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UPPER AIRWAY ELASTICITY ESTIMATION IN PEDIATRIC DOWN SYNDROME SLEEP APNEA PATIENTS USING COLLAPSIBLE TUBE THEORY

Dhananjay Radhakrishnan Subramaniam¹, Goutham Mylavarapu¹, Keith McConnell⁷, Robert J. Fleck⁶, Sally R. Shott^{2,5}, Raouf S. Amin^{3,4}, and Ephraim J. Gutmark^{1,2,†}

¹Department of Aerospace Engineering and Engineering Mechanics, University of Cincinnati, Cincinnati, OH

²Department of Otolaryngology – Head and Neck Surgery, University of Cincinnati Medical Center, Cincinnati, OH

³Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

⁴Department of Pediatrics, University of Cincinnati, College of Medicine, Cincinnati, OH

⁵Department of Pediatric Otolaryngology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

⁶Division of Pediatric Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

⁷Division of Pulmonary Biology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Abstract

Elasticity of the soft tissues surrounding the upper airway lumen is one of the important factors contributing to upper airway disorders such as snoring and obstructive sleep apnea. The objective of this study is to calculate patient specific elasticity of the pharynx from Magnetic Resonance (MR) images using a 'tube law' i.e. the relationship between airway cross-sectional area and transmural pressure difference. MR imaging was performed under anesthesia in children with Down syndrome (DS) and obstructive sleep apnea (OSA). An airway segmentation algorithm was employed to evaluate changes in airway cross-sectional area dilated by continuous positive airway pressure (CPAP). A pressure-area relation was used to make localized estimates of airway wall stiffness for each patient. Optimized values of patient specific Young's modulus for tissue in the velopharynx and oropharynx, were estimated from finite element (FE) simulations of airway collapse. Patient specific deformation of the airway wall under CPAP was found to exhibit either a non-linear 'hardening' or 'softening' behavior. The localized airway and tissue elasticity were found to increase with increasing severity of OSA. Elasticity based patient phenotyping can potentially assist clinicians in decision making on CPAP and airway or tissue elasticity can supplement well-known clinical measures of OSA severity.

[†]Corresponding author: Department of Aerospace Engineering & Engineering Mechanics, University of Cincinnati; 799 Rhodes Hall, Cincinnati, OH 45221-0070, USA. ephraim.gutmark@uc.edu (Ephraim J. Gutmark) Tel: 1-513-556-1227, Fax: 1-513-556-5038.

Key Terms

OSA; MRI; CPAP; tube law; elastic modulus; finite element analysis

1. Introduction

Sleep is accompanied by the physiologic relaxation of the muscles and soft tissue supporting the upper airway. Obstructive sleep apnea (OSA) is associated with partial or complete collapse of upper airway during sleep and often results from poor muscle tone and airway patency. Patency of the upper airway is controlled by a balance between forces in the soft tissue tending to dilate the airway and forces that promote airway collapse⁷. Airway narrowing or occlusion is likely to occur when the latter exceeds the former. The degree of relaxation varies across individuals and determines the severity of OSA. Polysomnography (PSG)¹² and tracheal breath sound analysis³⁵ are some of the diagnostic tests for OSA.

Several factors including ethanol ingestion⁶ and presence of fat deposits⁴³ result in reduced muscle tone during sleep thereby leading to an imbalance between dilatory and collapsing forces. The difference between the extraluminal tissue pressure and intraluminal pressure is known as transmural pressure. The value of transmural pressure at which the pharyngeal airway collapses completely is known as the critical transmural pressure (P_{crit})³⁹. Apnea-Hypopnea Index (AHI) is defined as the number of events per hour, when the airflow reduces (hypopnea) or ceases to flow (apnea) in the upper airway⁴². Both, P_{crit} and AHI indicate the level of OSA severity.

Hypotonia, obesity, midface hypoplasia, relative macroglossia, and excessively large tonsils and adenoids are some of the factors influencing pharyngeal airway collapse in DS pediatric patients⁴⁷. Decrease in airway muscular tone associated with anesthesia and sedation¹⁵, as well as the supine position, leading to changes in the anatomic positioning of structures that surround the airway is more pronounced in children with DS than other children. The current treatment options for OSA in pediatric patients, include both non-surgical options such as nasal continuous positive airway pressure (nCPAP) as well as surgical procedures such as removal of the tonsils and adenoids (T&A) the most commonly used first line treatment^{4, 51}. For OSA persistent after T&A, other surgeries such as midline posterior glossectomy and mandibular advancement are available. However, these surgeries have only had moderate success rates^{46, 47}. Improved understanding of the interaction between flow-induced forces and upper airway soft tissue can guide treatment and improve surgical outcomes.

Interest in patient specific airway modeling has increased greatly in the past decade⁵⁴. Computational tools enable accurate reconstruction of anatomical geometries from Magnetic Resonance (MR) images or Computed Tomography (CT) scans. Efficient computer codes can calculate flow features such as pressure and shear stress in an airway^{31, 32, 37, 52}, and also flow induced structural deformation of tissue⁵⁴. These simulations require inlet and outlet flow conditions and accurate elastic properties of the tissues. Published quantification of soft tissue elasticity is based on in-vivo experiments in cadavers or computational studies of simplified anatomical models, using prior knowledge of the various forces, boundary

conditions and resulting displacements. The major limitation of these studies is cadaver tissue properties are very different than live tissue and it varies significantly between individuals. Recently, a non-invasive method based on MR elastography has been developed to estimate material properties of the tongue and soft palate in control subjects¹⁰ and OSA patients⁸ during wakefulness.

The present paper models the interaction between the transmural pressure and the pharyngeal airway as a collapsible section¹. A tube law^{44, 50} has been used to describe pressure-area relations and flow limitation in the upper airway^{21, 22}. We employed the tube law to evaluate the pharyngeal stiffness and non-linearity of airway elasticity in pediatric OSA patients with DS (Section 2.3 and 3.1). We also developed and validated a methodology to iteratively estimate the patient specific mechanical properties of airway tissue from numerical simulations of airway collapse (Section 2.4 and 3.2). We performed this study to test the hypothesis that pharyngeal airway stiffness and Young's modulus of airway tissue in sedated patients, decreases with increasing severity of OSA. We present details of patient recruitment, experimental setup and acquisition of images in Section 2.1. We describe the algorithm employed to identify the airway boundary and its validation in Section 2.2.

2. Materials and Methods

2.1 MR Image Acquisition

The diagnostic sleep and MR imaging studies described in this section were approved by the Institutional Review Board (IRB). Overnight polysomnography was performed on volunteer patients using a computerized system (Grass-Telefactor, Astro Med Inc., West Warwick, RI) to record electroencephalogram (EEG), electrooculogram, electromyogram, electrocardiogram, desaturation index and AHI⁴⁷. A light anesthesia was provided by an anesthesiologist using dexmedetomidine, a sedative that reduces pharyngeal muscle tone and simulates natural sleep with minimal respiratory depression³⁸. The anesthetic dose was patient specific and dependent on the subject's BMI²⁰. MR images of twenty-two pediatric DS sleep apnea patients, with AHI ≥ 5 were obtained using a 1.5-THDxt MRI scanner (software version 16; General Electric), once adequate depth of anesthesia was attained. The patients were in a supine position with head and neck placed in a vascular coil. An adhesive tape was used to secure the subject's head to the vascular coil and minimize patient head motion²⁸. The imaging sequence was a 3-dimensional (3D) fast spin echo with proton density weighting (CUBE). Specific parameters included echotrain length, 64; acquisition matrix, 256 by 256; slice thickness, 1.60 mm and slice interval, 0.80 mm. The scans were obtained during the peak expiratory breathing phase at three pressures: zero pressure (baseline) and two positive pressures (CPAP1, CPAP2). A modified BiPAP device (Phillips Respironics Inc.) was used to record normalized inspiratory flow rate and administer CPAP using a face mask approved by the IRB. It should be noted that the choice of CPAP2 was patient specific and was based on the collapsibility or size of the airway. The highest CPAP level was below complete elimination of flow limitation. Narrow or extremely floppy airways needed a higher mask pressure to maintain airway patency²³. CPAP1 was a value of mask pressure greater than zero and approximately midway between baseline and CPAP2.

Exclusion criteria included: collapsed airway during baseline, paradoxical breathing, open oral airways, patient movement, or awakening during scan, and low quality scans that were not suitable for automated computer analysis. Patients included in our study depicted a reduction in the airflow channel, only with slight phase shifts in the abdominal and thoracic movements. On the other hand, patients who exhibited paradoxical breathing had thoracic and abdominal movement signals that were completely out of phase. In patients who awoke, the arousal did not follow the apneic event and therefore was not clinically significant. The arousal was recorded by a sleep technician and based on examination of body movements. The protocol to calculate P_{crit} of a patient under anesthesia includes gradual reduction of the mask pressure approaching conditions of total collapse. P_{crit} was calculated by extrapolating to zero flow the linear portion of the curve relating the negative pressure to flow³⁹. Additional details of P_{crit} , including the pressure-flow curve are described in section 3.2. Table 1 summarizes 22 patient's demographics, AHI, P_{crit} and the positive pressures at which scans were obtained.

2.2 Airway Segmentation

Airway boundaries of the baseline, CPAP1 and CPAP2 were identified in MR scans, using an in-house MATLAB based thresholding algorithm⁴¹. The algorithm was designed to read in an image and increase the contrast by mapping the intensity values to new values such that 1% of data was saturated at low and high intensities. After cropping to the region of interest, the grayscale image was converted to a binary image using a normalized threshold level of around 0.05. The airway was identified in the output binary image where all pixels with luminance greater than 0.05 were replaced with the value 1 and the remaining pixels were assigned a value of 0. Segmentation was performed using the axial scans from the hard palate to the base of tongue (Fig. 1a). The airway boundaries in the mid sagittal and mid coronal planes are shown in Figs. 1b and 1c, respectively, for the three pressures. The pixel values of the airway approximated as a polygon were converted to Cartesian co-ordinates using spatial transformations. The high spatial resolution of the axial image slices (512×512 pixels) enabled us to compute the airway cross-sectional area by counting the pixels and multiplying by pixel area. The process was repeated for each axial image slice that is part of the pharynx, to obtain the variation in the cross-sectional area of the baseline and dilated airways along the airway length (Fig. 1d). Variation in position and angulation of the airway with respect to image slices may generate spurious values of airway area changes. Thereby, the slice orientation was used to correct the areas for angulation using simple trigonometric identities.

A modified two dimensional Shepp-Logan phantom⁴⁵ was employed to determine the accuracy of the segmentation algorithm (Fig. 2a). The gray levels depicted in the phantom are similar to those observed in MR or CT images of the human airway. Figure 2b indicates the phantom with outlines of the ten ellipses identified using the thresholding algorithm. As shown in table 2, numerically identified areas of the phantom were within 6 percent of the measured values. Besides, the error was higher for the smaller ellipses (6 – 10). Furthermore, the airways analyzed in our study were similar in size to ellipse nos. 1 – 5. Thereby, the largest error in the calculation of their areas was approximately 2 percent. Boundaries of the patient's head and mandible for baseline, CPAP1 and CPAP2

configurations, were identified using the segmentation algorithm. The outlines were superposed to verify that lateral displacement of the mandible and change in head and neck position was negligible between pressures.

2.3 Estimation of Airway Elasticity

The index used to describe the local elasticity of the airway wall dilated by CPAP is the specific compliance²¹. The specific compliance is the normalized change in the cross-sectional area divided by the change in transmural pressure¹⁶.

$$\frac{1}{A} \frac{\delta A}{\delta P} = \frac{1}{S} \quad (1)$$

where δA is the absolute change in the cross-sectional area with respect to the reference configuration, A is the cross-sectional area of the reference airway, δP is the transmural pressure and S is the stiffness of the airway wall. Equation 1 can be rearranged to obtain an expression for the localized airway stiffness,

$$S = \frac{A \delta P}{\delta A} \quad (2)$$

In the present study, δA and A are obtained from MRI measurements described in section 2.2, where A is the reference area corresponding to either the baseline pressure or pressure CPAP1 and δA is the difference between the reference area and the area corresponding to the final pressure. δP is the transmural pressure i.e., the difference between the reference pressure (baseline or CPAP1) and the final pressure (CPAP1 or CPAP2). Extraluminal tissue pressure (ETP) varies with changes in the position of the head^{25, 26} and is greatest during the expiratory phase of the breathing cycle. The patient's head and neck position was found to be unchanged between CPAP levels in our study. The position being constant, the ETP distribution was assumed to remain the same for 2 values of mask pressure and baseline configuration. The transmural pressure was thereby affected only by changes in CPAP. The stiffness of the airway at each axial image slice is obtained from Equation 2. The average stiffness S_{avg} is obtained by evaluating the mean of the values obtained at every axial slice for the changes in transmural pressure described previously.

We evaluated the axial variation in elasticity²² for three different conditions: from baseline to CPAP1, baseline to CPAP2 and CPAP1 to CPAP2. The softest cross-section (location with smallest S i.e. more elastic or lowest stiffness) for each of the above conditions can be obtained using,

$$S'_{B-1} = \min(S_{B-1}) \quad (3)$$

$$S'_{B-2} = \min (S_{B-2}) \quad (4)$$

$$S'_{1-2} = \min (S_{1-2}) \quad (5)$$

where S_{B-1} , S_{B-2} and S_{1-2} are arrays of stiffness values along the airway, corresponding to the CPAP levels indicated by the subscripts (B for baseline, 1 for CPAP1, and 2 for CPAP2). The softest location is then determined by using the lowest stiffness of the three values of δP tested (Eqn. 6).

$$S' = \min (S'_{B-1}, S'_{B-2}, S'_{1-2}) \quad (6)$$

Stiffness values corresponding to the narrowest cross-section of the baseline airway were then determined for the three values of δP . The minimum of the three stiffness values was then evaluated to predict patient specific airway elasticity for the narrowest location.

2.4 Numerical Simulations of Airway Collapse

The floppiness of the airway wall is a consequence of the elasticity of the tissue supporting the pharynx. This section describes the procedure to iteratively determine the non-linear mechanical properties of airway tissue using finite element (FE) simulations of airway collapse. We illustrate the methodology for 3 patients (patient nos. 1, 9, 11). The patients were chosen based on the observations of P_{crit} (Patient 1 – positive P_{crit} , Patient 9 – largely negative P_{crit} , Patient 11 – moderately negative P_{crit}).

Figure 3a indicates an axial slice midway of the RG1 airway (between the tip of the soft palate and tip of the epiglottis). The structures surrounding the airway consist of the tongue (or palate in the RP airway), lateral fat-pads, spine, blood vessels and mandible. Due to the extremely complicated nature of these anatomical features, certain simplifying assumptions were made. Firstly, the tissue at an axial location was considered to be homogenous. Coupled or independent behavior of soft tissue structures was not considered in this study. Based on recommendations from the radiologist, the outline of the tissue structure was identified manually to include anterior soft tissue, thin mucosa overlying the spine, fat pads (to the right and left of the airway) and blood vessels (outline indicated by white dashed line in Fig. 3a). The resulting shape of the structural domain in the RG1 airway is shown in Fig. 3b. The process was repeated for the narrowest cross-section in the RP airway and a computational domain was suitably identified. The profile of the baseline airway or airway dilated by CPAP was chosen as the starting point for the numerical simulation. The choice was based on the starting value of mask pressure which was gradually reduced resulting in airway collapse. For example, in case of patient 1 and 11, the starting mask pressure was 4 cm of H_2O and for patient 9, the same was 0 cm of H_2O (i.e. no mask pressure).

Co-ordinates of the tissue outline and airway were imported into GAMBIT 2.4 (ANSYS Inc., Canonsburg, PA, USA) to generate planar CAD geometries. The planar geometry was then extruded by 1 mm in the Z-direction and the resulting volume was exported to the ABAQUS 6.12 (Simulia, Dassault Systems, Providence, RI, USA) finite element solver. Simulations of velopharyngeal collapse under gravitational loads in two dimensions⁴⁸ and tracheal collapse subject to negative transmural pressure loads at select axial locations¹¹ have been performed previously using the ABAQUS software. We adopted the procedure outlined in these aforementioned studies. The geometric models were meshed using 8-node, linear hexahedral elements (C3D8R)¹³ in ABAQUS. Reduced integration alleviates the volumetric locking phenomenon associated with full integration (C3D8) elements employed to model nearly incompressible solids. Hourglassing which results from the excitation of zero energy modes is a potential drawback of reduced integration elements. The hourglass control was thereby activated to minimize spurious deformations¹⁴. We tested 3 mesh resolutions corresponding to element sizes of 3, 2 and 1 mm (i.e. coarse, medium and fine). Accordingly the number of hexahedral cells for patient 1, 9 and 11 varied from 2000 to 7500, 1000 to 4500 and 800 to 4000 respectively. An element size of 1 mm was found to be optimum for all cases and generated grid independent solutions without excessive element distortion. The corresponding number of elements for patient 1, 9 and 11 were 7500, 4500 and 4000 cells respectively. Further reduction in the element size resulted in less than 1 per cent change in the measure of airway area following pharyngeal collapse. A neo-Hookean material model described by the following strain energy function (W) was used to approximate the non-linear behavior of airway tissue^{5, 48},

$$W = C_{10}(I_1 - 3) + \frac{1}{D_1}(J_{el} - 1)^2$$

$$C_{10} = \frac{\mu_0}{2} \quad (7)$$

$$D_1 = \frac{2}{\kappa_0}$$

Where, μ_0 is the shear modulus, κ_0 is the bulk modulus, I_1 is the first strain invariant and J_{el} is the elastic volume strain. The neo-Hookean material is the simplest hyperelastic model and can be used in the absence of accurate material data. Similar hyperelastic materials such as Mooney-Rivlin⁴⁹ and Yeoh¹⁸ have been employed to model airway tissue. The initial guess for the shear modulus ($\mu_{0ini} = 2530$ Pa) was obtained from previous MR elastography studies of the tongue and soft palate¹⁰. A Poisson's ratio (ν) of 0.475 has been reported for airway smooth muscle previously¹¹ and was adopted in our studies.

Figure 3c–f summarizes the boundary conditions employed in the simulations. The interface between the spine and posterior wall mucosa was fixed (Fig. 3c). A linearly increasing load corresponding to the negative transmural static pressure difference $\delta P_{collapse} = P_{crit} - CPAP$ was applied on the airway wall (Fig. 3d). Frictionless, hard contact was defined for the airway wall to model self-contact¹¹. A symmetry boundary condition in the Z direction was assigned to the top and bottom faces (Fig. 3e, f). Displacements and rotations about the

vertical axis were thereby constrained. The surfaces bounding the anterior, lateral walls and blood vessels were free to displace as observed in dynamic MR images of alternate airway dilation and contraction. Furthermore, since the MR images were acquired in supine position, gravitational forces were equilibrated and not considered in the governing equations⁵⁴. Airway collapse was assumed to be quasi-static and the updated lagrangian formulation of the continuum equations of motion for large strains³⁴ were solved using the ABAQUS Explicit module. All simulations were performed on a workstation computer with a single Intel i7-3770 Quad-core processor and 32 GB RAM. Finite element simulations of pharyngeal airway collapse at a given axial location required approximately 20 minutes of CPU time. The shear modulus was iteratively changed until the airway collapsed for the prescribed transmural pressure $\delta P_{\text{collapse}}$ and the difference between the slope of the experimental and numerical pressure-flow curves (described in Section 3.2) was minimized. In the present study, an area reduction of 97 percent or more was chosen as the criterion for airway collapse.

3. Results

3.1 Variation in Airway Cross-Sectional Area and Pharyngeal Stiffness

The variation in cross-sectional area along the airway length for six subjects (patient nos. 1, 5, 7, 9, 11, 15) is shown in Figure 4. The dotted curve represents the baseline airway, the dashed curve indicates the dilated airway corresponding to CPAP1 and the solid curve shows the dilated airway for CPAP2. Patients with larger differences between the three lines have more compliant airway. The narrowest cross-section in the baseline airway was located in the RP region (hard palate to soft palate) in patient 11 and 15, in the RG1 region (soft palate to epiglottis) in 2 patients (patient nos. 1, 9) and in the RG2 zone (epiglottis to base of tongue) in patient nos. 5 and 7. The site of narrowest cross-section is thus patient specific.

The average stiffness values (S_{avg}) corresponding to pressure change from baseline to CPAP1 (black bar) and CPAP1 to CPAP2 (gray bar) are then plotted as a bar-graph (Fig. 5a) to illustrate the nature and extent of non-linear behavior of individual airways. As can be seen, in GROUP D (patient nos. 5, 15, 16, 17, 18, 19) and GROUP B (patient nos. 6, 7, 11, 22), the stiffness is higher between baseline to CPAP1 and lower between CPAP1 to CPAP2, and indicates a ‘strain-softening’ behavior. Patients in GROUP D and GROUP B represent moderate and strongly ‘strain-softening’ behaviors, respectively. On the other hand, the stiffness was higher between CPAP1 to CPAP2 than from baseline to CPAP1, for GROUP C (patient nos. 1, 8, 9, 10, 14) and GROUP A (patient nos. 2, 3, 4, 12, 13, 20, 21), and represents a ‘strain-hardening’ behavior. Patients in GROUP C and GROUP A represent moderate and strongly ‘strain-hardening’ behavior, respectively. The variation in stiffness with CPAP for four representative patients (1, 11, 13 and 15) is plotted as a curve (Fig. 5b) to explain the differences between the four phenotypes. The values of the estimated stiffness (S'_{soft} and S'_{narrow}) for the twenty-two subjects and their respective anatomical locations are summarized in table 3. The softest cross-section was located in the retropalatal airway, in 11 out of the 22 patients (patient nos. 6, 7, 8, 10, 11, 12, 13, 14, 17, 22). The softest and narrowest cross-sections were located in the same anatomical region, in 16 patients (patient

nos. 1, 2, 3, 4, 5, 6, 9, 10, 11, 12, 14, 16, 17, 18, 20, 21). The softest and narrowest locations were coincident in 5 patients (patient nos. 9, 10, 11, 18, 21).

The twenty-two patients were grouped according to the AHI or P_{crit} values and an average airway stiffness was estimated for each group. The three groups were identified based on the severity of OSA⁴². Variations in group averaged stiffness (S'_{soft} and S'_{narrow}) with AHI and P_{crit} are plotted as a bar-graph in Figure 6. Scatter plots of variation in stiffness with AHI and P_{crit} at the softest and narrowest location are indicated in Fig. 6c and 6d. An exponential function of the form ae^{-bx} was employed to fit the data. The goodness of fit (R-value) for variation in stiffness with AHI was -0.41 and -0.76 , corresponding to the softest and narrowest locations respectively. The corresponding values for variation in stiffness with P_{crit} were -0.08 and -0.24 . Furthermore, the stiffness values for the female patients (patient nos. 1, 6, 11, 12 and 21) significantly influenced the correlation with P_{crit} (Fig. 6d). The airway stiffness at the softest and narrowest locations decreased with increasing AHI (Fig. 6a, c) and P_{crit} (Fig. 6b, d). This trend is especially clear at the narrowest locations.

3.2 Finite Element Simulations of Airway Collapse

At each load step, deformed configurations were exported from ABAQUS as an input file. Surface meshes of the deformed airway and surrounding tissue were reconstructed from the input files, to process the co-ordinates of the airway lumen surface (Fig. 3d) using FLUENT 6.3 (ANSYS Inc., Canonsburg, PA, USA). Lumen area prior to deformation and after each pressure load step was estimated from the surface meshes in GAMBIT, by summarizing the airway face information. A linear fit was employed to construct a pressure-area curve⁴⁰. The theoretical maximum inspiratory flow rate $\dot{V}_{i,max}$ was then determined using the following equation^{40, 44},

$$\dot{V}_{i,max} = \sqrt{A_{num}^3 / \rho C_{num}} \quad (8)$$

where A_{num} is the airway cross-sectional area obtained from numerical simulations, ρ is the density of air (1.2754 kg/m^3) and C_{num} is the slope of the numerical pressure-area curve.

Maximum inspiratory flow rates were computed for the areas obtained at the end of each load step using equation 8 and normalized by the flow rate corresponding to the lumen area prior to deformation. Numerical pressure-flow curves corresponding to the RP and RG1 airways were then generated using linear regression³⁹. The FE methodology was validated by comparing the pressure-flow curves obtained from numerical simulations of collapse in RP and RG1 airways to the pressure-flow curve obtained from experiments. As indicated in Fig. 7, a good match was achieved between the experimental data (dashed line) and simulation results (dash-dotted line – RP airway, solid line – RG1 airway) thereby validating our computational methodology. The optimized elastic or Young's modulus is obtained from the optimized shear modulus using the following relation,

$$E_{\text{corrected}} = 2\mu_{0\text{corrected}}(1 + \nu) \quad (9)$$

Where, $\mu_{0\text{corrected}}$ is the optimized shear modulus and ν is the Poisson's ratio. Figure 8 indicates the lumen profile of the airway prior to deformation (dotted outline) and the airway shape corresponding to the final load step (i.e. collapsed) (solid outline). Two distinct collapse modes were observed namely, U-shape (Fig. 8a, patient 1) and Y-shape (Fig. 8b, c, patient 9, 11). The optimized Young's modulus ($E_{\text{corrected}}$) for the 3 patients and their respective collapse modes is summarized in table 4.

4. Discussion

The change in airway elasticity between the two CPAP mask pressures is due to the non-linear response of the airway wall to positive pressures. The degree and nature of this non-linearity is patient specific as shown in Figure 5. Accordingly, 2 phenotypes were identified for the DS pediatric OSA patients considered in this study; airways that stiffen with increasing pressure (GROUP A and C) and ones that are floppier with increasing mask pressure (GROUP B and D). This implies that some OSA patients exhibited a decreasing change in compliance with increasing CPAP while others depicted an increasing change in compliance with CPAP. That is to say, for phenotype 2 (GROUP B and D), the locus of the pressure-stiffness co-ordinates is a curve with an initially positive slope followed by a negative one. Conversely, for phenotype 1 (GROUP A and C), the locus is a curve with a positive slope that increases with pressure. The smallest and largest values of localized airway stiffness for the 22 subjects analyzed in our study differed by nearly two orders of magnitude (table 3). The large spread further emphasizes that the choice of CPAP needed to maintain airway patency is patient specific. Moreover, identification of the softest point in the airway was significant, since it did not necessarily coincide with the narrowest location (table 3). In other words, CPAP would potentially generate non-uniform mechanical ventilation of the pharynx. Furthermore, increased local airway compliance (i.e. decreased airway stiffness) would be associated with increasing severity of OSA in DS patients, as indicated in Fig. 6. Besides, a detailed statistical analysis would be performed in future studies that would include controls and OSA patients without DS.

The airway static pressure employed in the numerical simulations has been described as an important indicator of airway collapsibility^{30, 31}. Moreover, similar studies involving finite element simulations of airway tissue collapse in animal models have been performed by applying static pressure boundary conditions at the airway tissue interface⁵³. Besides, the CPAP values employed in our studies are nearly an order of magnitude greater than the airway wall pressure obtained from computational fluid dynamics (CFD) of open³¹ and constricted³⁶ upper airways. Shear stresses arising from airflow^{32, 54} that stretch the airway tissue in the streamwise direction, were not included in this study. Moreover, the symmetry boundary conditions imposed on the top and bottom faces of the computational domain (described in Section 2.4) constrains tissue motion in the vertical direction. The computational modeling would be significantly enhanced by accounting for flow induced pressure and shear forces. Furthermore, accurate identification of the nasal airway from MR

images is quite challenging. We thereby estimated the nasal pressure drop using a clinical correlation based on patient age⁴⁰. The mean and median values of nasal airway pressure drop for all patients considered in this study (~ 0.35 cm of H_2O) were much smaller compared to the measures of CPAP. A major limitation of the present methodology is that ETP was assumed to be unchanged with CPAP. Besides, CPAP alters lung volume and increasing lung volume reduces ETP²⁷. Furthermore, ETP varies along the airway length and periphery^{2,3}. Accurate evaluation of transmural pressure would be possible through a combination of CFD^{31,32,36} and ETP measurements with specialized IRB approved catheters or the use of pressure transducers²¹ and IRB approved cannula. Evaluation of patient arousal resulting from body movements was based on findings from previous studies that described the presence of periodic limb movements during sleep (PLMS) in OSA patients treated with CPAP^{9,17}. Besides, in order to accurately distinguish between arousal and non-arousal body movements, additional instrumentation would have to be incorporated into the MRI scanner, to precisely identify PLMS that precede changes in sleep EEG consistent with patient arousal¹⁷.

The lowest and highest moduli of elasticity ($E_{corrected}$) determined from FE simulations of airway collapse differed by an order of magnitude. Besides, the Young's modulus of tissue in the RP airway was lower than that in the RG1 airway for the 3 patients examined in our study (table 4). These observations suggest that the RP airway is more floppy and susceptible to collapse. Moreover, the moduli were found to decrease with increasing P_{crit} (i.e. increasing severity of OSA). Estimated mechanical properties of soft tissue are extremely sensitive to the adopted methodology¹⁰. For instance, the Young's modulus of the soft palate determined from FE simulations⁵ was found to vary from 500 to 97500 Pa. The corresponding value obtained from MR elastography was 7465 Pa¹⁰. Similarly, the elastic modulus of the tongue varied from 1100 Pa (obtained from ex-vivo compression¹⁸) to 250000 Pa (obtained from FE simulations³³). The material properties reported in our study were within the aforementioned range of values. Differences between live tissue properties estimated in the current study and MR elastography could be attributed to several factors including differences in the patient population being studied and conditions under which the imaging was performed. Moreover, the inverse relationship between tissue stiffness and OSA severity established using MR elastography⁸, was also identified using the proposed method. Imaging static airway collapse in human subjects during inspiration can be extremely challenging. In the absence of MR images or endoscopic views of the collapsed airway²⁹, the experimental inspiratory pressure-flow curve was compared to the pressure-flow curve obtained from computer simulations, to validate the numerical procedure (Fig. 7). Besides, the expiratory and inspiratory compliance contours are not coincident due to significant hysteresis in the pressure-flow curves for sleep disordered breathing¹⁹. The proposed numerical methodology can be employed to non-invasively estimate the Young's modulus of upper airway tissue in OSA patients during sleep. Furthermore, the estimated values of tissue elasticity would serve as input to a virtual computational tool, to assess the success or failure of different surgeries prior to application.

The current study assumed that the airway collapsed at the same closing pressure in the RP and RG1 airways. However, previous studies have shown that P_{crit} for the velopharynx is

less negative compared to that in the oropharynx²². Furthermore, this study assumed that airway collapse would occur midway in the RG1 airway or at the narrowest point in the RP airway. It should be noted that this assumption was made to assess the regional differences in tissue properties along the airway length. The study assumed that mechanical properties at an axial location were homogenous and isotropic. However, tissue properties of the upper airway are not only non-linear but also anisotropic or heterogeneous^{2, 10}. This observation emphasizes the need to calculate a more comprehensive 3D map of tissue elasticity accounting also for circumferentially varying mechanical properties.

The mode of airway collapse was found to be either U (2 fold) or Y-shaped (3 fold). The fold number was smaller for the patient with greater severity of OSA²⁴ (i.e. with positive P_{crit}). The pattern of airway collapse was found to strongly depend on the profile of the airway lumen prior to deformation. This emphasizes the need to accurately image and segment the airway dilated by CPAP. An additional limitation is that muscle activity and independent or coupled behavior of different anatomical structures⁷ was not considered in this study. Besides, the dynamic elastic modulus arising from muscle activity and temporal changes in the pressure profile can significantly vary from its passive counterpart.

5. Conclusions

We presented a patient specific, non-invasive method to evaluate the stiffness of the airway wall from MR images. The localized airway stiffness at the narrowest cross-section was greater than or equal to the stiffness at the softest location. The locations of the narrowest and softest sections were thus patient-specific. Strain-hardening and strain-softening behaviors were the two elasticity phenotypes identified in this study. These phenotypes can influence the decision making on CPAP levels needed to maintain airway patency. The inverse relationship between localized airway stiffness and clinical parameters such as AHI and P_{crit} suggests that airway elasticity could supplement clinical measures of the severity of OSA. A novel methodology was developed to evaluate the regional variations in tissue elasticity from FE simulations of airway collapse. The values reported in this study were within the range of values published elsewhere. The estimated tissue stiffness was also found to decrease with increasing P_{crit} . In order to account for heterogeneities or anisotropy in mechanical properties of soft tissue the circumferential variation in elasticity needs to be evaluated. Thus, the uniform structural domain needs to be replaced by a heterogeneous one and finally with anatomically accurate three dimensional structures. Overcoming the limitations in the current model and generating an improved measure of airway and tissue elasticity forms the basis of our future research.

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Figure 1.

a) Extents of the pediatric pharyngeal airway and corresponding soft tissue domain (patient no. 13) in mid-sagittal MR image. Outline of the boundaries of the baseline (dotted) and dilated (dashed, solid) airways in b) mid-sagittal and c) coronal plane. d) Axial variation in cross-sectional areas in the pharyngeal airway corresponding to the baseline (dotted), CPAP1 (dashed) and CPAP2 (solid) (A – Anterior, P – Posterior, R – Right, L – Left, RP - Hard palate to soft palate, RG1 - Soft palate to epiglottis, RG2 - Epiglottis to base of tongue).

Figure 2. Modified Shepp-Logan phantom a) before segmentation b) after segmentation using the thresholding algorithm. The error between the theoretical and computed areas ranges from 0.2 to 6.3 %. (Note: Ellipse 1: red (outermost), Ellipse 2: blue, Ellipse 3: green, Ellipse 4: Yellow, Ellipse 5: Cyan, Ellipse 6, 7: Magenta, Ellipse 8, 10: black, Ellipse 9: white).

Figure 3.

a) Axial MR image (patient no. 9) indicating the anatomical structures (tongue, lateral walls and blood vessels) that constitute upper airway tissue (indicated by dashed white outline). b) CAD geometry and unstructured hexahedral mesh of the computational domain for FE simulations. c) No displacement boundary conditions applied on the posterior wall tissue d) Pressure load corresponding to P_{crit} -CPAP and self-contact applied on airway wall. Symmetry boundary conditions in the Z direction applied on the e) top and f) bottom faces of the domain. (Note: The CAD geometry has been extruded by 1 mm in the Z direction. A – Anterior, R – Right, P – Posterior, L – Left).

Figure 4.

Variation in the cross-sectional area over the airway length for 6 patients (a – f). Variation in area corresponding to the baseline airway is indicated by a dotted curve, the same for CPAP1 and CPAP2 are represented using a dashed and solid line, respectively. Location of the tip of the soft palate is indicated by the dashed light gray line while the dashed dark gray line represents the tip of the epiglottis.

Figure 5.

a) Overall response of individual airways indicated by plotting the variation in stiffness with CPAP as a bar graph, for the 22 patients considered in this study. Patients in GROUP D exhibit a moderately 'strain-softening' behavior and patients in GROUP B depict a strongly 'strain-softening' behavior. Patients in GROUP C indicate a moderately 'strain-hardening' behavior and patients in GROUP A represent a strongly 'strain-hardening' behavior. b) Representative line plots of variation in stiffness with CPAP for the four phenotypes identified in the study (Patient 13 – GROUP A, Patient 11 – GROUP B, Patient 1 – GROUP C, Patient 15 – GROUP D).

Figure 6.

Variation in group averaged airway stiffness at softest (S'_{soft}) and narrowest location ($S'_{\text{narrowest}}$) location with a) AHI (GROUP 1 – Mild OSA (AHI values 0 to 5), GROUP 2 – Moderate OSA (AHI values 5 to 14), GROUP 3 – Severe OSA (AHI values above 14)) b) P_{crit} (GROUP 1 – Mild OSA (P_{crit} values from -11 to -5 cm), GROUP 2 – Moderate OSA (P_{crit} values from -5 to 0 cm), GROUP 3 – Severe OSA (P_{crit} values above 0 cm)). Scatter plots depicting variation in individual airway stiffness at softest and narrowest location with c) AHI (semi-log plot) and d) P_{crit} . An exponential function of the form $ae^{\text{minus}bx}$ is used to fit the individual data sets. The trend lines indicate an inverse relationship of airway stiffness with AHI and P_{crit} .

Figure 7.

Comparison between the pressure-flow curves obtained from numerical simulations of airway collapse (dot-dashed line – RP airway, solid line – RG airway) and pressure-flow curves obtained from experimental estimation of P_{crit} (dashed line), for a) patient 1 b) patient 9 c) patient 11. A linear fit has been used to describe the pressure-flow curves. (Note: Black square markers indicate experimental data points. Black asterisk indicates P_{crit} . The flow values (experimental) and numerical) have been normalized by the respective peak values).

Figure 8.

Superposed axial cross-sectional shapes of the airway lumen prior to deformation (dotted line) and after collapse (solid line), predicted from FE simulations a) Patient no. 1 (RP Airway - U shaped collapse) b) Patient no. 9 (RP Airway - Y shaped collapse) c) Patient no. 11 (RP Airway - Y shaped collapse).

Table 1

Summary of patient clinical history (Note: Pressure (P_{crit} , CPAP1 and CPAP2) is in cm of water, 1 cm of $H_2O \sim 100$ Pa)

Patient No.	Age (years)	Gender	AHI	P_{crit}	CPAP1	CPAP2	OSA Severity (AHI Based)	OSA Severity (P_{crit} Based)
1	11	F	20.2	1.3	4	10	Severe	Severe
2	13	M	7.4	-1.7	3	6	Moderate	Moderate
3	17	M	8.2	-1.8	3	9	Moderate	Moderate
4	5	M	5	-11.6	4	8	Mild	Mild
5	3	M	6.8	-7.9	3	8	Moderate	Mild
6	5	F	13.1	6.6	8	15	Moderate	Severe
7	9	M	142.2	2	10	18	Severe	Severe
8	14	M	6.4	-4.3	3	7	Moderate	Moderate
9	4	M	9.3	-8.1	2	8	Moderate	Mild
10	7	M	8.7	1.3	7	12	Moderate	Severe
11	9	F	9.1	-3.8	4	6	Moderate	Moderate
12	3	F	5.9	-10	2	6	Moderate	Mild
13	10	M	4	-10.8	4	10	Mild	Mild
14	17	M	21.3	N/A	10	15	Severe	N/A
15	12	M	5.9	-0.2	4	8	Moderate	Moderate
16	9	M	6.1	7	10	14	Moderate	Severe
17	9	M	14.7	0.2	5	10	Severe	Severe
18	16	M	9.4	1.9	8	12	Moderate	Severe
19	8	M	7.5	-0.8	8	14	Moderate	Moderate
20	11	M	5.5	-8.4	5	10	Moderate	Mild
21	12	F	6.8	2.1	6	12	Moderate	Severe
22	12	M	13.8	-3.4	5	9	Moderate	Moderate

Table 2

Comparison between measured and computed areas (Note: Semi-major axis length, semi-minor axis length and corresponding ellipse areas are dimensionless)

Ellipse No.	Semi-major axis	Semi-minor axis	Measured Area	Computed Area	Percent Error (Absolute)
1	0.92	0.69	1.9942	2.0381	2.2
2	0.874	0.6624	1.8187	1.8557	2
3	0.31	0.11	0.1071	0.1061	0.9
4	0.41	0.16	0.206	0.2064	0.2
5	0.25	0.21	0.1649	0.1673	1.5
6	0.046	0.046	0.0066	0.0064	3
7	0.046	0.046	0.0066	0.0064	3
8	0.046	0.023	0.0033	0.0031	6.1
9	0.023	0.023	0.0016	0.0015	6.3
10	0.046	0.023	0.0033	0.0031	6.1

Table 3

Summary of softest, narrowest locations in the pharyngeal airway

Patient No.	Phenotype	S'_{soft} (Pa)	Location	$S'_{\text{narrowest}}$ (Pa)	Location
1	GROUP C	450	RG1	470	RG1
2	GROUP A	25	RG2	35	RG1
3	GROUP A	15	RG2	20	RG2
4	GROUP A	15	RG3	20	RG3
5	GROUP D	25	RG2	50	RG2
6	GROUP B	600	RP	695	RP
7	GROUP B	350	RP	1025	RG2
8	GROUP C	440	RP	950	RG1
9	GROUP C	220	RG1	220	RG1
10	GROUP C	220	RP	220	RP
11	GROUP B	150	RP	150	RP
12	GROUP A	625	RP	650	RP
13	GROUP A	1180	RP	3385	RG2
14	GROUP C	150	RP	185	RP
15	GROUP D	1000	RG1	1240	RP
16	GROUP D	380	RG2	630	RG2
17	GROUP D	35	RP	35	RP
18	GROUP D	30	RG2	30	RG2
19	GROUP D	220	RG1	900	RG2
20	GROUP A	160	RG2	420	RG2
21	GROUP A	60	RG2	60	RG2
22	GROUP B	270	RP	400	RG2

Table 4

Summary of results from FE simulations

Patient No.	$\delta P_{collapse}$ (Pa)	RP - $E_{corrected}$ (Pa)	RG1 - $E_{corrected}$ (Pa)	Collapse Mode (RP)	Collapse Mode (RG)
1	-275	1700	5000	U shape	U shape
9	-810	21500	37500	Y shape	U shape
11	-780	15000	14000	Y shape	Y shape