Published in final edited form as:

Auris Nasus Larynx. 2010 December ; 37(6): 720–729. doi:10.1016/j.anl.2010.02.008.

Timing of Tensor and Levator Veli Palatini Force Application Determines Eustachian Tube Resistance Patterns during the Forced Response Test

Samir N. Ghadiali, Ph.D.^{1,2}, E. David Bell, B.S.³, and J. Douglas Swarts, Ph.D.⁴

¹Department of Biomedical Engineering, The Ohio State University, Columbus, OH 43210

²Department of Internal Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Ohio State University Medical Center, Columbus, OH 43210

³Department of Mechanical Engineering and Mechanics, Lehigh University, Bethlehem, PA 18015

⁴Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh, Pittsburgh, PA 15213

Abstract

Objectives—The Forced-Response test (FRT) is used to assess Eustachian tube (ET) function in patients with middle ear disease (Otitis media). This test often documents a dynamic pattern of luminal dilation and constriction during swallowing which can be quantified as a function relating active tubal resistance with time. The goal of this study is to use a generalized finite element model (FEM) to test the hypothesis that the relative timing of muscle force application by the tensor veli palatini muscle (mTVP) and levator veli palatini muscle (mLVP) on the ET determines the form of active resistance functions.

Methods—Seven resistance waveforms were obtained during the FRT in five adult subjects. A 2D FEM of the ET was constructed from an adult histological specimen and viscoelastic tissue mechanical properties were specified based on measurements obtained in each subject. Least-squared regression routines were used to vary the timing and magnitude of mTVP and mLVP force applications to the ET in order to match the active resistance functions recorded during the FRT.

Results—Variation of muscle force timing and magnitude in the FEM simulations reproduced the seven active resistance waveforms with high fidelity. Early application of mTVP force in combination with mLVP force produced a waveform characterized by an initial dilation (low resistances) followed by lumen constriction (higher resistances), while delayed mTVP force application caused an initial lumen constriction followed by dilation.

Conclusions—These results indicate that the active resistance waveforms observed during the FRT reflect differences in the temporal pattern of mLVP and mTVP force application to the ET and emphasize that, like the mTVP, the mLVP functionally interacts with the ET. Results also indicate that in normal adults contraction of the mLVP promotes lumen constriction and that the

© 2010 Elsevier Ireland Ltd. All rights reserved.

Contact Information: Samir N. Ghadiali, Associate Professor, Department of Biomedical Engineering, 270 Bevis Hall, 1080 Carmack Rd., Columbus, OH 43221, ghadiali.1@osu.edu, Phone: (614) 292-7742, Fax: (614) 292-7301.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

initial lumen constriction is highly sensitive to the relative delay timing of mTVP and mLVP force application.

Keywords

Muscle timing; Finite Element Method; tissue mechanics; Otitis Media; Eustachian tube function

I. Introduction

Otitis Media and ET dysfunction

There is a large body of evidence which clearly demonstrates that adequate Eustachian tube (ET) function is required to maintain a healthy middle ear system (1). The ET represents an important communication pathway between the posterior nasopharynx and the middle ear, and is believed to serve three functions: clearance of middle ear secretions and detritus from the middle ear; protection of the middle ear from nasopharyngeal pathogens, other noxious substances and pressure transients; and equalization of middle ear pressures to ambient conditions. To accommodate these functions, the ET is equipped with a functional mucociliary clearance system continuous with that of the middle ear (clearance), is usually closed by periluminal pressures that are greater than ambient pressure (protection), and is periodically opened by transient contraction of the tensor veli palatini muscle (mTVP) which allows for gas exchange between the middle ear and nasopharynx (pressure regulation) (2).

A commonly used method to evaluate ET function in ears with a non-intact tympanic membrane is the Forced Response Test (FRT). The FRT was specifically designed to evaluate the adequacy of the protection and pressure-regulating functions (3). The FRT can measure passive properties such as the middle ear pressure required to open the ET, the periluminal pressure acting to close the ET lumen and the steady-state resistance to airflow. In addition, continuous monitoring of pressure and airflow during a swallowing event allows for the calculation of dynamic changes in airflow resistance as a function of time. Although the passive measures can assess the protective function, monitoring of dynamic changes in airflow resistance can be used to investigate the active pressure-regulating function and, specifically, the ability of the mTVP to further dilate a pre-dilated ET lumen.

The FRT is performed by applying a constant airflow to the ME via a perforated tympanic membrane while continuously measuring the flow rate through the ET and middle ear pressure (see Figure 1a). Application of the airflow causes an increase in middle ear pressure to a level that passively opens the ET at the opening pressure, P_{open} , which is followed by dilation of the ET lumen to yield steady state pressure and airflow conditions, P_s and Q_s , in a partially dilated ET. The steady-state resistance to airflow at this point is calculated as a ratio of pressure to airflow, i.e. $R_s = P_s / Q_s$. After achieving steady state, contraction of the mTVP is induced by swallowing, which for individuals with adequate ET function, disturbs the equilibrium condition by further dilating the ET lumen. This results in a lower luminal pressure (P_a) and increased airflow (Q_a) during active swallowing (see Figure 1B), and thus a decrease in the active resistance to airflow, $R_a = P_a / Q_a$. The ratio of steady-state to active resistance during swallowing, R_s / R_a , for a specific applied airflow provides a measure of the tubal dilatory efficiency, i.e. the pressure-regulating function of the ET. Finally, after a swallowing event, the applied airflow is terminated and the pressure remaining at the time of ET closure ($Q=0$) is recorded as the ET closing pressure, a measure of the periluminal pressure that maintains a closed ET lumen.

In certain populations at risk for otitis media with effusion or with a history of that disease, the FRT documents a reproducible abnormality characterized by a tubal dilatory efficiency,

$R_s/R_a < 1$. This is interpretable as constriction (vs dilation) of the pre-dilated ET lumen during swallowing (3–8). Using simultaneous videoendoscopy of the ET lumen in the area of the posterior nasopharynx combined with the FRT, Takahashi and colleagues (7) reported that in the presence of hypertrophied adenoids, ET luminal edema or nasal discharge, the constriction phenomenon was attributable to blockage of the ET's nasopharyngeal orifice by elevation of the soft palate during contraction of the levator veli palatini muscle (mLVP). However, other pressure-flow patterns during swallowing not indicative of pure tubal dilations or pure tubal constrictions were also documented during FRT testing in individuals from different populations (6,9). These “mixed” patterns include elements of both ET constriction and dilation, but neither the cause nor the significance of these types of responses is known.

While the mTVP is recognized as the only dilator of the ET lumen, the mLVP is responsible for palatal elevation during swallowing and is anatomically related to the ET (10–11). The mTVP attaches to the lateral wall of the membrano-cartilaginous portion of the ET and exerts an anterior-inferior-laterally directed force to that wall during contraction while the mLVP takes origin from the inferior border of the bony portion of the ET, lies along the floor of the membrano-cartilaginous ET throughout its extent and inserts into the soft palate (10,12). Contraction of the mLVP muscle elevates the soft palate and imposes a superiorly directed force upon the cartilaginous and membranous components of the floor of the ET. This force application could compress the cross-sectional area of a predilated ET lumen and thereby increase the resistance to airflow. From these anatomical considerations, we hypothesized that the more complex resistance patterns documented during the FRT reflect the temporal interaction between the forces applied to the ET by the mLVP and mTVP during swallowing with the mTVP force application associated with tubal dilation and mLVP force application associated with tubal constriction.

In the present study, seven FRT pressure-flow patterns obtained from five normal adult individuals were converted to resistance vs time functions and analyzed using a finite element model (FEM) of ET function. The model was constructed using histological sections from a single adult specimen and the tissue mechanical properties for each model was appropriately specified for each individual based on measurements obtained via the oscillatory ET compliance (ETC) test (13–14). For each FEM, which simulated the pressure-flow conditions during the FRT, the relative timing and magnitudes of mTVP and mLVP force applications to the ET were varied to yield a best fit between the simulated and observed resistance vs. time functions during swallowing. The hypothesis tested was that the complex resistance functions observed during swallowing could be reproduced in the FEM by varying those parameters.

II. Materials and Methods

Human Studies

For this study, five healthy adult (>21 years) with no reported past history of middle ear disease were enrolled after obtaining written informed consent. To allow for ET function testing, a unilateral myringotomy was performed by an otolaryngologist after topical anesthesia of the ipsilateral tympanic membrane. Ipsilateral ET function was then evaluated in all subjects using the standard FRT and the oscillatory ETC test (3,14). The human subject protocol for performing voluntary myringotomies in healthy adults was approved by the University of Pittsburgh Institutional Review Board.

A previously described pressure-flow rate monitoring system (13–16) was used to conduct the standard FRT and monitor pressure and flow rate during swallowing events (see Figure 1 for example data). As shown in Fig. 1A, the ME was first inflated at a constant flow rate

until the ET opened at a pressure P_{open} . Once opened, airflow was continued until steady-state pressure and flow rate were recorded (P_s , Q_s). The subject was then instructed to swallow and high temporal resolution data of the pressure and flow rate, $P(t)$ and $Q(t)$, were recorded during the swallowing event (see Fig. 1B). To facilitate direct correlations between experiments and computational models, the pressure and flow rates waveforms shown in Fig. 1B were converted to a time-dependent resistance function, $R_v(t)=P(t)/Q(t)$, as shown in Fig. 1C. Note that R_v is inversely related to the degree of opening such that increases in R_v represent lumen closure or constriction while decreases in R_v represent lumen openings/dilations. As shown in Fig. 1C, the resistance waveforms may demonstrate three distinct patterns, i.e. a pre-swallow constriction (increase in R_v), followed by lumen dilation (decrease in R_v) and finally a post-swallow constriction. The main objective of this study is to use computational models of ET function to analyze and interpret these experimentally measured pressure-flow rate waveforms.

Our lab has previously demonstrated that several tissue biomechanical properties, including the ET's compliance (ETC) and hysteretic properties (η), may be important determinates of ET function (15–16). In addition, the computational models to be developed in this study for analysis of transient $R_v(t)$ data require accurate specification of tissue biomechanical properties. We therefore conducted the oscillatory FRT described by Ghadiali et al. (14) in each subject to accurately quantify ETC and η . Briefly, the oscillatory FRT, which was performed with the same pressure-flow monitoring system used during the standard FRT, imposed a sinusoidal flow rate between 11 and 33 ml/min with a period of 72 s and recorded the subsequent oscillation in luminal pressure. Data was recorded as a pressure-flow rate (P – Q) hysteresis loop (see points in Fig. 2) and was correlated with a previously developed (14) mathematical model of airflow in a collapsible tube (solid line in Fig. 2) to obtain ETC and η for each subject. Note that the average slope of the P – Q loop is inversely related to ETC whereas the area enclosed by the loop is directly related to η . Analysis of P – Q loops from all five patients resulted in coefficients of determination (r^2) that were consistently > 0.95 .

Finite Element Models

A generalized, two-dimensional (2D) FEM of the ET's soft tissue structures was constructed (see Figure 3a) as previously described (17). Briefly, serial histological sections containing the cranial base, ET cartilage, periluminal mucosal tissue (PMT), mTVP and mLVP were obtained from a representative adult subject (male, 69 years old, no history of ME disease or ET dysfunction). The use of a single representative specimen for model construction ensured that simulations were not influenced by differences in tissue anatomy and is justified by past results that reported minimal anatomical variability in the ET system in a population of normal adult subjects (17). The most distal cross-section in which the mTVP was not attached to the cranial base but was attached to the cartilage and PMT was selected for modeling. For that section, the Metamorph image analysis software (Sunnyvale, CA) was used to generate high quality outlines of the ET cartilage, PMT and medial surface of the ET lumen. Surface locations that included the superior attachment of the ET cartilage to the cranial base ("Fixed to cranial base" in Fig. 3A), the attachment of the mTVP to the lateral ET cartilage and PMT (F_{TVP} in Fig. 3A) and the region of contact between the mLVP and the inferior borders of the PMT and ET cartilage (F_{LVP} in Fig. 3A) were identified for specification of boundary conditions. Similar boundary condition locations were utilized in a previously developed 2D FEM of static ET function (17). Also, the insertion angle of the mTVP was measured at two locations, the superior PMT-cartilage junction (θ_s) and the inferior-lateral surface of the PMT (θ_l). Contour tracings were imported into the ADINA finite element program (Watertown, MA) which was used to mesh the cartilage and PMT tissue into the six-node triangular finite elements (see Figure 3A). Tissue deformation and lumen opening were simulated by either applying an oscillatory pressure to the lumen

interior (P_{lumen} in Fig. 3A) to simulate oscillatory FRT conditions or applying mTVP and mLVP muscle forces on the appropriate surfaces in a time dependent manner to simulate swallowing during a standard FRT. All simulations in this study used a no-slip boundary condition to model the fixed attachment of the medial-superior cartilage surface with the cranial base. In addition, the interior surfaces of the lumen were defined as contact surfaces to prevent element overlap. Although our previous study (17) assumed hyperelastic tissue properties, in order to accurately simulate the transient dynamics of ET function observed during both the standard FRT and oscillatory ETC test, this study utilizes viscoelastic tissue properties based on data obtained in each subject (see below).

Specification of Tissue Mechanical Properties

For purposes of functional modeling, the mechanical properties of the cartilage and PMT were specified. The cartilage was modeled as a neo-Hookean elastic solid with a shear modulus, G , equal to $E/[2*(1+\nu)]$, and a bulk modulus, κ , equal to $E/[3*(1-2\nu)]$, where E is the Young's modulus and ν is the Poisson's ratio. The Young's modulus for the cartilage was assigned a value of 3.4MPa based on *ex-vivo* measurements in conchal cartilage (18) and the cartilage was assumed to be nearly incompressible, $\nu=0.49$. The use of a hyperelastic neo-Hookean constitutive model for soft biological tissues is well established (19–20) and more accurately simulates the potentially large tissue deformations (i.e. strains > 5%) when compared to simple linear elastic models. The viscoelastic properties of the PMT was modeled using a Maxwell viscoelastic constitutive relationship with a time-dependent Young's Modulus, shear modulus and bulk modulus defined by,

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

where $\tau_r=\mu_{\text{PMT}}/E_{\text{PMT}}$ is the relaxation time and μ is the viscosity of the tissue. This material model is implemented in the finite element formulation through the following convolution integrals which relate stress and strain history.

$$\begin{aligned} s_{ij}(t) &= 2G(0)e_{ij}(t) + 2 \int_0^t e_{ij}(t-\tau) \frac{dG(\tau)}{d\tau} d\tau \\ \sigma_{kk}(t) &= 3K(0)e_{kk}(t) + 3 \int_0^t e_{kk}(t-\tau) \frac{dK(\tau)}{d\tau} d\tau \end{aligned} \quad (2)$$

where $s_{ij}=\sigma_{ij}-\frac{1}{3}\delta_{ij}\sigma_{kk}$ is the deviatoric stress, $e_{ij}=\varepsilon_{ij}-\frac{1}{3}\delta_{ij}\varepsilon_{kk}$ is the deviatoric strain, δ_{ij} is the Kronecker delta, σ_{ij} is the stress, and ε_{ij} is the strain. Maxwell viscoelastic models have been used previously to describe soft biological cells and tissues and implementation of the decay functions for $G(t)$ and $\kappa(t)$ is straightforward in the ADINA FE package (21). We also note that this viscoelastic formulation is compatible with the large deformation solvers used in the ADINA software package (22).

The measurements of ETC and η obtained in each subject during the oscillatory FRT (see Table I) were used to individualize the generalized FEM. Specifically, the ETC and η measured in each subject was used to calculate the PMT viscoelastic properties E_{PMT} and μ_{PMT} . First, the generalized FEM was used to simulate the oscillatory FRT protocol by applying an oscillatory pressure, $P_{\text{lumen}}(t)=P_a+P_o*\sin(\omega t)$ to the lumen surface where $P_{\text{lumen}}(t)$ had a range and oscillation period corresponding to the average values observed

during testing; i.e. $P_a=200$ mmH₂O, $P_o=100$ mmH₂O and $\omega=0.087$ rad/s. For these simulations, the PMT was assumed to be nearly incompressible ($\nu=0.49$), the cartilage was modeled with neo-hookian properties (see above) and zero mLVP and mTVP forces were imposed. The applied pressures resulted in time-dependent changes in cross-sectional lumen area, $A(t)$. The shape independent area $A_2(t)=A(t)/\Gamma_S^{1/2}$, where Γ_S is the hydraulic-geometric shape factor, and time derivative of $A_2(t)$, $dA_2(t)/dt$, were then calculated as previously described (14). A least-squared regression was performed using the following tube law to determine ETC and η .

$$P(t)=\frac{A_2(t)}{ETC}+\eta\frac{dA_2(t)}{dt} \quad (3)$$

The ETC and η values obtained from the nonlinear regression were then compared to the experimentally measured values for a given subject. The E_{PMT} and μ_{PMT} specified in the FEM were then adjusted and the simulation and regression analysis repeated until the regression values of ETC and η obtained in the computational models were within 10% of the experimental measurements. The results of this analysis are reported in Table I for the 5 subjects and demonstrate the close match between the measured and simulated PMT properties.

Simulation of Dynamic ET Opening Phenomena

Once the appropriate E_{PMT} and μ_{PMT} values were specified for each subject, dynamic changes in ET luminal area during swallowing and muscle contraction were simulated. First, a constant intraluminal pressure, P_{lumen} , was applied to the lumen to simulate the steady-state pressure and flow conditions prior to a swallow. We then applied time-dependent mTVP and mLVP muscle forces to the ET cartilage and PMT structures. The temporal profile of mTVP mLVP forces used in this study are shown in Figure 3B and were obtained by multiplying the magnitudes of the applied mTVP and mLVP forces, F_{TVP} and F_{LVP} , by time functions which incorporated a sustained mLVP force application and a rapid mTVP force application that could occur before, during or after the mLVP force application. The shape of these muscle force profiles are based on previous electromyography (EMG) studies which documented asynchronous mTVP and mLVP EMG activity during swallowing and also demonstrated that mLVP EMG activity is sustained for longer times compared with the mTVP (23–24). Short duration EMG for mTVP was assumed to produce a simple positive half sine wave with a duration of t_3 seconds. Sustained EMG activity for the mLVP was assumed to result in tetanic contraction where the muscle rapidly obtains maximal isometric tension and remains at this tension until the EMG activity ceases (25). The LVP time function therefore consisted of a quarter sine wave from 0 to 1 with a duration of t_1 seconds followed by constant phase with a duration of t_4 seconds and finally a quarter sine wave from 1 to 0 with duration t_1 . Note that we assume that the time required to reach maximum isometric tetanic tension, t_1 , is the same as the time required for decay of contraction, t_1 . This assumption allows us to minimize the number of “free” parameters in our model and leads to more a stable least-squared algorithm (see below). The time between onset of mLVP and mTVP force applications was defined as t_2 seconds which could be either positive (mTVP force application after mLVP) or negative (mTVP force application before mLVP).

The location and direction of the applied mTVP and mLVP forces were consistent with our previous study (17). Briefly, contraction of the mTVP was simulated by applying forces to the lateral surfaces of the cartilage and PMT. mTVP force vectors applied to the cartilage were directed at an angle θ_S and the force vector applied to the PMT varied from θ_S to θ_1 to

account for the variation in insertion angles observed by Takasaki et al. (26). The total TVP force, F_{TVP} , was uniformly distributed over the cartilage and PMT surfaces while the mLVP force, F_{LVP} , was modeled as a distributed load $w = F_{LVP}/L_{LVP}$ where L_{LVP} is the contact length of mLVP with cartilage and PMT tissues. Note that for the current study, we assume uniform expansion of the LVP and thus uniform application of mLVP forces.

Data analysis and Correlation with Experiments

Application of time-dependent muscle forces resulted in dynamic changes in open lumen area as a function of time, $A(t)$. This area was used to determine the hydraulic-geometric shape factor, $\Gamma_s(t)$, which accounts for the non-circular shape of the lumen (14) and to calculate a transient flow resistance parameter during swallowing,

$$R_v(t) = \frac{\mu_a L \Gamma_s(t)}{A(t)^2} \quad (4)$$

where L is the assumed length of the ET (3 cm) and μ_a is the viscosity of air. A non-linear least squared regression algorithm was then used to correlate the computational prediction of $R_v(t)$ calculated in Eqn. (4) with the experimental measurements of $R_v(t)$ obtained in each subject, e.g. Fig 1C. For these purposes, the function, $R_v(t)$, included the time interval during muscle force applications as well as a lead-in time of one second to account for baseline conditions. A regression algorithm, written in MATLAB, was then used to vary seven “free” parameters, P_{lumen} , F_{TVP} , F_{LVP} , t_1 , t_2 , t_3 and t_4 , and to obtain the parameter set that produced the best fit between the experimentally measured and computational values of $R_v(t)$. The strength of the correlation was monitored by calculating the coefficient of determination (r^2) which is a measure of the percent variance explained by the regression.

III. Results

There were no adverse events (e.g. secondary infection of the middle ear, hearing loss etc.) associated with the myringotomy procedure and all tympanic membrane perforations healed within 1 week. As shown in Table I, analysis of the standard and oscillatory FRT data yielded a distribution of opening pressures, P_{open} , ET compliance, ETC, and ET hysteresis, η . The average ($\pm$ std) P_{open} was 394 ± 109 mmH₂O, the average ETC was $10.3 \pm 5.80 \times 10^{-7}$ cm²/mmH₂O and the average η was $6.49 \pm 2.55 \times 10^8$ Poise/cm². Table I also shows the viscoelastic tissue properties, E_{PMT} and μ_{PMT} , obtained for each subject by correlating computational simulations of the oscillatory ETC test with experimental data. The simulation values of ETC and η are in excellent agreement with the experimental measures and the average ($\pm$ std) of E_{PMT} was 258 ± 159 kPa and the average μ_{PMT} was 94.0 ± 34.4 kPa*sec.

The standard FRT was performed in all five subjects and a single swallowing event was captured in three subjects while two swallowing events were captured in two subjects. As a result, seven different active resistance functions were available for analysis (Figure 4). These functions include a lead-in ET luminal resistance which corresponds to the passive resistance at the steady-state condition. This was followed by a resistance waveform with regions of greater and lesser resistances than the lead-in resistance which reflects the changes in ET luminal resistance during swallowing. Resistances less than the lead-in resistance indicate periods of further tubal dilation while those greater than the lead-in resistance indicate periods of partial tubal constriction. There was a wide variation in these waveforms both between and within individuals. In addition to the raw experimental data (circles in Fig 4), Fig. 4 also shows the corresponding resistance vs. time functions predicted by the FEM simulation using the least-squared regression algorithm (solid lines). The best

fit parameters obtained for each waveform is listed in Table II along with the coefficient of determination (r^2). The high r^2 values for all examples indicate an excellent fit of the simulated data to the observed waveforms.

Figure 5 shows the corresponding F_{TVP} and F_{LVP} timing sequences for each of the seven waveforms shown in Figure 4. For 2 waveforms (AM105-1 and AM105-2), the F_{TVP} was applied to the ET prior to F_{LVP} , while in the other waveforms the F_{LVP} was applied to the ET prior to F_{TVP} . In general, earlier mTVP force application to the ET relative to mLVP force application resulted in a waveform characterized by an initially lower resistance *vis a vis* the steady state resistance followed by a variable period of higher resistance, while delaying the timing between the mLVP and mTVP force applications caused an initially higher pre-swallow resistance *vis a vis* the steady state resistance followed by a decreased resistance.

IV. Discussion

The results of the present study emphasize the ability of the developed finite element models to reproduce the results of ET function tests. Specifically, when appropriately parameterized, those models can simulate both the oscillatory ETC test and the active flow resistance patterns recorded during the standard FRT in individual subjects with high fidelity. A primary finding of those simulations is that the resistance vs. time functions for the FRT documented during swallowing can be reproduced by varying the timing of mLVP and mTVP force applications to the ET. Early studies in animals demonstrated that mLVP EMG activity is observed much earlier than mTVP activity (24) during swallowing events. However, it should be noted that mLVP EMG activity does not necessarily correlate with mLVP force application to the ET since onset of EMG activity is primarily associated with initial elevation of the soft palate. Although palatal elevations may not have a direct effect on the ET during activities such as speech (27–29), soft palate elevations have been correlated with constriction during the FRT in children with otitis media with effusion (7). Indeed, some studies suggest that the timing between palatal elevations and ET openings by mTVP activity is highly variable (30), a result supported by the wide variation in force application waveforms predicted by the FEM analysis (see Fig. 5).

Previous studies in patients with otitis media did not document a myogenic origin for the associated ET dysfunction (23,31). However, those studies generally focused on the EMG activity of each paratubal muscle in isolation and did not consider the phase relationships between the activities for the two muscles. The current computational analysis of experimental waveforms obtained during the FRT indicates that the relative timing between mLVP and mTVP force application is an important determinant of lumen constriction in normal adults. Specifically, if the forces due to elevation of the soft palate via mLVP contraction during swallowing occur before the application of the mTVP forces, pressure-flow patterns exhibit a clear “pre-swallow” constriction of the lumen prior to the larger lumen dilation. In addition, if the duration of the mLVP forces is long enough such that it persists beyond the transient application of mTVP forces, this can result in a “post-swallow” constriction of the lumen following dilation.

We note that the FRT responses analyzed in the current study from normal adult subjects did not show evidence of ET dysfunction since all subjects were able to generate significant tubal dilations and lower active resistance values (i.e. a tubal dilatory efficiency >1). Rather, the analyzed responses, which focused on perturbations in the cross-sectional area of the tubal lumen during swallowing, document how relative muscle timings influence the presence of pre-swallow or post-swallow constrictions patterns. Although partial lumen constrictions did not result in complete closure for normal adults, experimental studies (7)

clearly indicate that during inflammatory otitis media these constrictions become “irreversible” due to the presence of adhesion forces within the ET lumen. As a result, an understanding of how changes in muscle timing patterns influence the presence and/or magnitude of the pre-swallow constriction might be important in understanding disease pathogenesis.

Although simulation of “irreversible” constriction is beyond the scope of the current study (see below), we have used data from the current study to investigate the sensitivity of pre-swallow constriction behavior to the relative delay time between mTVP and mLVP force application. For this analysis, we calculated the relative change in pre-swallow resistance as $\Delta R_v = R_v^{\text{pre}} - R_s$, where R_v^{pre} is the maximum simulated pre-swallow resistance and R_s is the steady-state resistance before application of muscle forces. In addition to relative delay timings, the magnitude of ΔR_v may also depend on the magnitude of mLVP forces applied to the ET, F_{LVP} , as well as the ET compliance, ETC. Specifically, larger F_{LVP} and ETC would lead to more tissue deformation, more lumen constriction (i.e. larger R_v^{pre}) and thus a larger ΔR_v . Therefore, a normalized form of ΔR_v , $\Delta R_v / (F_{\text{LVP}} * \text{ETC})$, is plotted in Figure 6 as a function of t_2 , the delay time between mTVP and mLVP force application where circles represent data from the seven different active resistance functions and the line represents a fit of the data to a sigmoidal function. For small and/or negative t_2 values, the mTVP force application occurs early enough such that there is minimal increase in pre-swallow resistance, i.e. $\Delta R_v \approx 0$. However, the amount of pre-swallow lumen constriction is highly sensitive to the delay timings between mLVP and mTVP force applications as evidenced by the sharp increase in ΔR_v at $t_2 \sim 0.2$ sec. This data indicates that a delay timing between mLVP and mTVP force application greater than ~ 0.2 seconds strongly promotes lumen constriction which may in turn promote “irreversible” constriction during inflammatory otitis media.

As with all computational studies, the current models contain limitations which should be addressed in future studies that seek to apply these models to otitis media prone populations. First, although the current models can simulate friction-free contact between the medial and lateral side of the lumen, these models cannot simulate the adhesion forces responsible for “irreversible” constriction during inflammatory Otitis media. These adhesion forces may be due to glycoprotein interactions (32) and/or surface tension forces (15). Therefore, in order to investigate how the constriction/dilation patterns observed during swallowing influence ET dysfunction (i.e. irreversible constriction), future studies should focus on developing computational models that account for these adhesion dynamics. In addition, morphological alterations in tissue structures may significantly influence constriction/dilation patterns during swallowing. Specifically, several populations with a high risk for developing ET dysfunction and otitis media, i.e. young children and cleft palate subjects, have known morphological alterations compared with adults. Future studies could investigate how muscle timings influence constriction/dilation patterns in these patient populations by applying the modeling techniques described in this manuscript to the appropriate histological data sets.

Although the current models were able to reproduce the experimentally measured resistance waveforms with high fidelity ($r^2 > 0.76$), we note that the experimental data was not “perfectly” fitted in certain regions. For example, the swallow profile for AM100-2 documents a long steady elevation of resistance after dilation that is not captured by the current computational models. We speculate that this deviation may be due to adhesive interactions within the ET and that advanced models that allow for the formation and rupture of adhesive bonds within in the ET (see above) may be required to capture this sustained elevation in resistance. We also note that for swallow profiles AM100-1 and AM110 there is a small dilation (decrease in R_v) following the second contraction (increase in R_v) that is not

captured by our current models. The inability to capture this “post-contraction” behavior may be due to the fact that our current models are 2-dimensional and only account for anatomical relationships in one cross-sectional plane of the ET. However, the ET has a very complex 3-dimensional morphology and advanced FEM models that account for the full 3D anatomy of the ET might be needed to capture “post-contraction” phenomena. Alternatively, the inability to capture the “post-contraction” behaviors may be due to the fact that we have assumed relatively simple muscle force profiles (Figure 3B) in order to minimize the number of free parameters in our model. However, the “true” muscle force profile might be more complicated, i.e. the time required to reach maximum isometric tetanic tension in the mLVP may not be equal to the time required for decay of contraction. Although future models could explore if more complicated muscle force timing patterns can capture “post-contraction” behaviors, this increase in complexity (i.e. increase in the number of free parameters) would have to be balanced with the potential for numerical instabilities in the least-squared regression algorithm.

In summary, by correlating computational simulations with experimental data, we have demonstrated that the dynamic pressure-flow rate patterns observed during swallowing in normal adults is due to changes in relative timings of mLVP and mTVP force application to the ET. Our correlations also strongly indicate that mLVP forces promote constriction of the ET lumen and that the development of pre-swallow constrictions is highly sensitive to delay timings. Future applications and development of advanced models that account for inflammatory conditions may be useful in identifying the biomechanical and anatomical mechanisms of ET dysfunction in patients with otitis media.

Acknowledgments

This work was supported in part by NIH/NIDCD grants DC007230 and DC007667. We thank Dr. Charles Bluestone for performing the myringotomies, Ms. Julianne Banks for her assistance in preparing the histological specimens and Dr. William J. Doyle for editorial assistance in the preparation of the manuscript.

References

1. Bluestone CD, Doyle WJ. Anatomy and physiology of eustachian tube and middle ear related to otitis media. *J Allergy Clin Immunol* 1988 May;81(5 Pt 2):997–1003. [PubMed: 3286738]
2. Bluestone CD. Current concepts in eustachian tube function as related to otitis media. *Auris Nasus Larynx* 1985;12 Suppl 1:S1–S4. [PubMed: 3915201]
3. Cantekin EI, Saez CA, Bluestone CD, Bern SA. Airflow through the eustachian tube. *Ann Otol Rhinol Laryngol* 1979 Sep–Oct;88(5 Pt 1):603–612. [PubMed: 573980]
4. Doyle WJ, Cantekin EI, Bluestone CD. Eustachian tube function in cleft palate children. *Ann Otol Rhinol Laryngol Suppl* 1980 May–Jun;89(3 Pt 2):34–40. [PubMed: 6778343]
5. Cantekin EI. Eustachian tube function in children with tympanostomy tubes. *Auris Nasus Larynx* 1985;12 Suppl 1:S46–S48. [PubMed: 3915208]
6. Doyle WJ, Reilly JS, Jardini L, Rovnak S. Effect of palatoplasty on the function of the Eustachian tube in children with cleft palate. *Cleft Palate J* 1986 Jan;23(1):63–68. [PubMed: 3484683]
7. Takahashi H, Miura M, Honjo I, Fujita A. Cause of eustachian tube constriction during swallowing in patients with otitis media with effusion. *Ann Otol Rhinol Laryngol* 1996 Sep;105(9):724–728. [PubMed: 8800060]
8. Swarts JD, Bluestone CD. Eustachian tube function in older children and adults with persistent otitis media. *Int J Pediatr Otorhinolaryngol* 2003 Aug;67(8):853–859. [PubMed: 12880664]
9. Beery QC, Doyle WJ, Cantekin EI, Bluestone CD, Wiet RJ. Eustachian tube function in an American Indian population. *Ann Otol Rhinol Laryngol Suppl* 1980 May–Jun;89(3 Pt 2):28–33. [PubMed: 6778327]
10. Rood SR, Doyle WJ. The nasopharyngeal orifice of the auditory tube: implications for tubal dynamics anatomy. *Cleft Palate J* 1982 Apr;19(2):119–128. [PubMed: 6951658]

11. Finkelstein Y, Talmi YP, Nachmani A, Hauben DJ, Zohar Y. Levator veli palatini muscle and eustachian tube function. *Plast Reconstr Surg* 1990 May;85(5):684–692. discussion 93–97. [PubMed: 2326351]
12. Rood SR, Doyle WJ. Morphology of tensor veli palatini, tensor tympani, and dilator tubae muscles. *Ann Otol Rhinol Laryngol* 1978 Mar–Apr;87(2 Pt 1):202–210. [PubMed: 646288]
13. Ghadiali SN, Federspiel WJ, Swarts JD, Doyle WJ. Measurement of the viscoelastic compliance of the eustachian tube using a modified forced-response test. *Auris Nasus Larynx* 2002 Jan;29(1):1–5. [PubMed: 11772482]
14. Ghadiali SN, Swarts JD, Federspiel WJ. Model-based evaluation of eustachian tube mechanical properties using continuous pressure-flow rate data. *Ann Biomed Eng* 2002 Sep;30(8):1064–1076. [PubMed: 12449767]
15. Ghadiali SN, Banks J, Swarts JD. Effect of Surface Tension and Surfactant Administration on Eustachian Tube Mechanics. *Journal of Applied Physiology* 2002;93:1007–1014. (Journal Article). [PubMed: 12183497]
16. Ghadiali SN, Swarts JD, Doyle WF. Effect of Tensor Veli Palatini Muscle Paralysis on Eustachian Tube Mechanics. *Annals of Otology, Rhinology, and Laryngology* 2003;112(8):704–711.
17. Ghadiali SN, Banks J, Swarts JD. Finite element analysis of active Eustachian tube function. *J Appl Physiol* 2004 Aug;97(2):648–654. [PubMed: 15047672]
18. Zahnert T, Huttenbrink KB, Murbe D, Bornitz M. Experimental investigations of the use of cartilage in tympanic membrane reconstruction. *Am J Otol* 2000;21(3):322–328. [PubMed: 10821543]
19. Qi L, Funnell WR, Daniel SJ. A nonlinear finite-element model of the newborn middle ear. *J Acoust Soc Am* 2008 Jul;124(1):337–347. [PubMed: 18646981]
20. Qi L, Liu H, Lutfy J, Funnell WR, Daniel SJ. A nonlinear finite-element model of the newborn ear canal. *J Acoust Soc Am* 2006 Dec;120(6):3789–3798. [PubMed: 17225406]
21. Karcher H, Lammerding J, Huang H, Lee RT, Kamm RD, Kaazempur-Mofrad MR. A three-dimensional viscoelastic model for cell deformation with experimental verification. *Biophys J* 2003 Nov;85(5):3336–3349. [PubMed: 14581235]
22. Bathe, KJ. *Finite Element Procedures*. New Jersey: Prentice-Hall; 1996.
23. Honjo I, Kumazawa T, Honda K, Shimojo S. Electromyographic study of patients with dysfunction of the Eustachian tube. *Arch Otorhinolaryngol* 1979;222(1):47–51. [PubMed: 426723]
24. Honjo I, Ushiro K, Nozoe T, Okazaki N. Cinerentgenographic and electromyographic studies of Eustachian tube function. *Arch Otorhinolaryngol* 1983;238(1):63–67. [PubMed: 6882281]
25. Widmaier, EP.; Raff, H.; Strang, KT. *Vander's human physiology : the mechanisms of body function*. 11th ed. Boston: McGraw-Hill Higher Education; 2008.
26. Takasaki K, Sando I, Balaban CD, Miura M. Functional anatomy of the tensor veli palatini muscle and Ostmann's fatty tissue. *Ann Otol Rhinol Laryngol* 2002 Nov;111(11):1045–1049. [PubMed: 12450182]
27. Moon JB, Collins DR, Canady JW. Single motor unit activity in levator veli palatini during speech and nonspeech tasks. *Cleft Palate Craniofac J* 2003 May;40(3):256–262. [PubMed: 12733953]
28. Kuehn DP, Moon JB. Velopharyngeal closure force and levator veli palatini activation levels in varying phonetic contexts. *J Speech Lang Hear Res* 1998 Feb;41(1):51–62. [PubMed: 9493733]
29. Niimi S. Pharyngeal wall movement during speech. *Auris Nasus Larynx* 1981;8(1):27–34. [PubMed: 7283886]
30. Hamlet SL, Momiyama Y. Velar activity and timing of eustachian tube function in swallowing. *Dysphagia* 1992;7(4):226–233. [PubMed: 1424836]
31. Sapci T, Mercangoz E, Evcimik MF, Karavus A, Gozke E. The evaluation of the tensor veli palatini muscle function with electromyography in chronic middle ear diseases. *Eur Arch Otorhinolaryngol* 2008 Mar;265(3):271–278. [PubMed: 17851675]
32. Caye-Thomasen P, Tos M. Eustachian tube gland changes in acute otitis media. *Otol Neurotol* 2004 Jan;25(1):14–18. [PubMed: 14724485]

Figure 1.

Figure 1ABC: A) Pressure and flow rate recorded during a standard FRT. B) Temporal patterns of pressure and flow rate during a swallowing event. C) Dynamic resistance to airflow (R_v), defined as pressure/flow rate during the swallowing event.

Figure 2.

Example pressure-flow rate (P-Q) loop obtained during the oscillatory FRT in one adult subject. Points represent raw experimental data. Solid line represents the correlation with the mathematical model used to determine ETC and η (14).

Figure 3. Figure 3AB: A) Generalized 2D FEM of ET and locations of boundary conditions, applied muscle forces (F_{LVP} and F_{TVP}) and lumen pressure (P_{lumen}). B) Asynchronous muscle timing sequence for mLVP and mTVP force application.

Figure 4. Seven different dynamic resistance functions measured in five different subjects. Open circles represent raw experimental measurements while solid lines represent computational predictions of flow resistance as a function of time obtained via the least-squared regression algorithm.

Figure 5. Muscle timing profiles of mLVP and mTVP used to obtain the correlations shown in Figure 4.

Figure 6.

Sensitivity of pre-swallow resistance magnitude (ΔR_v) with delay timing between mLVP and mTVP force application (t_2). ΔR_v data is normalized with respect to mLVP force and ET compliance measured in each subject.

Table I

Oscillatory FRT measurements (P_{open} , ETC and η) in 5 adult subjects. Tissue mechanical properties (E_{PMT} and μ_{PMT}) obtained by correlating computational predictions of ETC and η with experimental data.

Patient	P_{open} (mmH ₂ O)	Experimental ETC ($\times 10^{-7}$ cm ² /mmH ₂ O)	Experimental η ($\times 10^8$ Poise/cm ²)	E_{PMT} (kPa)	μ_{PMT} (kPa-s)	Predicted ETC ($\times 10^{-7}$ cm ² /mmH ₂ O)	Predicted η ($\times 10^8$ Poise/cm ²)
AM100	325	12.3	3.01	190	43.8	12.5	3.00
AM101	566	6.18	9.76	294	138	6.22	9.52
AM105	403	3.88	7.99	509	109	3.90	7.88
Am107	279	18.8	6.11	83.1	92.9	19.2	5.63
AM110	397	10.2	5.58	214	86.4	10.3	5.46

Table II

Muscle timing and force parameters obtained by correlating computational predictions of $R_v(t)$ with experimental data.

Swallow pattern #	F _{TVP} (N)	F _{LVP} (N)	t ₁ (sec)	t ₂ (sec)	t ₃ (sec)	t ₄ (sec)	R ²
AM100-1	146	89.1	0.49	0.12	0.67	0.49	0.967
AM100-2	97.5	43.5	0.48	0.21	0.53	1.5	0.761
AM101	20.0	19.3	0.65	0.65	0.90	0.25	0.796
AM105-1	108	68.8	0.28	-0.0999	0.88	1.2	0.914
AM105-2	122	77.4	0.50	0.00	0.80	1.0	0.944
AM107	37.1	23.1	0.88	0.24	2.02	2.81	0.952
AM110	67.7	41.3	0.26	0.28	0.46	0.33	0.892