A computational study of the role of the aortic arch in idiopathic unilateral vocal-fold paralysis

Megan J. Williams, Avinash Ayulasomayajula, Reza Behkam, Andrew J. Bierhals, M. Eileen Jacobs, Julia D. Edgar, Randal C. Paniello, Julie M. Barkmeier-Kraemer, and Jonathan P. Vande Geest

A computational study of the role of the aortic arch in idiopathic unilateral vocal-fold paralysis. J Appl Physiol 118: 465–474, 2015. First published December 4, 2014; doi:10.1152/japplphysiol.00638.2014.—Unilateral vocal-fold paralysis (UVP) occurs when one of the vocal folds becomes paralyzed due to damage to the recurrent laryngeal nerve (RLN). Individuals with UVP experience problems with speaking, swallowing, and breathing. Nearly two-thirds of all cases of UVP is associated with impaired function of the left RLN, which branches from the vagus nerve within the thoracic cavity and loops around the aorta before ascending to the larynx within the neck. We hypothesize that this path predisposes the left RLN to supraphysiological, biomechanical environment, contributing to onset of UVP. Specifically, this research focuses on the identification of the contribution of the aorta to onset of left-sided UVP. Important to this goal is determining the relative influence of the material properties of the RLN and the aorta in controlling the biomechanical environment of the RLN. Finite element analysis was used to estimate the stress and strain imposed on the left RLN as a function of the material properties and loading conditions. The peak stress and strain in the RLN were quantified as a function of RLN and aortic material properties and aortic blood pressure using Spearman rank correlation coefficients. The material properties of the aortic arch showed the strongest correlation with peak stress \( \rho = -0.63, 95\% \text{ confidence interval (CI), } -1.00 \text{ to } -0.25 \) and strain \( \rho = -0.62, 95\% \text{ CI, } -0.99 \text{ to } -0.24 \) in the RLN. Our results suggest an important role for the aorta in controlling the biomechanical environment of the RLN and potentially in the onset of left-sided UVP that is idiopathic.

biomechanics; finite element; nerve; recurrent laryngeal nerve; vocal-fold paralysis

Submitted 15 July 2014; accepted in final form 24 November 2014

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http://www.jappl.org
onetti (34) reported that eight of 168 patients (4.8%) with TAA presented with hoarseness, and all of these had type I aneurysms (DeBakey classification) involving the ascending root and aortic arch. Thus growing evidence in the literature indicates that the aortic region of the thorax may be important to study as a source of impaired left RLN function.

The evaluation and simulation of the mechanical loading of the left RLN can be used to study the effects of various physiologic scenarios in the aortic arch, including healthy and diseased states of the aortic tissue. Finite element methods have been used extensively to study pressure vessels and other soft tissues (5, 14, 28). However, to the authors’ knowledge, there have not been any finite element studies used to investigate mechanical behavior of the RLN.

In previous work, the authors reported variations in the mechanical properties of porcine left RLN based on proximity to the aortic arch (1, 37). The average range of the material properties (α and β) of the left RLN in adolescent pigs, determined from previous experimental work (17), was implemented in this model. The material properties of the aortic arch were obtained from previously published work from our laboratory that is based on the Holzapfel model (15). The geometry of the aortic arch was determined from three-dimensional (3D) reconstruction of patient-specific data using a circular, cross-sectional area. The geometry of the nerve was assumed from observation during dissection.

The purpose of this study is to develop a computational model using finite element methods that can assess the effect of changes in left RLN connective tissue and the aortic arch properties on the mechanical response of the left RLN. This model is vital for formulating predictions of the typical ranges of stresses and strains in response to physiologic and supra-physiologic levels of stretch. These predictions may be important to future investigations using an animal model to determine levels of stretch and compression associated with onset of UVP.

METHODS

Geometry

The geometry of this finite element model includes the aortic arch and the left RLN. The geometry of the aortic arch is determined from analysis of MRI data from a single patient, provided by collaborators in and approved by the Department of Radiology, Washington University (St. Louis, MO; Washington University Institutional Review Board Protocol #201206033). The material properties, implemented in two aortic arch models (each representing different age groups), of this study come from a previous study from which we do not have MRI images. Because we do not have the MRI data specific to the patients from whom we obtained material properties, we chose to create a general model by using the image set from a single patient to determine the overall size and orientation of the aortic arch. The patient who was used to generate the geometry used in both models was a 52-year-old man.

MRI image retrieval. The images were acquired using the Generalized Autocalibrating Partially Parallel Acquisitions (GRAPPA) par-
allel imaging technique for several reasons. The use of GRAPPA reduces the scan time and as such, makes it possible to acquire the data set in a manageable, single breath hold (≈15 s). This ultimately improves image quality by using k-space lines from multiple coils, reduces artifacts, and improves signal-to-noise ratio, allowing better evaluation of the aorta throughout the cardiac cycle. Lastly, the GRAPPA method has advantages over other parallel imaging, as it is less affected by local inhomogeneities that are created by the lungs.

Scanning was completed using a 32-channel Avanto 1.5 Tesla MRI (Siemens, Melvern, PA) scanner with a maximum gradient amplitude of 45 mT/m and maximum slew rate of 200 mT · m/s along each physical axis.

Heart rate and blood pressure measures were acquired before scanning procedures with participants in the supine position. Once positioned for scanning, a 3D-segmented, steady-state, free-precession sequence with nonselective radiofrequency excitation was used to acquire images. ECG gating with data acquisition during diastole and systole was also used to control for cardiac motion artifacts during image acquisition. The following imaging parameters were set: repetition time 2.3 ms, echo time 1.0 ms, flip angle 90°, readout bandwidth 980 Hz/pixel, field of view 400–400 mm², matrix size 256–256 leading to in-plane resolution of 1.6–1.6 mm².

A total of 44–64 3D partitions was measured with a slice thickness of 1 mm, interpolated to 88–128 slices of 1.5 mm. Fifty-one to 77 lines were measured during each cardiac cycle depending on the heart rate. To shorten the scan time, a parallel imaging technique—GRAPPA, 26 with an acceleration factor of two—was applied. Data acquisition was obtained, first using ungated MRI in the sagittal and axial orientations, followed by gated Fast Imaging Employing Steady-state Acquisition MRI scanning of the oblique, coronal, and axial orientations. Asymmetric data sampling of k-space with a navigator acceptance rate of 30–60% was used, resulting in a scan time of 15–20 min.

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Table 2. Mean ± SD of the polynomial model parameters of the RLN implemented in the finite element model

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RLN, recurrent laryngeal nerve.

### Aortic arch segmentation

3D reconstruction of the arch in its diastolic configuration was used to determine the aortic arch spatial orientation. A 3D geometry was created using a custom MATLAB program, written previously in the Soft Tissue Biomechanics Laboratory, University of Arizona (Tucson, AZ) (2). Briefly, the entire 3D segmentation and smoothing algorithm were implemented using a graphical user interface in MATLAB. The image data were regener-

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length of the aorta. Figure 2B displays the final geometry generated in SolidWorks.

Geometry of nerve. The left RLN was fixed in space at a constant distance from the location on the aortic arch that is midway between the left common carotid and the left subclavian arteries. The left RLN was assumed to be adjacent to the inferior aortic surface, as has been observed during prior anatomical dissections of porcine subjects by the authors. The diameter of the nerve was 1.95 mm, as it has been reported as the average value of the left RLN in humans (27).

Finite Element Mesh

The aortic arch was discretized into 8,500 homogenous, four-node, quadrilateral, stress/displacement shell elements with reduced integration and a large-strain formulation (S4R). Due to the more complex geometry of the RLN, it was discretized into two types of elements. The RLN mesh contains 33,700 homogenous, eight-node linear brick, reduced integration solid elements (C3D8R) and homogenous four-node linear tetrahedron solid elements (C3D10).

Material Properties

Constitutive model of the aortic arch. An incompressible, anisotropic, hyperelastic material model was adopted to characterize the mechanical behavior of the aortic arch. The model is based on the fiber-reinforced hyperelastic material model proposed by Holzapfel et al. (15), which has been shown to capture accurately the behavior of blood-vessel inflation under internal pressurization and is one of the forms of the strain energy potentials currently available in Abaqus (v 6.13; Simulia, Providence, RI) to model anisotropic hyperelastic materials. Briefly, the aortic tissues were assumed to be composed of a matrix material with two families of imbedded fibers, each of which has a preferred direction. The fiber directions (γ) can be mathematically described using two unit vectors. The strain energy function W can be expressed as

\[ W = C_{10} (I_1 - 3) + \frac{1}{D} \left( \frac{J^2 - 1}{2} - \ln J \right) + \frac{k_1}{2k_2} \sum_{n=1}^{N} \left\{ \exp \left[ k_2 (\bar{E}_n)^{1/2} \right] - 1 \right\} \]  

where \( J = \det(C)^{1/3} \), \( E_n = \kappa (I_1 - 3) + (1 - 3\kappa) I_{(4\alpha)} - 1 \). \( I_1 \) is the first deviatoric strain invariant, \( I_{(4\alpha)} \) are pseudoinvariants of \( C \) and the directions of the fibers \( A_n \). The axial and circumferential stretches are represented with \( \lambda_1 \) and \( \lambda_0 \), respectively, where \( I_1 = \lambda_1^2 + \lambda_0^2 + (\lambda_1 \lambda_0)^{-2}, I_{(4\alpha)} = \lambda_0^2 \sin^2 \gamma + \lambda_1^2 \cos^2 \gamma \). \( C_{10} \), \( k_1 \), \( k_2 \), and \( D \) are material constants. \( C_{10} \) is used to describe the matrix material, \( D \) is the material constant that controls near-incompressibility, whereas \( k_1 \) is a positive material constant with the dimension of stress, and \( k_2 \) is a dimensionless parameter. The fiber dispersion parameter \( \kappa \) was used to describe the distribution of fiber orientation. When \( \kappa = 0 \), the fibers are perfectly aligned (no dispersion); when \( \kappa = 0.33 \), the fibers are distributed randomly, and the material becomes isotropic (15, 17). The material constants implemented in this study are the result of an experimental study previously published in the Soft Tissue Biomechanics Laboratory, University of Arizona, in which mechanical data were acquired from specimens of three different age groups (young, middle-aged, and old) (17). One representative aortic arch specimen was chosen from two of the age groups (30–60 and >60 yr). Our goal in the selection of the material constants from our previous work was to choose a set of constants that had a biomechanical response that represented a middle-aged (30–60 yr) and older (>60 yr) age group. Specifically, we chose the specimen with the median value of maximum tangential modulus in both groups. The stretch vs. strain data were plotted for each specimen to confirm that the median value of maximum tangential modulus in both groups. The stretch vs. strain data were plotted for each specimen to confirm that the median value of maximum tangential modulus in both groups. The stretch vs. strain data were plotted for each specimen to confirm that the median value of maximum tangential modulus in both groups.

Fig. 6. A: representative system of maximum principal strain distribution. B: undeformed and deformed configuration of a representative RLN specimen.
group, who was the best mechanical representative of the age group, was 60 yr of age. The specimen from the 60 age group, who was the best representative, was 73 yr of age. The anisotropic, hyperelastic material model was implemented into Abaqus 6.13. Discrete, local coordinate systems were defined to include fiber orientations (γ) for each region of the arch along its length. The fiber orientations are displayed in Fig. 3. The material constants and fiber orientations used for each representative aorta are shown in Table 1.

Constitutive model of RLN. An isotropic, hyperelastic constitutive model was used in our previous work to capture the behavior of porcine RLN tissue (37). Briefly, Cauchy stress, $T_{11}$, was calculated at each time point as

$$T_{11} = \left( \frac{f_1}{A_0} \right) \lambda_1$$

where $f_1$ is the instantaneous load, $A_0$ is the initial cross-sectional area (assumed to be circular), and $\lambda_1$ is the stretch. The RLN material properties $\alpha$ and $\beta$ were fit to this constitutive model following the work of Raghavan and Vorp (25).

The mean and SD values for the material properties of the RLN were taken directly from the results of the adolescent pigs, reported previously in our lab (37) (see Table 2). All animal use and experimental procedures for pig-tissue acquisition were performed according to the approved protocols [Institutional Animal Care and Use Committee (IACUC) Protocol #09-109 and #12-374] of the University of Arizona IACUC.

Load and Boundary Conditions

To simulate a state of prestress in the RLN, the aortic arch diameter (measured from its diastolic configuration) was reduced so that when a static 80 mmHg (0.012 MPa; diastolic pressure) was applied to the internal surface in the finite element model, the new geometry accurately represents the arch geometry from the MRI data in the diastolic configuration. This process is illustrated in Fig. 4A. To do this, an automated optimization scheme was used to minimize the sum of the squares of the residuals between the Euclidean distance between the location of the nodes of the diastolic MRI configuration geometry and the location of the nodes on the corresponding, computationally reduced geometry. In each iteration of the custom-written MATLAB program, the parameter $\delta$ ($\delta =$ percent of the initial diameter) is updated until the optimum value of $\delta$ is determined. Optimization occurred without the RLN as part of the model. This was done for both cases of aortic arch material parameters. For the 73 yr old, $\delta$ was calculated to be 0.940; for the 60 yr old, $\delta$ was calculated to be 0.863. The original and reduced geometries of the 73-yr-old aorta, calculated from the optimization scheme, are shown in Fig. 4B.

Once the new, optimized geometry was determined, the RLN was added to the model. For the aorta and RLN to deform in a physiological manner, the distal ends of the arch were fixed in all directions except radially to accommodate expansion due to internal pressure. The distal and proximal ends of the RLN and its vagus branch were also fixed in all directions. A tie constraint was generated between the surface of the RLN and the aortic arch. This boundary condition has been observed in situ with the nerve tethered to the aortic arch by surrounding connective tissues. The effects of stiffness due to the connective tissues are assumed to be negligible. Finally, an intraluminal static pressure is applied with three different magnitudes (80, 120, and 150 mmHg). The load and boundary conditions are displayed in Fig. 5.

Data Processing

Postprocessing of the analytical model provided maximum principal RLN stress and maximum principal RLN strain for each combi-
nation of five material constants at each element for the region of interest. The computational simulation was done to output the Cauchy stress and logarithmic strain of the RLN. Cauchy stress is the stress determined by the instantaneous load, acting on the instantaneous cross-sectional area. In one dimension, logarithmic strain ($\varepsilon$) and stretch ($\lambda = \text{ratio of deformed to undeformed length}$) are related by: $\varepsilon = \ln(\lambda)$. Therefore, a line segment with a logarithmic strain of 20% has a stretch of $0.2^{0.2} = 1.2$. The material constants investigated were the properties of the RLN $\alpha$ and $\beta$, the static systolic pressure of the internal aortic arch, and the two Holzapfel model parameters of the aortic arch with units of stress, $C_{10}$ and $k_1$. Plots of maximum RLN principal stress and principal strain were generated as a function of each independent variable (aortic and RLN material constants and pressure).

Scatter-plots of each variable and peak maximum stress and peak maximum strain in the RLN region of interest were constructed to provide graphical indications of association. Spearman's rank correlation was used to provide a mathematically objective assessment of the association between each variable and peak stress and peak strain (10). A correlation coefficient of 0.95 was interpreted to indicate a reliable association. The Spearman's rank correlation coefficient was used to assess which parameters are the most influential on left RLN stress and strain.

RESULTS

A representative distribution of maximum principal strain for both the RLN and the aorta is shown in Fig. 6A. Figure 6B displays the undeformed and deformed configuration of a representative RLN specimen. From these figures, we can see that the location of peak maximum principal strain occurs in the most cephalic portion of the RLN, where it loops around the aorta.

Representative maximum principal strain contours for the RLN with average values of $\alpha$ and $\beta$ and the 60-yr-old aorta and each pressure are shown in Fig. 7A. The same maximum principal strain contours are shown for the average properties of the RLN and the old aorta at each pressure in Fig. 7B. From these figures, we can see an increase in strain with increased

Fig. 8. Peak maximum principal stress for the region of interest of the RLN for all combinations of RLN parameters, material properties $\alpha$ and $\beta$, of both aortas at each level of pressure.
intraluminal pressure of the aorta. Additionally, there is an increase in strain in the RLN of the 60-yr-old aorta model compared with the 73-yr-old aorta model.

Figures 8 and 9 show the peak maximum principal stress and strain, respectively, for all combinations of parameters of the RLN, aortic arch, and pressure. For the RLN region of interest, the range of peak maximum principal stress for all cases was 0.33–8.24 MPa. The range of peak maximum principal strain for all cases was 0.02–0.16 (mm/mm). After assessing all models, the largest value of RLN stress and strain occurred in the 60-yr-old aorta model with the highest values of RLN α and β and 150 mmHg of pressure.

Spearman’s rank correlation coefficients are calculated for each model parameter. To determine whether these co-vary in a significant fashion, a t-test can be applied to the correlation coefficient at a given $n = 2$ degrees of freedom and confidence level; in this case, 95%. If the 95% confidence interval (CI) envelopes show a correlation coefficient of 0.0, then the association is not significant. The Spearman’s correlation coefficients, along with the 95% CI, are shown in Fig. 10, signifying sensitivity of maximum principal stress and maximum principal strain to the input parameters.

For peak maximum principal stress and peak maximum principal strain, the parameters that exhibited the greatest correlation coefficients were $k_1$ and $C_{10}$ (material properties of the aorta) with the same correlation coefficient [stress: −0.63 (−1.00 to −0.253); strain: −0.62 (−0.997 to −0.243)]. There was no significant correlation with pressure in either case [stress: 0.31 (−0.076 to 0.638); strain: 0.35 (−0.027 to 0.727)]. α was not correlated in a 95% CI in either case [stress: 0.14 (−0.237 to 0.517); strain: −0.24 (−0.617 to 0.137)]; however, β did significantly influence maximum principal nerve stress. The correlation coefficient with stress was 0.40 (0.032–0.787), and with strain, it was −0.12 (−0.497 to 0.365).

**DISCUSSION**

The highest value of RLN strain reported in any case occurred in the 60-yr-old aorta (most compliant aorta) with the lowest values of α and β (most compliant RLN) and in the...
RLN at the highest amount of intraluminal pressure condition (150 mmHg). This is expected, as the highest value of compliance applied with the greatest value of load would yield the greatest amount of deformation and hence, strain in the nerve. The highest value of RLN stress reported in any case also occurred in the 60-yr-old aorta with an average value of α but a maximum value of β in the RLN and 150 mmHg. This can be explained by the consideration that achievement of a high value of RLN stress requires a high value of stiffness in the RLN and 150 mmHg. This can be demonstrated in our prior publication (1).

Whereas there has not yet been any published data on the functional deficit of the RLN to different degrees of applied load or stretch, these types of studies have been performed on other peripheral nerves. For example, the isolated tibial nerve of the rabbit can sustain tensile strains as large as 15% before any appreciable stress develops in that tissue (19, 24). Such nerve tension has been found to reduce blood flow and nerve conduction velocity. At strains of 6–8%, blood flow within the tibial and sciatic rat nerves begins to decrease and is blocked completely at strains of 14–16% (12, 22). Another group reports that the extant data indicate that strain of 6–8% for short duration causes transient physiological changes that appear to be within the normal stress tolerance of the tissue, whereas acute strains of 11% or greater cause long-term damage and may be considered to be excessive stress states (35). A study of guinea pig tibial nerves in 2007 included the application of incremental quantities of stretch and measuring corresponding changes in compound action potential (CAP) (21). Results of this study showed that a longitudinal strain of 5% caused a 16% reduction in the CAP, a strain of 10% caused a 50% reduction in the CAP, and with 20% strain, severe conduction block with minimal recovery was observed (21). Given the differences in the species and types of nerves described above, the comparison of quantitative data among studies is challenging. Several studies have been done that demonstrate that the morphology and mechanical behavior of peripheral motor nerves vary among different types of nerves, as well as along the length of an individual nerve (1, 4, 8, 37). However, until function-deficit studies are done in human RLN tissues, these previously published works provide some indication of the quantity of strain required to elicit damage to a peripheral nerve.

There are several limitations of the current study. It is important to note that the properties of the aortic arch and the RLN came from healthy specimens, and the patients and animals were not screened for vocal-fold paralysis. Due to the aims of the current research, this computational model does not simulate vocal-fold paralysis; rather, it allows us to make predictions about the magnitudes of stress and strain that the left RLN typically may be able to withstand for future disease-state models of interest. Additionally, we used material properties from the porcine RLN. Previous studies, however, have shown that the pig RLN is similar in structure to that of the human (8). The material properties of the aortic arch used in this study, however, were used from a large study focusing on the location-dependent (e.g., ascending, arch, descending) biomechanical and microstructural properties of human aorta from autopsy (17). Another limitation of the study is the use of
biomechanical data from only one single representative aortic specimen from each age group. The constitutive model for the aorta includes several parameters (constants) that are coherent and therefore, cannot be averaged within an age group. Additionally, the geometry of the aortic arch was generated based on the dimensions of a single patient’s MRI scan. In the future, more accurate geometry may be obtained from averaging the dimensions of data sets from multiple patients’ MRI data. Finally, lack of inclusion of surrounding structures, including the pulmonary artery, is a limitation of this study. This may be important, considering prior studies have shown that compression may also induce functional deficit in peripheral nerves.

Future studies should include experimentally derived compression behavior of the RLN implemented in a computational model that takes into account the effects of stretch and compression on the RLN by the surrounding vessels, including the pulmonary artery. Assuming that the caudal-cephalic motion of the aortic arch and pulmonary artery is different, we would expect to see an increased stress on the left RNL. Further research should also be done to determine what amount of stretch causes significant functional deficits in the RNL to make a more accurate prediction of the effects of cardiovascular disease on RNL injury. This can be done using similar methods, as described by Li and Shi (20), by measuring CAPs while imposing different degrees of RNL stretch. The functionality of the RNL under applied stretch can be tested further in an in vivo model by measuring the electromyography activity from the muscles in the larynx. Similar methodology has been used previously (6, 7, 26, 33).

In this work, we report which model parameters have the greatest influence on RLN stress and strain. Based on reported prior studies and our current results, we conclude that there may exist properties of the aortic arch and RNL that result in levels of strain (6–16%) that are large enough to cause injury to the left RNL. The current study demonstrates, for the first time, that the mechanical strain imposed on the RNL by the pulsing aorta can reach levels that have been reported to reduce the functionality of peripheral nerves. Our approach can be used to develop future animal models investigating the association of aortic arch deformation with RNL damage. Knowledge of the RLN biomechanical environment may be useful in minimizing nerve damage during thoracic surgery. A better understanding of the underlying cause of idiopathic UVP may provide novel diagnostic tools and treatment options for UVP.

GRANTS

Funding for this research was provided by the National Institute on Deafness and Other Communication Disorders (R01DC011311-01A1). M. J. Williams was also partially supported by the Computational and Mathematical Modeling of Biomedical Systems Training Grant (National Institute of General Medical Science Grant GM084905).

DISCLOSURES

There are no competing interests for the authors to declare.

AUTHOR CONTRIBUTIONS


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