$). The sensitivity of ET function to PMT stiffness was also larger than the sensitivity to cartilage stiffness ($p < 0.01$). However, in contrast to the adults, the sensitivity of ET function to PMT stiffness was larger than the sensitivity to TVPM forces in young children ($p < 0.04$). In addition, no statistically significant difference between unity and the sensitivity values for lateral, superior or distal hamulus movement was observed in young children ($p > 0.44$).

In the cleft palate population, the sensitivity of ET function to TVPM forces, cartilage elasticity and mucosal elasticity were all greater than the sensitivity to LVPM forces ($p < 0.03$) and the LVPM sensitivity was not statistically different from unity ($p = 0.633$). Although there was no statistically significant difference between the PMT and cartilage sensitivity values ($p = 0.094$), there was a trend towards higher sensitivity of ET function to PMT stiffness. In addition, there was a trend towards increased sensitivity of ET function to PMT stiffness compared to TVPM forces ($p = 0.07$). Finally, as with the young children, there was no statistically significant difference between unity and the sensitivity values for lateral, superior or distal hamulus movement in the infants with cleft palate ($p > 0.125$).

In addition to conducting repeated measures, within-group comparisons, we also conducted between-groups comparisons for the tissue mechanical parameters shown in Figure 8A. Multivariate ANOVA and post-hoc analysis indicates that the sensitivity of ET function to TVPM forces was greater in adults compared to both young children and infants with cleft

palate ($p < 0.05$). However, there were no significant differences among the three groups (adult, children and cleft palate) for the F_{LVP} , E_{cart} or E_{PMT} sensitivity ratios.

4.0 Discussion

Eustachian tube dysfunction is the primary etiology responsible for chronic Otitis Media and it is well established that several patient populations (i.e. young children and cleft palate subjects) are at a higher risk for developing chronic OM due to ET dysfunction. Although previous histological studies^{14,17–18} have documented anatomical variations between these patient populations, the precise mechanisms responsible for ET dysfunction in these populations are not known. In this manuscript we have developed 3D finite-element based computational models that can simulate the complex physical phenomena (i.e. tissue deformation and air flow) that govern ET function. These finite element models account for the complex 3D anatomy of various tissue elements in adults, young children and infants with a cleft palate. Important advantages of these computational models include the ability to investigate how isolated changes in specific biomechanical and anatomical parameters influence ET function and the ability to quantitatively assess the relative importance of these parameters on ET function. In addition to obtaining results that correlate with known mechanisms of normal ET function, the current study has provided important insights into the biomechanical mechanisms responsible for ET dysfunction in young children and cleft palate infants.

4.1 ET opening depends on TVPM but not LVPM forces

It is well established that the TVPM is the only effective dilator of the ET lumen³ and that procedures which reduce the TVPM forces applied to the ET result in dysfunction^{7–8}. For all three groups, the computational models predict that ET function is sensitive to TVPM forces, i.e. mean sensitivity values greater than unity, and are therefore consistent with experimental observations. Furthermore, the computational models from all three groups predict that changes in LVPM forces has no effect on ET opening phenomena, i.e. sensitivity values statistically equal to unity. This lack of importance for LVPM with respect to tubal opening is also supported by past studies^{29,31–32}. It is important to note that in this study we only assessed static opening phenomena in response to isolated changes in muscle forces. Recently, our lab developed 2D finite element models of transient ET opening and closure during swallowing.²² These models indicate that contraction of the LVPM results in lumen constriction and that the amount of constriction depends on the relative delay timing between TVPM and LVPM contraction.

4.2 ET function is sensitive to Periluminal Mucosal Tissue (PMT) mechanics

In addition to functional interpretations that are consistent with previous experimental findings, the 3D finite element models have provided new information regarding the mechanisms of ET function and dysfunction. First, results from all groups indicate that the mechanical properties of the cartilage and PMT, i.e. stiffness, have a statistically significant impact on ET function (i.e. mean sensitivity > 1). Although previous studies have suggested that cartilage and PMT compliance might influence ET function^{10,44}, these studies could not provide a quantitative analysis of the relative importance of cartilage and PMT stiffness. Importantly, our computational models indicate that the relative importance of the cartilage and PMT stiffness, as well as TVPM forces, on ET function is highly dependent on the differential anatomy observed in adults, young children and cleft palate infants. For adults, “normal” ET function is equally sensitive to changes in TVPM forces and PMT stiffness. However, in the young children and cleft palate groups, ET opening phenomena is more sensitive to changes in PMT stiffness than to changes in TVPM forces. Furthermore, between-group comparisons indicate that the sensitivity of ET function to TVPM forces is

significantly lower in the young children and cleft palate groups than for adults. We therefore conclude that the anatomical/morphological differences of young children/cleft palate subjects with respect to adults results in a reduced ability of the TVPM to dilate the ET lumen. These results have important clinical implications since they suggest that augmenting TVPM forces might not be effective in the young children and cleft palate groups due to the reduced sensitivity. Conversely, techniques that alter/reduce the stiffness of the periluminal mucosa tissue via surgical or pharmaceutical techniques are predicted to be more effective in improving ET function. In fact, Poe et al.⁴⁵ have used laser ablation techniques in adults to “vaporize” areas of hypertrophic mucosa and have reported ~30–40% success rates with this technique. Alternatively, selective injection of enzymes (i.e. hyaluronidase) that degrade components of the extracellular matrix (i.e. hyaluronic acid) may be used to lower the elastic modulus of soft tissues⁴⁶. In addition, other studies have suggested that peritubal hyperplasia due to nasal soiling with food, which could lead to increased mucosal stiffness, may reduce ET function in cleft palate subjects⁴⁷. Finally, we note that model results from all subject groups indicate that ET function is more sensitive to PMT stiffness than cartilage stiffness. Therefore, targeting the periluminal mucosal tissue might be more effective than targeting the cartilage.

4.3 TVPM vector relationships influence ET function in adults only

In addition to tissue mechanics, we have also systematically investigated the relative importance of hamulus position on ET function. In adults with a “normal” anatomy, changing the distal or lateral location of the hamulus had a minor but statistically significant effect on ET opening phenomena. First, lateral displacement of the hamulus resulted in a minor decrease in R_v or increase in ET opening (Figure 7A). In adults, the lumen is located primarily in the yz (superior-distal) plane and the x-component of the TVPM force is the most significant force component pulling the lumen open. Lateral or x-displacement of the hamulus results in an increase in the x-component of the TVPM force vector and therefore larger lumen openings (decrease in R_v). Distal displacement of the hamulus (<60%) also resulted in a minor reduction in R_v (Figure 7C). Initially, as the hamulus moves from the nasopharynx (NP) to the middle ear (ME) in the z direction (i.e. distally), the aggregate magnitude of the x component for all TVPM force vectors increases, resulting in larger openings and a decrease in R_v . However, the maximum opening (i.e. minimum R_v) occurs when the hamulus is located half-way between the NP and ME. As the hamulus moves past this half-way point, the aggregate magnitude of the x component for all TVPM force vectors begins to decrease, resulting in a minor increase in R_v . Finally, we note that in adults, superior displacement of the hamulus had no consistent or statistically significant effect on R_v (Figure 7B).

Interestingly, lateral, superior or distal displacements of the hamulus in the young children or cleft palate infant population had no statistically significant effect on ET function. This suggests that altering TVPM vector relationships may not be an effective way to restore normal ET function in these groups with “abnormal” tissue anatomies. In support of this prediction, previous studies indicate that surgical procedures that alter TVPM vector relationships by fracturing the hamulus^{48–49} or by transposing the TVPM tendon medial to the hamulus⁵⁰ have little effect on ET function or the development of OM. It is important to note that in our computational model, changing the hamulus position only changes the insertion angle of the TVPM vector with respect to the PMT and cartilage. *In-vivo*, movement of the hamulus might also change the TVPM’s resting length and therefore reduce TVPM forces. As shown in Figures S1A and S3A (online supplement), reduced TVPM force magnitude in young children or infants with cleft palate may result in larger R_v and reduced ET function. Although experimental techniques, such as hamular fracture, might have simultaneous effects on both TVPM vector relationships and TVPM force, our

computational models are able to investigate how isolated changes in these parameters influence ET function. The data from these models clearly indicates that ET function is sensitive to TVPM force but is insensitive to TVPM vector relationships. However, validation of these sensitivity relationships may require direct experimental measurements of both TVPM vector relationships and TVPM forces during procedures such as hamular fracture or tendon translocation.

4.4 Hamulus Position influences stress distribution within the ET

Although the data in Figure 7C indicates that placing the hamulus half-way between the ME and NP results in the largest ET openings, it is well established that the hamulus is normally located near the NP in adult subjects³⁴. We hypothesized that this discrepancy between model prediction of hamular location for maximal opening and the normal *in-vivo* location is likely due to a limitation of the current FE models. Specifically, the current models do not account for mucosal adhesion forces within the lumen that keep the ET closed until the stress generated at the lumen surface exceeds a yield value. These adhesion forces may be due to glycoprotein interactions⁵¹ or surface tension forces¹². Although incorporating the molecular scale phenomena responsible for adhesion into the FE models is beyond the scope of the current study, we have incorporated a simple modification in order to investigate how hamulus position might affect force/stress transmission to the lumen surfaces. For this analysis, an adult FE model was modified by incorporating rigid links between lumen surfaces such that the ET will not open regardless of the applied muscle forces. Although the lumen does not open, the effective Von Mises stress at the lumen surface can be quantified as

$$\sigma_M = \sqrt{3/2 S_{ij} \cdot S_{ij}} \text{ where } S_{ij} = \sigma_{ij} - 1/3 \sigma_{ij} \delta_{ij} \quad (7)$$

where S_{ij} is the deviatoric stress tensor and δ_{ij} is the Kronecker delta function. For baseline tissue mechanical properties, the contour plots in Figure 9 show how σ_M varies as a function of hamulus location (hamulus locations is denoted by a + sign). In Figure 9A the hamulus is located near the NP, and the relatively large stresses that develop on the lumen surface near the NP would promote opening of the collapsed ET in this region. However, moving the hamulus towards the ME results in a significant decrease in σ_M (Figures 9B and 9C) and this reduction in force may lead to an inability to open an initially closed ET. Therefore, although Figure 7C indicates that a hamulus location half-way between the NP and ME may lead to a slight decrease in flow resistance, Figure 9 indicates that a hamulus location near the NP allows for more effective stress transmission to the lumen surface which may be critical for opening a collapsed ET during conditions of increase adhesion (i.e. inflammation). The data in Figure 9A are also consistent with previous studies which indicate that dilation of the ET occurs in a wave-like manner⁵² where the high surface stresses would initially open the NP end of the ET followed by a wave of lumen openings progressing towards the ME.

4.5 Limitations and Future Studies

As with all modeling studies, the current models contain limitations with respect to the *in-vivo* system. First, the current models do not account for the viscoelastic properties of ET tissues⁸⁻⁹ and/or the transient nature of opening/closing that occur during swallowing. We recently used 2D finite element modeling techniques to account for tissue viscoelasticity and time-dependent muscle contraction sequences in an adult population²². Correlation of these 2D FE models with experimental data indicate that the relative delay timing between LVPM and TVPM forces may be responsible for ET constriction. However, the models developed in that study did not account for the 3D anatomy of the ET or the pathological anatomy of

ET tissues in young children and cleft palate subjects. Therefore, incorporating transient dynamics into the 3D FE models described in the current study may lead to additional information about the mechanisms responsible for ET dysfunction. We note that incorporating a transient analysis into the current models will require the use of advanced fully-coupled fluid-structure simulation techniques in which the equations governing solid deformation and fluid mechanics are solved simultaneously. Although this study was primarily interested in how variations in tissue biomechanical properties and hamulus position influence ET function in different populations, it is clear from Figures 6, S1 and S2 that anatomical variations within subject groups significantly influences the magnitude of R_v . Therefore, future studies that use parameterized geometric models of the ET may be useful in investigating the anatomical mechanisms of ET dysfunction. Finally, as stated above, the current models do not account for adhesion forces within the ET lumen. During inflammatory OM, these adhesion forces could be elevated due to the interaction between mucus glycoproteins expressed on the apical surface of epithelial cells⁵¹ and/or surface tension forces at the air-liquid interface¹². Future studies that incorporate both molecular level adhesion forces and surface tension dynamics into the current tissue deformation models may provide a more accurate representation of ET function during disease.

5.0 Conclusion

In conclusion, we used histological data from both normal and pathological populations to develop anatomically accurate 3D finite element models of the tissue deformation and airflow dynamics responsible for ET opening phenomena. Results from the adult FE models indicate that normal ET function is equally sensitive to TVPM forces and mucosal tissue elasticity. Although the current models indicate that hamulus position only has a minor effect on the degree of lumen opening, model results do indicate that hamulus position may influence ET opening phenomena during conditions of inflammation and elevated adhesion forces. In addition to the mechanisms of normal ET function, the FE models in the young children and cleft palate populations were used to identify several biomechanical and anatomical mechanisms of ET dysfunction. For example, the models indicate that the abnormal morphology of ET tissues in young children and infants with cleft palate leads to a less effective TVPM and a reduced sensitivity of ET function to TVPM forces. As a result, the models suggest that augmenting TVPM forces may not be an effective treatment strategy in these populations. In contrast, the models also indicate that ET function is sensitive to changes in periluminal mucosal tissue stiffness in young children and infants with cleft palate. Therefore modifying the elasticity of this tissue warrants further investigation as a clinical target. The continued development of these advanced models of ET function in pathological populations may lead to novel targeted therapies for Otitis Media and ET dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

OM Otitis Media

ET	Eustachian tube
NP	Nasopharynx
ME	Middle Ear
TVPM	Tensor Veli Palatini Muscle
LVP	Levator Veli Palatini Muscle
PMT	Periluminal Mucosal Tissue
FE	Finite Element
σ	Cauchy stress tensor
W	Strain energy density
e	Tissue strain
d_i	Displacement of a finite element node
G	Shear modulus
κ	Bulk modulus
E	Young's modulus
ν	Poisson's ratio
R_v	Flow resistance parameter
v_i	Fluid velocity vector
μ	Viscosity of air
ρ	Density of air
F_{TVP}	Total force applied by TVPM
F_{LVP}	Total force applied by LVP
E_{PMT}	Young's modulus of PMT
E_{cart}	Young's modulus of cartilage
σ_M	Von Mises stress

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Figure 1. Serial histological sections of the ET at cross-sectional locations near the middle ear (column i), in the middle of the ET (column ii) and near the nasopharynx (column iii). Images were obtained from healthy adults (top row), young children (middle row) and infants with cleft palate (bottom row). Outlines used to generate 3D finite element models are also shown.

Figure 2AB.

a) 3D FE model of the ET for a healthy adult subject. b) Superior-Inferior view of the of the TVPM forces directed towards the pytergoid hamulus under baseline conditions.

Figure 3ABC.

Slice plots of the deformed solid geometry depicting lumen opening (column i). Grey represents ET cartilage and black represents the mucosal tissue. Finite element meshes within the open lumen used for CFD analysis (column ii). Velocity field within the lumen after simulating pressure driven flow (column iii). Data is shown for one representative subject in each population (a: healthy adults, b: Young children and c: Cleft Palate Infant).

Figure 4AB.

(A) Solid models created from histological data in all three populations. All models are shown to the same scale and grey represents ET cartilage while black represents the mucosal tissue. (B) Morphological measurements of medial-lateral, inferior-superior and proximal-distal dimensions in each model for the adult, young children and CP infant groups. Horizontal line indicates mean and * indicates differences with respect to ($p < 0.05$).

Figure 5ABC.

Data related to model validation. a) Effect of mesh density/number in CFD simulations on the calculation of R_v . b) Effect of closed lumen line location on R_v vs. F_{TVPM} relationship. c) Effect of 3D reconstruction algorithm on R_v vs. F_{TVPM} relationship.

Figure 6ABCD.

Variation of flow resistance (R_v) as a function of a) TVPM forces, b) LVPM forces, c) cartilage stiffness and d) PMT stiffness in the normal adult population. All parameter studies were conducted by varying the selected parameter and holding the other parameters at baseline values. Dashed lines represent upper and lower limits for calculation of the sensitivity ratio reported in Figure 8.

Figure 7ABC.

Variation of flow resistance (R_v) as a function of a) lateral, b) superior and c) distal hamulus position in the normal adult population. Hamulus location is reported as a percentage of the maximal size of the ET in the selected direction. Dashed lines represent upper and lower limits for calculation of the sensitivity ratio reported in Figure 8.

Figure 8AB.

Mean sensitivity values for a) tissue mechanical properties (TVP forces, LVP forces, cartilage stiffness and PMT stiffness) and b) x, y, z hamulus location in the adult, young children and cleft palate populations. All data is reported as mean $\pm$ 95% confidence interval. * indicates statistically significant differences ($p < 0.05$) with respect to unity (dashed line).

Figure 9ABC.

Von Mises stress generated at the lumen's interior surface as a function of hamulus position. Data collected in a model with rigid links to simulate very high adhesion with no ET opening.