

RESEARCH EDUCATION PLAN – ANDREW WISNESKI, MD

Primary Research Project

My proposed project is titled “**An Endovascular Device for Treatment of Ascending Thoracic Aortic Aneurysms/Type A Dissection.**” My clinical interest in cardiothoracic surgery and research interest in biomechanics and rupture risk assessment of ascending thoracic aortic aneurysms (aTAA) have inspired me to pursue this opportunity. I will begin with a literature review on current standards of treatment, the state of transcatheter aortic valve replacement, and existing aortic endovascular devices and their limitations. Understanding the challenges of the proposed project and formulating testable solutions leading to an eventual device design will require multi-disciplinary expertise from engineers, cardiac surgeons, cardiologists, and radiologists. Specific device testing experiments to evaluate performance and function will have to be created, and data collection/analysis will be performed, leading to iterations of design modification and further testing.

Rationale: Rupture or dissection of an aTAA can lead to sudden death or high mortality (up to 60%) even with acute surgical repair. Current guidelines recommend that aTAA patients undergo elective surgical repair when diameter reaches ≥ 5.5 cm in the absence of connective tissue disorder, family history of aneurysm, dissection, or rupture, or rapid growth rate. However, a large proportion of patients (59-97%) presenting with acute type A aortic dissection have ascending aortic diameters under the cutoff for elective surgery¹⁻⁴. Patients who undergo emergency surgery for aortic rupture/dissection experience high mortality (up to 26%). Thus, a certain population of patients with aTAA are at risk for rupture/dissection but do not meet the current criteria for surgical intervention. Current endovascular technology offers patients with aortic aneurysms beyond the ascending aorta (aortic arch, descending thoracic, and abdominal aorta) a minimally invasive, lower risk alternative to open surgery. Today, there is no endovascular device specifically designed to treat ascending thoracic aortic dissection or aneurysms. The anatomy and physiologic environment of the aortic root and ascending aorta is vastly different compared to the remainder of the aorta, and will require a dedicated understanding of the ascending aortic biomechanics involved in order to design a successful endovascular device. The **goals of this project** are to 1) apply advanced computational modeling techniques to characterize the biomechanics of the ascending thoracic aorta and ascending thoracic aortic aneurysms < 5.5 cm and ≥ 5.5 cm and 2) utilize these results to guide the development of a prototype endovascular device specifically designed to accommodate the unique factors of the ascending aorta. The **long term goal** of this project is to use computational modeling data to better identify patients with aTAA at higher risk for rupture dissection and be able to offer them a minimally invasive, lower risk treatment option to reduce the incidence of potentially fatal rupture/dissection.

Specific Aims

Aim 1: Develop accurate computational models of aTAA and simulate physiologic hemodynamic loading. Accurate patient-specific computational models require zero pressure aTAA geometry, wall thickness, and material properties. Patient-specific geometry of < 5.5 cm and > 5.5 cm aTAA will be obtained from computed tomography angiography (CTA). ATAA wall thickness and material properties will be experimentally determined from biaxial tensile testing of ex-vivo surgical aTAA specimens. ATAA finite element (FE) modeling simulations with physiologic blood pressures will be performed using LS-DYNA FE software to determine wall stress magnitudes and distribution in circumferential and longitudinal directions.

Aim 2: Compare circumferential and longitudinal wall stresses between < 5.5 cm (non-surgical) and ≥ 5.5 cm (surgical) aTAA patients. For each aTAA model, mean and peak wall stresses in the circumferential and longitudinal axes will be obtained. Statistical analysis will be conducted to compare the non-surgical and surgical groups' average mean and peak stresses and correlation between wall stress and aneurysm diameter.

Aim 3: Apply results from computational models of aTAA towards prototype design of an endovascular device to accommodate the ascending aorta. Computational modeling techniques will help guide design by providing data on tissue-device interaction, anatomical constraints, and can model device efficacy by assessing wall stress reduction. A virtual device and simulations will allow demonstration of potential device designs interactions with the ascending aortic tissue. Designs can then be translated into physical prototypes for ex-vivo testing and eventual implantation in animal models.

Research Design and Methods

Patient Selection: Human research approval was obtained from the UCSF Committee on Human Research and SFVAMC Institutional Review Board. All patients referred for ascending thoracic aortic aneurysms (aTAA)

evaluation will be considered for this study, focusing specifically on aTAA <5.5cm. Using these criteria, 150 aTAA patients (120 TAV aTAA and 30 BAV aTAA) to date will be included in this study.

1.A. Mesh Development of aTAA Geometry

1.A.1. CTA of aTAA: ECG-gated computed tomography angiography (CTA) scans are performed with a 256-slice GE Revolution scanner (GE Healthcare, Chicago, IL) with intravenous injection of 80-120mL of nonionic iodinated contrast (Omnipaque 350, GE Amersham, Milwaukee, WI). DICOM (Digital Imaging and Communications in Medicine) CTA images will be analyzed using ITK-Snap software's image segmentation algorithm⁵.

1.A.2. Zero-Pressure aTAA Configuration: Aortic geometry acquired by CTA under *in-vivo* conditions is pressurized based on systemic blood pressure, while hemodynamic loading simulations require an initial zero pressure configuration. The *in-vivo* geometry obtained from CTA image reconstruction will undergo an iterative, reverse FE modeling protocol to reconstruct the zero pressure geometry⁶⁻⁹. Zero pressure aTAA configuration will be validated by ensuring that the pressurized aTAA model geometry corresponds to the original *in-vivo* geometry from the patients' CTA.

1.B. Material Properties and Wall Thickness of aTAA

1.B.1. Experimentally Derived aTAA Material Properties and Wall Thickness

Dr. Tseng's laboratory has previously performed bi-axial stretch testing on surgically resected aTAA specimens, providing stress-strain curves and wall thickness for use in material properties for computational simulations¹⁰. Bi-axial tensile testing and wall thickness measurements of surgical aTAA specimens will be performed.

1.B.2. aTAA Material Model: The aTAA wall will be modeled as an incompressible hyperelastic material, which is comprised of non-collagen matrix reinforced with dispersed collagen fibers.

The strain energy function enforces the incompressibility of the aortic tissue. The non-collagenous ground matrix will be assumed to be isotropic and to have a neo-Hookean-like strain energy density function. The dispersed collagen fibers will be modeled using the general structure tensor¹¹.

1.C. Creation of Finite Element Models (FEM)

1.C.1. Mesh Generation: Contour points of the inner aortic surfaces will be exported into Rapidform (INUS Technology, Inc., Sunnyvale, CA, USA). Three dimensional surfaces will be created and using aortic wall thicknesses from 1B, aortic wall with inner and outer aortic surfaces will be filled with 8-noded brick to generate a volumetric mesh using Truegrid (XYZ Scientific Applications, Inc., Livermore, CA).

1.C.2. Hemodynamic Loading Simulations: LS-DYNA (LSTC Inc., Livermore, CA) FE software will be used to run simulations of hemodynamic loading and to analyze results.

Distensibility, aTAA diameter, first principal (FPS, circumferential wall stress) and second principal (SPS, longitudinal wall stress) wall stresses will be recorded. Zero pressure derived geometry will be validated by comparing three dimensional geometry of FE aTAA at systemic pressure to that from the CTA.

2.A.1. Data analysis of wall stress and aTAA diameters. For each aTAA FEM peak and mean first and second principal wall stress will be recorded at systole (120mmHg) and diastole (80mmHg) in kilopascals. Aggregate data will be represented by a value $\pm$ standard deviation. At systole, the color fringe plots generated by LS-DYNA enable visualization of regions where peak stress concentrates in the aTAA. Maximum aTAA diameter will be determined from centerline 3D reconstructions and recorded in millimeters at the aortic annulus, Sinuses of Valsalva, sinotubular junction (STJ), and ascending aorta at systole and diastole. Plots of peak and mean stresses versus maximum diameter will be made to assess degree of correlation of diameter versus stress.

3.A.1. Creation of a virtual endovascular device for aTAA. Use of data from the aTAA computational models, anatomic dimensions, and physiologic behavior of the ascending aorta will go into design of an endovascular device design specifically for the ascending aorta with the goal of achieving a compatible device design that can demonstrate wall stress reduction. Initial designs will be based on ring-supported endovascular stent grafts with branches to perfuse the coronary arteries, and an expandable percutaneous heart valve that would sit in the aortic valve position.

3.A.2. Simulation of device in aTAA environment and impact on wall stresses. Hemodynamic loading simulations, as described in 1.C.2 can provide evidence that a potential design can reduce wall stress. Demonstration of reduced aortic wall stress provides computational evidence of decreased risk of rupture or dissection. The virtual device's design can be modified to achieve this goal.

3.B.1. Creation of physical device prototype based on simulation results and ex-vivo testing. A successful virtual design can then translated into construction of a physical prototype along with guide catheters and wires that would be used in the delivery procedure. Initial ex-vivo testing can be performed with physical models of aortic anatomy and pulse-duplicator liquid flow loops. Ultimately, animal testing will be needed to demonstrate device function and safety before consideration of clinical trials in patients.

Expected Outcomes

Aim 1: Accurate patient-specific computational models of aTAA will be created, and hemodynamic loading simulations will be performed.

Aim 2: Wall stress data from simulations will be analyzed, and correlation between wall stress and diameter will be studied. Wall stress distribution patterns in aTAA will be analyzed.

Aim 3: A virtual prototype of an endovascular device for the ascending aorta will be created with computational evidence of reduced wall stress. The prototype will be physically constructed and ex-vivo testing will be performed, with the goal of pursuing animal implantation studies.

Mentorship

I am fortunate to have the mentorship of Dr. Julius Guccione and Dr. Elaine Tseng for this proposed project. In particular, Dr. Guccione will serve as my research mentor, providing technical and scientific leadership on my project. I will meet with him weekly and learn from his expertise in cardiothoracic medical devices and experience as a NIH-funded investigator. Dr. Tseng will serve as my career mentor, providing guidance on my career goals and personal development, in addition to mentorship on the research project. I have worked in Dr. Tseng's lab since 2011 and have greatly benefited from her mentorship over the years. With their combined expertise in cardiovascular biomechanics, computational techniques, and clinical experience, Drs. Guccione and Tseng are well equipped to help with the design of the device. Through ongoing mentor and team meetings, I can provide updates on progress and receive feedback about the project directions and challenges.

Coursework

I will plan to enroll in the following courses throughout the fellowship to enhance my skillset, which can be directly applied to my project: UCSF Department of Surgery Scientific Writing Course, Translational Challenges: Diagnostics, Devices & Therapeutics, Ethics and Responsible Conduct of Research, Biostatistical Methods in Clinical Research, Computer Aided Design, and Finite Element Analysis.

Future Goals

After my general surgery residency, my goal is to pursue a cardiothoracic surgery fellowship and eventually become an academic cardiothoracic surgeon with a career encompassing research, teaching, and patient care. Having developed a research interest in aortic biomechanics and computational modeling to gain better insight into the rupture risk of aTAA, my goal is to use research to enhance rupture risk prediction and better select patients for intervention. The proposed endovascular device that would be developed in the Innovation pathway would offer patients with aTAA or Type A dissection a lower risk, minimally invasive treatment option. My participation in the UCSF Biodevice Innovation Pathway will give me the skills and knowledge necessary to identify clinically relevant issues, design research and engineering processes to go about solving these issues, and use the results to benefit the clinical community. The proposed research plan will also help me reach the goal of becoming an independent investigator with NIH funding. After assuming a faculty position, I would plan to apply to NIH Early Career Development Awards (K awards) to continue my research efforts. As an extension of my interest in aTAA rupture risk assessment, I believe there are exciting avenues for investigation into more accurate means of rupture risk assessment. Working towards combining what is known about individual patient risk factors, genetics, and aneurysm biomechanics could lead to a clinical decision making tool to guide appropriate intervention for aneurysms, of which the aforementioned device would have a role. This would serve as a suitable project for an NIH K-award during my early career.

Signed:



Andrew Wisneski, M.D.



Julius Guccione, Ph.D.

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