

Computational Growth Modeling and Surgical Planning of Arterial Patch Reconstructions

by

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A Dissertation Submitted to the
Graduate School of Sciences and Engineering
in Partial Fulfillment of the Requirements for
the Degree of

Doctor of Philosophy

in

Mechanical Engineering



KOÇ ÜNİVERSİTESİ

August 10, 2020

**Computational Growth Modeling and Surgical Planning of Arterial Patch
Reconstructions**

Koç University

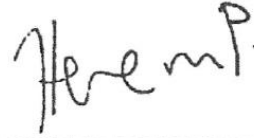
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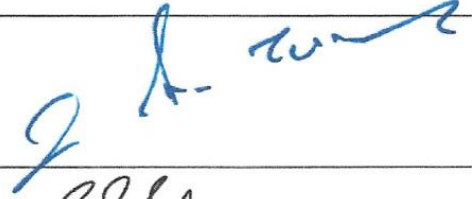
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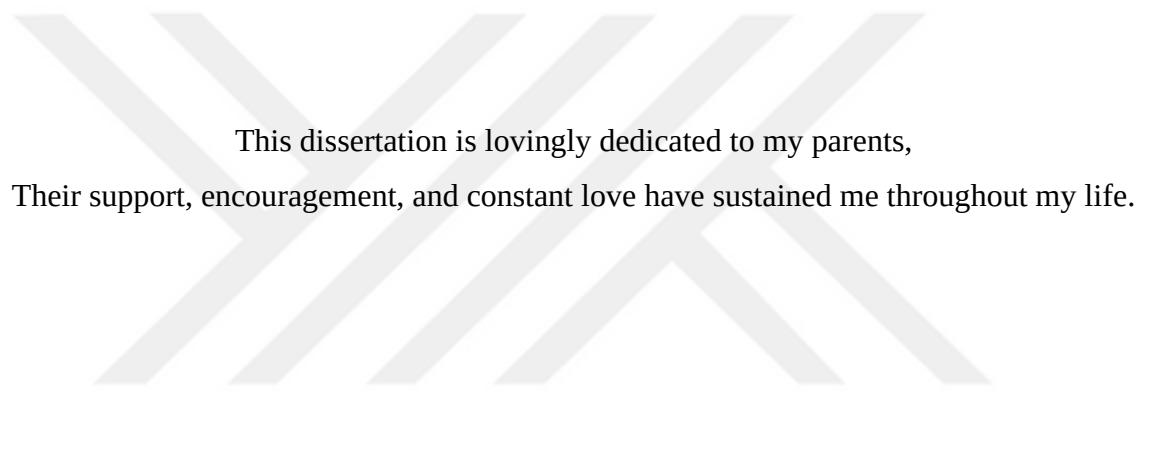
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Date: August 10, 2020



This dissertation is lovingly dedicated to my parents,
Their support, encouragement, and constant love have sustained me throughout my life.

ABSTRACT

Computational Growth Modeling and Surgical Planning of Arterial Patch Reconstructions

Seyedeh Samaneh Lashkarinia

Doctor of Philosophy in Mechanical Engineering

August 10, 2020

Approximately 1 in 100 children are born with a clinically significant congenital heart defect. Surgical treatment of congenital heart disease (CHD) involves complex vascular reconstructions utilizing artificial and native surgical materials. The objective of this thesis is to establish a predictive computational model for the volumetric growth of arterial tissue following complex cardiovascular patch reconstructive surgeries for pediatric and newborn patients. For the first time in the literature, the growth mechanics and performance of the growing arterial tissue domain in contact with artificial cardiovascular patches is established in this thesis.

In the first part, this thesis proposes a new *in silico* patient-specific pre-surgical planning framework for patch reconstruction and investigates its computational feasibility. The proposed protocol is applied to the patch repair of main pulmonary artery (MPA) stenosis in the Tetralogy of Fallot CHD template. Implantation of different unloaded patch shapes is simulated through a quasi-static finite-element vascular model with shell elements and the effects of stenosis grade, the three-dimensional shape of the surgical incision and material properties of the artificial patch are investigated. Stress-strain data obtained in-house, through the biaxial tensile tests to obtain the mechanical properties of common surgical patch materials, Dacron, Polytetrafluoroethylene (PTFE), human pericardium and porcine xenopericardium. Finite-element model is experimentally validated through the actual patch surgery reconstructions performed on the 3D printed anatomical stenosis replicas. According to our findings, the shorter incisions made at the throat result in relatively low local peak stress values compared to other patch design alternatives. Longer cut and double patch cases are the most effective in repairing the initial stenosis.

The microstructure for mature vessels has been investigated in detail in literature while there is limited information about the embryonic stages, in spite of their importance in the prognosis of congenital heart defects. It is hypothesized that the embryonic vasculature represents a disorganized but dynamic soft tissue, which rapidly evolves towards a specialized multi-cellular vascular structure under mechanical loading.

Hence in the second part of thesis, the microstructural evolution process of the embryonic pharyngeal aortic arch structure was simulated using an *in ovo* validated long-term growth and remodeling computational model, implemented as an in-house FEBio plugin. Optical coherence tomography-guided servo-null pressure measurements are assigned through the critical embryonic stages. The accumulation of key microstructural

constituents was recorded through zoom confocal microscopy for all six embryonic arch arteries. The total amount and the radial variation slope of the Collagen along the arch wall thickness in different arches and for different embryonic times, with different dimension scales, were normalized and compared statistically. The arch growth model shows that the stress levels around the lumen boundary increases from ≈ 270 Pa (embryonic Stage 18) to a level higher than ≈ 600 Pa (embryonic Stage 24), depending on matrix content production rates, while the homeostatic strain level is kept constant. The statistical tests show that although the total Collagen level changes with embryonic time, it proves radial localization around lumen, in accordance with numerical model results.

In third part, combining the methodology developed in the Part 1 and 2 of this thesis, an elastic-growing material model was developed in the open source FEBio software suite to first examine the surgical patch reconstruction process for an idealized MPA anatomy as a benchmark model and then for the patient-specific pulmonary arteries of a newborn. Following patch reconstruction, high levels of stress and strain are compensated by growth on the arterial tissue. As the growth progresses, the arterial tissue is predicted to stiffen to limit elastic deformations. We simulated this arterial growth up to the age of 18 years, when somatic growth plateaus. Our research findings show that the non-growing patch material remains in a low strain state throughout the simulation timeline, while experiencing high stress hot-spots. This new computational approach is effective for the pre-surgical planning of complex patch surgeries to quantify the unbalanced growth of native arteries and artificial non-growing materials to develop optimal patch biomechanics for improved postoperative outcomes.

ÖZÇETE

Bilişimsel Büyüme Modellemesi ve cerrahi arteriel rekonstrüksiyon Planlaması

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Makine Mühendisliği, Doktora

August 10, 2020

Yaklaşık 100 çocuktan 1'i klinik olarak önemli konjenital kalp hastalıkları ile doğar. Konjenital kalp hastalığının (CHD) cerrahi tedavisi, yapay ve doğal cerrahi materyalleri kullanan karmaşık vasküler rekonstrüksiyonları içerir. Bu tezin amacı, pediatrik ve yenidoğan hastalar için kardiyovasküler yama tamirlerini takiben damar dokusunun volümetrik büyümesi için öngörücü bir hesaplama modeli oluşturmaktır. Yapay vasküler yamalarla temas halinde büyüyen arteriyel doku alanının büyüme mekaniği ve performansı, literatürde ilk kez bu tezde yer almıştır.

İlk bölümde, yama rekonstrüksiyonu için hastaya özgü yeni bir ameliyat öncesi planlama protokolü önerilmiş ve hesaplamalı analize uygunluğu araştırılmıştır. Sunulan protokol, Fallot tanılı olgularda ana pulmoner damar (MPA) darlığının yama onarımında uygulanmıştır. Farklı yama şekillerinin implantasyonu yarı statik sonlu elemanlar vasküler modeli ile simüle edilmiş ve stenoz derecesinin etkileri, cerrahi insizyonun üç boyutlu şekli ve yapay yamanın malzeme özellikleri araştırılmıştır. Tamirlerde en çok tercih edilen yama materyalleri olan Dacron, Politetrafloroetilen (PTFE), insan perikard ve domuz ksenoperikardiyumunun mekanik özelliklerini elde etmek için çift eksenli çekme testleri yapılmış gerilme-şekil değiştirme verileri elde edilmiştir. Sonlu elemanlar analizi sonuçları, üç boyutlu prototipleme ile oluşturulan anatomik stenoz modellerinde gerçekleştirilen gerçek yama cerrahisi rekonstrüksiyonları ile deneysel olarak doğrulanmıştır. Bulgularımıza göre, darlıkta yapılan daha kısa insizyonlar, diğer yama tasarımı alternatiflerine kıyasla nispeten düşük lokal tepe gerilim değerlerine neden olmaktadır. Uzun kesiler ve çift yama vakaları ilk stenozu onarmada en etkilidir.

Erişkin damarlar için mikroyapı; konjenital kalp defektlerinin prognozundaki önemine rağmen, embriyonik aşamalar hakkındaki sınırlı bilgi olmamakla birlikte literatürde ayrıntılı olarak incelenmiştir. Embriyonik damarlanma, mekanik yük altında, çok hücreli vasküler yapıya doğru hızla dönüşen düzensiz fakat dinamik yumuşak bir dokuyu temsil ettiği varsayılmaktadır.

Bu nedenle tezin ikinci bölümünde; embriyonik faringeal aortik arkın mikroyapısal evrim süreci, valide edilmiş bir açık kaynak eklenti olan FEBio ile uzun dönem bir büyüme ve yeniden şekillenme hesaplama modeli oluşturularak simüle edilmiştir. Optik koherens tomografi eşliğinde basınç ölçümleri, kritik embriyonik aşamalara göre atanmıştır. Anahtar mikroyapısal bileşenlerin akülumasyonu, altı embriyonik ark için zoom konfokal mikroskopi ile kaydedildi. Kollajenin farklı arklarda, farklı boyutlarda ve farklı embriyonik zamanlar boyunca kemer duvarı kalınlığı boyunca toplam miktarı ve radyal varyasyon eğimi normalleştirilmiş ve istatistiksel olarak karşılaştırıldı. Ark büyüme modeli, lümen sınırındaki gerili seviyelerinin, matris içeriği üretim oranlarına bağlı olarak ≈ 270 Pa'dan (embriyonik Aşama 18) ≈ 600 Pa'dan (embriyonik Aşama 24)

daha yüksek bir seviyeye yükseldiğini gösterirken, homeostatik gerinim seviyesi sabit tutuldu. İstatistiksel testler; toplam kollajen seviyesi embriyonik zamana bağlı olarak değişse de, sayısal model sonuçlarına göre lümen etrafında radyal lokalizasyon olduğunu kanıtlamıştır.

Üçüncü bölümde; birinci ve ikinci bölümde geliştirilen metodoloji birleştirilerek, ideal bir MPA anatomisi için cerrahi yama rekonstrüksiyon sürecini ilk önce bir kıyaslama modeli olarak incelemek üzere açık kaynak FEBio yazılım paketinde elastik büyüyen bir malzeme modeli geliştirilmiştir. Daha sonra da model, yenidoğanın hastaya özgü pulmoner damar üzerinde uygulanmıştır. Yama rekonstrüksiyonunu takiben, arteriyel dokudaki büyüme ile yüksek düzeyde gerilim ve gerinim dengelenmektedir ve büyüme ilerledikçe, arteriyel dokunun elastik deformasyonları sınırlamak için sertleşmesi beklenir. Bu çalışmada; arteriyel büyüme somatik büyüme platolarının olduğu 18 yaşına kadar simüle edildi. Araştırmanın bulguları, büyümeyen yama malzemesinin simülasyon zaman çizelgesi boyunca düşük gerilme durumunda kalırken yüksek gerilimli önemli noktaların bulunduğunu göstermektedir. Bu yeni hesaplama yaklaşımı, postoperatif sonuçların iyileştirilmesi için optimal yama biyomekaniği geliştirmek üzere doğal arterlerin ve yapay ve büyümeyen malzemelerin dengesiz büyümesini ölçmek için kompleks pediatrik yama ameliyatlarının ameliyat öncesi planlamasında etkilidir.

ACKNOWLEDGEMENTS

Firstly, I would like to express my deepest gratitude to my advisor Prof. Kerem Pekkan for the persistent support of my PhD study and related research, for his patience, incentive and supreme knowledge. His guidance helped me in all aspects of my research. I could not have assumed having a better advisor for my PhD study.

I would like to thank all my thesis committee: Prof. Demircan Canadınç, Prof. Can Yücesoy, Dr. Ece Salihoğlu and Dr. Kerem Uğuz, for their thoughtful comments and morale which helped me to widen my research from various perspectives.

I thank all my lab mates in Pekkan Lab for the fruitful discussions, for the memorable days we were working together, and for all the fun and friendships we have had in the last five years. In particular, I am grateful to Dr. Şenol Pişkin and Dr. Gürsan Çoban for enlightening me the first glance of research.

I would like to acknowledge European Research Council (ERC) for Proof of Concept Grant KidsSurgicalPlan, ERC Starting Grant 307460 and TUBITAK for 1003 priority-research program grant 115E690 that supported my research generously throughout my PhD study.

Last but not the least, I would like to thank my parents and my husband for supporting me spiritually all over writing this thesis.

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Abbreviations

AMG	Algebraic Multi-grid
BSA	Body Surface Area
CFD	Computational fluid dynamics
CHD	Congenital heart disease
COL-I	Collagen Type I
DNS	Direct Numerical Simulation
ECM	Extra Cellular Matrix
FEM	Finite Element Model
FSI	Fluid Structure Interaction
G&R	Growth and Remodeling
IF	Immunofluorescence
LAL	Left Arterial Ligation
LPA	Left Pulmonary Artery
MPA	Main Pulmonary Artery
NCC	Neural Crest Cell
OCT	Optical Coherence Tomography
PA	Pulmonary Artery
PTFE	Polytetrafluoroethylene
RP	Rapid Prototyping
RPA	Right Pulmonary Artery
RV	Right Ventricle
SMC	Smooth Muscle Cell
TOF	Tetralogy of Fallot
VEGF	Vascular Endothelial Growth Factor
WSS	Wall Shear Stress

Chapter 1

1 INTRODUCTION

Approximately 1 in 100 children are born with a clinically significant congenital heart defect. These patients customarily require three consecutive open-heart surgeries to survive. During these surgeries, the abnormal great vessel anatomy is reconstructed with a cardiovascular patch using native tissue and artificial materials (Bouma and Mulder 2017; Hoffman 1995). A typical example of patch reconstruction surgery is the repair of vascular anomalies of the right side, as in the Tetralogy of Fallot (TOF) disease (Bailliard and Anderson 2009; Freedom and Benson 1992). In these operations, through the relief of main pulmonary artery (MPA) stenosis with an arterial patch, a balanced PA flow distribution is desired, which is influenced by the post-surgery conduit geometry and pressure levels. Unfavorable post-operative pulmonary hemodynamics may further result in abnormal pulmonary vascular remodeling (McElhinney et al. 1998). Achieving optimal hemodynamics through the surgical pathways is essential for healthy multi-organ physiology, which in turn will result in improved postoperative quality-of-life and neurodevelopment. Furthermore, post-surgery soft tissue and patch stress distributions should be uniform for improved patch patency and reduced calcification. Unfortunately, due to complex 3D anatomies and significant patient-to-patient clinical variation, it is not possible for the surgeon to ensure optimal patch biomechanics unless sophisticated bioengineering analysis is performed for each patient before the surgery.

Most importantly, surgical planning needs to consider the natural somatic growth of the native vessels, including the tissue response to changes in mechanical loading, as well as the disproportionate deformation of native and artificial materials. Considering the complexity of the problem, a biomechanical optimization tool is required to enable surgeons to implant a patch in a 1-year-old baby for as long as possible while native tissue vessels continue to rapidly grow before the need to re-operate. Recent progress in vascular growth mechanics has involved the use of computational algorithms to address clinical problems with the use of three-dimensional patient specific geometries.

The main objective of this thesis is to establish a predictive computational model for the volumetric growth of pulmonary arterial (PA) tissue following complex

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cardiovascular patch reconstructive surgeries for congenital heart disease patients. For the first time in the literature, the growth mechanics and performance of artificial cardiovascular patches in contact with the growing PA tissue domain is established in this thesis. Moreover, to our knowledge, this is the first study published in the literature where a temporal vascular growth and remodeling formulation is validated by *in vivo* measurements.

In terms of thesis organization; in Chapter 2, we develop a pre-surgical patch planning and biomechanical performance prediction system for TOF surgeries. It is hypothesized that this tool will assist the surgical team to achieve the best patch-reconstructed MPA conduit flow-pattern and mechanical stress customized for the individual patient *in silico*. While the framework demonstrated in this study is for MPA reconstruction, the methodology is equally applicable to the aortic patch repair surgeries (such as aortic coarctation and hypoplastic arch) with modifications on vessel dimensions, material property models and pre- post- operative loading.

In Chapter 3, a parallel study investigates the evolution of 3D vascular stress distribution during a critical period in embryonic (pharyngeal) aortic arch development. The dynamic multi-scale interactions between the mechanical loading modes and the vascular structures can be studied practically in early avian embryo animal models, since embryonic avian great arteries (i.e. pharyngeal aortic arch arteries), have high vascular cell density (in contrast to transgenic zebrafish models (Roman and Pekkan 2012)) and are coupled to a bi-ventricular circulation system, similar to human circulation. As in hypertension, there is a critical period where blood pressure level increases linearly during early embryonic development (Clark and Hu 1982; Kowalski et al. 2013; Zahka et al. 1989), but without pathogenesis, as a healthy physiological response to the growing embryo. It is known that major signaling molecules, such as TGF-beta receptor (TGF- β RII) and vascular endothelial growth factor-A (VEGF-A) dominate the evolution of arch structure and morphogenesis by means of cellular differentiation and regulation of extracellular biological content gradients (Plein et al. 2015; Ruhrberg et al. 2002). However, the effects of this complex signaling network can be tracked by reducing the dimension of the problem by means of tracking the rate of change in mechanical growth parameters, such as the growth stretch. This study is designed to simulate the vascular growth of a relatively long time period during early aortic arch development reaching 1.5

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days. A theoretical growth model that explains the growth and remodeling path of aortic arch during embryonic development is constructed and validated by *in vivo* data.

In Chapter 4, a predictive computational model for finite growth of arterial native tissue after cardiovascular patch reconstructive surgeries in CHD patients is presented. In this chapter we combine the patch reconstruction framework presented in Chapter 2 with the growth formulation which is established and validated in Chapter 3. Over the past decades, the role of mechanical loading in biological G&R in arteries has been investigated in detail (Ambrosi et al. 2011; Jones and Chapman 2012; Kuhl 2014; Menzel and Kuhl 2012; Taber 1995), including our recent study that clarified the role of elastin and collagen in growing arteries (Celik et al. 2020). The growth model presented in this chapter is calibrated to represent the postnatal pulmonary artery growth. Our contribution to previous growth formulations is including material stiffening of tissue due to growth in the model. Long-term complication of the patch surgeries can be predicted in the presented framework.

We conclude main achievements of this thesis focusing on arterial growth modeling and predictive surgical planning of patch reconstructions in Chapter 5.

Only the major elements of the multiple methodological approaches that require specific expertise and validation are provided in the Methods Section of each chapter and further details are provided in extensive Appendix sections.

Chapter 2

2 COMPUTATIONAL PRE-SURGICAL PLANNING OF ARTERIAL PATCH RECONSTRUCTION

2.1 Introduction

Pre-surgical hemodynamic planning (Hong et al. 2013; Yoshida et al. 2013) integrated with the 3D rapid-prototyping technology (Ejaz et al. 2014) has emerged as a useful tool in the surgical management of the complex congenital cardiovascular defects (Piskin et al. 2017). Our recent investigations on the hemodynamic performance of right ventricular outflow conduits, suggested an improved performance when customized valve leakage area and orientation are considered (Dur et al. 2010). Following the success in patient-specific computational fluid dynamics (CFD) simulations (Antiga et al. 2008; Pekkan et al. 2008; Sundareswaran et al. 2007), the pre-surgical planning concept, based on soft-tissue finite element models (FEM) has also been demonstrated (Biglino et al. 2016; Tang et al. 2011; Tang et al. 2013; Wenk et al. 2010; Yang et al. 2007). Particularly, the implementation of FEM in the pre-surgical planning of complex heart valve repair procedures is well-established (Bloodworth et al. 2016; Morgan et al. 2016; Rausch et al. 2016; Rim et al. 2015; Sanders et al. 2016; Zhang et al. 2017). Likewise, computational soft-tissue models are essential in the evaluation of stenting procedures of aorta, pulmonary and carotid arteries (Debusschere et al. 2015; Pasta et al. 2013; Sandoval et al. 2016). A relevant study by Tang et al (Tang et al. 2011) have investigated the effects of flow and stress-strain distributions in dilated right ventricle (RV) of a TOF patient using FEM method. Their findings showed that, artificial patches with similar material properties as the native RV tissue and small size lead to better RV function and recovery. This knowledge lead to an alternative RV patch strategy for contracting myocardium having decreased stress levels on the patch, improved RV function and reduced patch area (Tang et al. 2011; Yang et al. 2007).

In this Chapter, we present a pre-surgical, computer-aided surgical patch design framework for great arteries having arbitrary 3D stenosis sections. The proposed framework is validated through the actual surgical patch reconstructions performed on rapid-prototype replicas (Appendix A). This approach allows us to predict the intra- and

post-operative anatomy, mechanical loading and the hemodynamics of the surgical reconstructions. It also allows the structural optimization of the reconstructed patch region before the surgical execution, leading improved performance. Particularly, pre-surgical planning of the 3D patch shape will reduce cardiopulmonary bypass time and consequently could influence the probability of post-operative complications (Uzark et al. 2017).

2.2 Methods

The effect of geometric parameters in the proposed pre-surgical patch design framework is studied through a realistic main pulmonary artery segment having a symmetric stenosis that needs repair. A symmetric MPA stenosis is clinically the most common case. The model's anatomical dimensions correspond to a 9 year-old child's MPA that was taken from reference values reported in a statistical clinical study (Kutty et al. 2012). Model has an inner diameter of 18 mm and 1 mm uniform vessel wall thickness. Two stenosis levels of 70% and 80% in vessel cross-sectional area, which are typically repaired through a patch implantation, are considered as an indication for surgical intervention. The dimensions of the initial stenosed, pre-operative loading state is in agreement with our earlier study that employed clinical patient MRI and CT scans (Dur et al. 2010), typically operating at a mean intramural blood pressure of 60 mmHg for Tetralogy of Fallot (McManus 2006).

The pre-surgical patch design framework consists of multiple simulation steps partially summarized in Figure 2.1. The sequence of surgical operations or processes simulated through the finite element model, starts with the reduction of intramural pressure to the zero level, due to the cardiopulmonary by-pass and aortic cross-clamp. At this stage, only the residual stresses remain in the artery, which could be estimated prior to the operation non-invasively, if needed (Donmazov et al. 2015). The residual stresses are introduced through the “pressure-equivalent residual stress” technique where a finite intramural pressure corresponding to the desired residual stress distribution is applied to the unloaded configuration (Donmazov et al. 2015), which is typically 5 mmHg. Along the narrowed arterial segment, the surgical incision is introduced as a surface curve created interactively through an anatomical editing tool (Geomagic Inc, NC, USA) (Figure 2.1a). This 3D curve of incision is converted to a zero-gap slit in the FEM model

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where the cross-sectional area of the cut in both sides are opened slightly due to the release of residual stresses (Figure 2.1b). Next, an extra pull, if required by the surgeon is represented through a distributed traction boundary condition, normal to cut surface of the vessel (Figure 2.1c). The width of the opened region depends on the magnitude and direction of the force applied by the surgeon and the residual stress level. This gap, which is prepared just before the patch-implantation stage, can be precisely controlled in the current surgical procedure, as this opening is an important intra-operative geometrical parameter. To cover this gap, an initial patch shape needs to be selected and there are several alternatives explored in the present work (please see 2.4 Discussion). However, in order to standardize this process for the different parametric cases considered, a “tangent patch” that matches the local curvature of surrounding native tissue is employed (Geomagic Inc, NC, USA) (Figure 2.1c). This patch is then sutured to the native artery along the mid-artery layer by creating a bonded connection in the FEM model (ANSYS Inc, Somerset, PA, USA) (Figure 2.1d).

In order to simulate the post-operative stage after the heart is re-introduced to the circulation (following cardio-pulmonary bypass) and to simulate the performance of the designed patch, the patched PA configuration is pressurized to the typical intramural post-surgery blood pressure levels of 25 and 45 mmHg (Figure 2.1e) (McManus 2006), typically measured via routine cardiac catheterization.

Ten different scenarios have been simulated in the present study as detailed in Table 2.1. Case Baseline represents the conventional surgical configuration as implemented in clinics, where a straight slit, equal to the stenosis length is made on the artery. This is chosen as the nominal case and the simulation results of the other cases are compared to the Baseline case. To investigate the effects of various geometric parameters, the arteries with 70% stenosis level are cut by three different incision lengths; equal to (Baseline), shorter (Length_1) or longer (Length_2) than the stenosis length. Different slit shapes, such as oblique (Shape_1) and straight cut (all other cases) on the artery are also tested to determine the optimized shape of the patch. Shape_2 represents the double cut and double patched scenario. Case name Stenosis represents 80% stenosis level with a straight cut equal to the stenosed region’s length. The effects of patch material and thickness on reconstructed PA’s post-operative performance are investigated through Material group cases. Table 2.2 details the properties of all materials used in the present study. Finally, case Pressure presents the patched artery with different post-operative blood pressure.

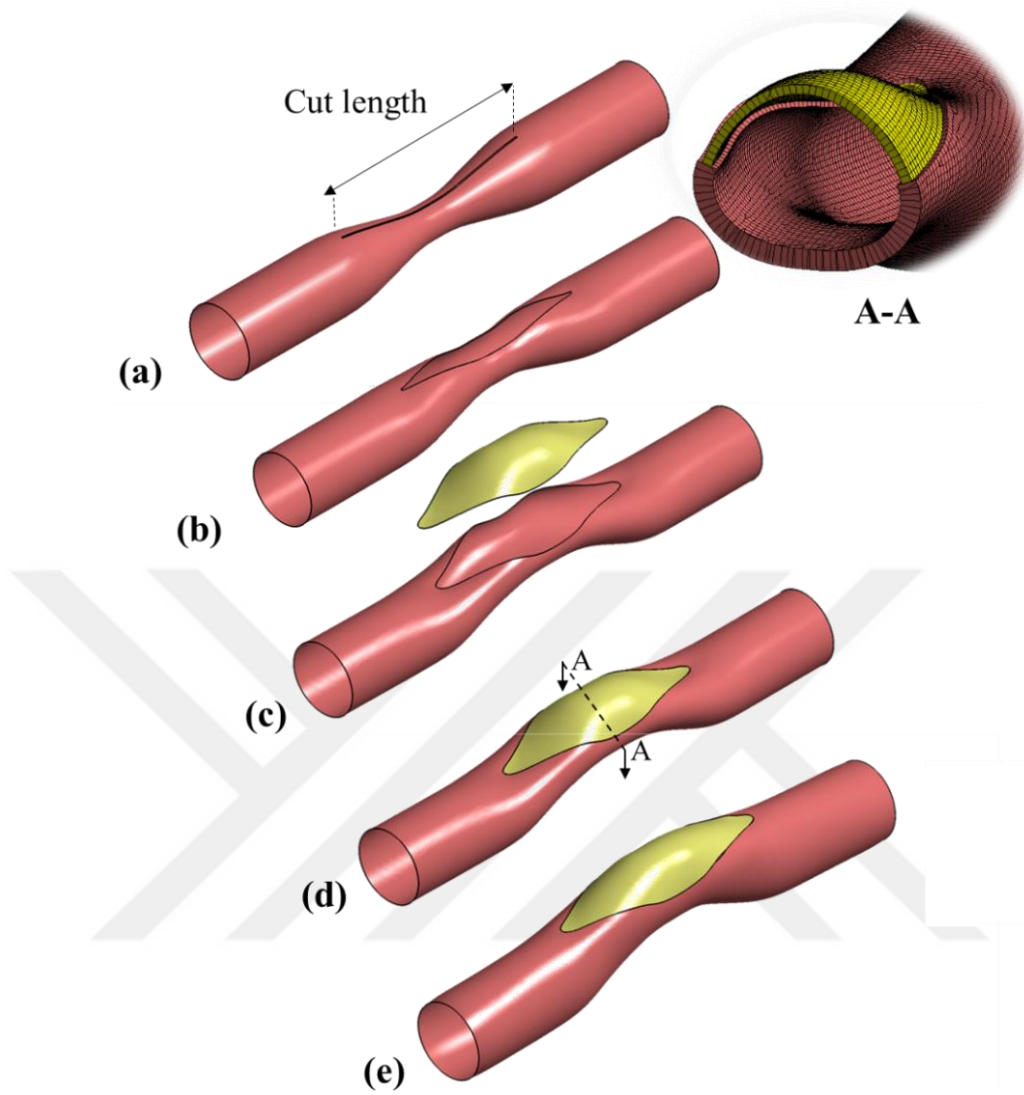


Figure 2.1: An idealized main pulmonary artery having symmetric stenosis leading to an asymmetric post-operative conduit after patch repair. The sequence of virtual surgical instances is illustrated in sequence. (a) Cutting an incision slit on the artery, (b) load-free state due to the release of residual stress after the incision, (c) intraoperative stretching of the incision gap for enlarging and deforming an initially flat patch to 3D shape that is tangent to the suture line curvature, (d) the suturing of patch to the artery, (e) following cardiopulmonary bypass, the arterial pressure is established and the reconstructed PA conforms to its acute post-operative shape.

A quasi-static finite element model is employed using high-quality tetrahedral shell elements (ANSYS Inc, Somerset, PA, USA). Mesh convergence runs are performed with edge lengths of 50 to 150 μm and a relatively finer grid-size (100 μm) is chosen. The sensitivity of results to different boundary condition schemes is tested to replicate the intra-operative clinical characteristics. For example, fixing both vessel ends at all degrees of freedom, lead to excessive patch deformations that have not been observed clinically. Thus, the simulations are performed by completely fixing the boundary close to the

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outflow tract, while at the other end, free-movement in the axial direction is specified. The selected boundary condition scheme closely described the surgical state based on the clinicians input.

The finite element solver is validated experimentally, where the entire sequence of pre-operative surgical actions are replicated using a flexible rapid-prototype stenosis model (please see Appendix A). The rapid-prototype replica of Baseline case is patched using a PTFE material (Hemashield Gold Knitted Double Velour Vascular Graft, Maquet Getinge group, Rastatt, Germany) and tested in a mock-up static pressure set-up. The error in computed deformations is less than 2.7%, compared to the experimental post-op measurements.

Table 2.1: Simulated patch scenarios and their corresponding geometric parameters.

Group Name	Case No.	Cut length (mm)	Cut shape	Slit stretch (mm)	Patch material	Stenosis percentage	Post-op pressure (mmHg)
Baseline	-	50	Straight	16	PTFE	70	25
Length	1	40	Straight	16	PTFE	70	25
	2	60	Straight	16	PTFE	70	25
Shape	1	50	Oblique	16	PTFE	70	25
	2	50	Double-Straight	16-16	PTFE	70	25
Stenosis	-	50	Straight	16	PTFE	80	25
Material	1	50	Straight	16	Human Pericardium	70	25
	2	50	Straight	16	Porcine Xeno pericardium	70	25
	3	50	Straight	16	Dacron	70	25
Pressure	-	50	Straight	16	PTFE	70	45

CFD analysis is performed using commercial software ANSYS Fluent 17.0 (ANSYS, Inc, Somerset, PA, USA). Simulations are first run with a grid size with the 500 μ m edge length. Based on a grid convergence runs targeting a constant pressure drop throughout the patched vessel, a grid size of 200 μ m, leading to 10⁻³ Pa pressure drop difference, is chosen. The CFD software is configured to implement an Algebraic Multi-grid (AMG) scheme to accelerate the convergence of the incompressible Newtonian

solver and employ a second-order accurate discretization scheme (Donmazov et al. 2015; Lara et al. 2011; Pekkan et al. 2009; Wang et al. 2007). The cardiovascular solver has been validated experimentally in our earlier studies (Chen et al. 2014). Velocity inlet boundary conditions are employed having a plug flow velocity profile (which is typical for outflow tracts) at 4 LPM mean pulmonary flow rate (Cheng et al. 2005b). Zero pressure outlet boundary condition is assigned at the vessel exit. The calculated average Reynolds number varies in 1531 to 1758 range along the vessel for post-surgery cases. For the pre-surgery case (70% stenosis), the average Reynolds number reaches 2607. Therefore, a direct numerical simulation (DNS)-like transient laminar flow model is implemented in the flow simulation of all cases. All flow simulations are continued until convergence of 10^{-5} residue. We reported converged running average results for pressure. To reach fully developed flow at the inlet and overcome the downstream end-effect on the model, the inlet and outlet are extruded accordingly while just the main geometry is shown in Figures.

Table 2.2: Linear elastic material properties and patch thickness of different surgical materials commonly used in pediatric cardiovascular operations obtained from in-house biaxial mechanical tests *except, the Main Pulmonary Artery Human- 9 year old which is provided from Wagenseil J.et al.'s study (Wagenseil and Mecham 2009).

Patch Material	Poisson's ratio (-)	young's modulus (MPa)	Thickness (mm)
Glutaraldehyde Treated Porcine Xenopericardium	0.39	2.89	0.4
Fresh Human Pericardium	0.4	3.4	0.5
PTFE	0.31	1.4	0.7
Dacron	0.42	1.19	0.6
Main Pulmonary Artery Human- 9 year-old*	0.45	0.75	1.0

The state-of-art cardiovascular patch materials conventionally used in pediatric surgeries include Dacron (Polytetrafluoroethylene Gore-tex Stretch Vascular Graft, Gore, Arizona, USA), PTFE (Hemashield Gold Knitted Double Velour Vascular Graft, Maquet Getinge group, Rastatt, Germany), Glutaraldehyde treated porcine xenopericardium and fresh or glutaraldehyde treated human pericardium. Biaxial mechanical tests are conducted for each material and corresponding stress-strain data are obtained by

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sinusoidal stretching of square shaped samples (10x10mm) up to 20% in both axial directions, using four linear motor configurations in the BOSE planar biaxial test system (BOSE, Framingham, Massachusetts). Strains are measured in both directions through the tissue dye-marked fiducial points as well as linear motor positions. The linear elastic material properties (Poisson's ratio and Young's modulus) are extracted from this data through a multi-dimensional least square fit corresponding to the operating range of the MPA (Donmazov 2016) – Please see Appendix B for details.

Finite element analysis shows that the thickness of the patch is an important parameter that affects the post-operative performance and shape of the patched artery critically. To overcome conventional measurement errors, the wall thickness of the Glutaraldehyde treated porcine xenopericardium, fresh human pericardium and artificial patches are measured using an optical coherence tomography (OCT) system (Thorlabs Inc, NJ, USA). Table 2.2 shows the extracted material properties and thickness of the tested graft tissues. As such, the material properties of the main pulmonary artery are assumed to be almost incompressible linear elastic (Wagenseil and Mecham 2009). Young's modulus and Poisson's ratio values are reported in Table 2.2.

Finite element and CFD simulations enabled the computation of multiple biomechanical performance indices, which are employed here to evaluate and compare the different patch designs and intra-operative strategies. These performance indices are listed below:

- Intra-operative stress introduced on the vessel due to opening of slit.
- Post-operative, equivalent von Mises stress distribution and gradients of the native artery/artificial patch providing maximum post-operative stress levels.
- Post-operative total deformation of patch and native artery.
- Post-operative stress gradients at the suture line due to material mismatch.
- Percentage of post-operative recovery of the initial stenosed lumen area and the corresponding hemodynamic post-operative pressure drop through the repaired anatomy.
- Post-operative arterial tortuosity; offset deviation of vessel centerline from the initial MPA pathway.

For the last two performance parameters, the cross-sectional areas normal to the centerline of artery for pre-surgery and post-surgery conditions are obtained using the vascular modelling toolkit library (Antiga et al. 2008). Achieving larger cross-sectional areas through the reconstructed surgical pathway is essential for optimal blood flow distribution in the PA. Local percentages of stenosis along the centerline are calculated by dividing the cross sectional area at the specific point to the maximum cross sectional area in model in post-operative situation. Tortuosity of the arterial model in post-operative condition is also measured in terms of the centerline's offset from the initial MPA's centerline at the throat.

2.3 Results

The equivalent stress distribution on the native MPA for the case Baseline is plotted in Figure 2.2a, immediately after that surgeon has opened the slit to enlarge the patch implantation gap. Stress concentrations at this intra-operative stage occur at both ends of cut native tissue. Another region with high stress levels (300 - 330 kPa) is observed at the initial stenosis throat. The relation between the width of the opening and the stress level is nonlinear. For example, when the model with 10% higher stenosis level (case Stenosis) is compared to case Baseline, the average stress around the gap increases 40% for obtaining a 16 mm-wide initial gap opening in both cases.

Figure 2.2b shows the stress distribution on the native artery for case Baseline after the patch implantation and pressurization (corresponding to the early post-operative stage). Maximum stress occurs at areas proximal to the stitch on the artery reaching 100 - 190 kPa levels. Patch tips also experience 63% of maximum stress on the artery while the un-patched native side of the stenosed region has moderate stress levels (30 - 80 kPa). All simulated cases predicted similar stress distribution on the artery and patch, but with considerable differences in stress levels.

Figure 2.3 shows the 3D post-operative shape of designed patches for the cases in Length group. The effect of slit length on the post-operative shape of the patch is examined using the results of these cases. All patches are designed for a standard 16 mm-width initial gap opening. For the shorter slit length, a patch area of 488 mm² is required which increases to 610 mm² and 807 mm² for Baseline and Length_2 cases, respectively. Likewise, the maximum stress value on these models increases from 135 to 239 kPa as

the slit length is increased from 4 to 6 mm, respectively. For the case Baseline and case Length_2, maximum stress occurs at the artery while for case Length_1, the implanted patch bears the highest stress. As the slit length decreases, high stress regions extend further such that they overlap with the highly deformed cambered center region of the patch.

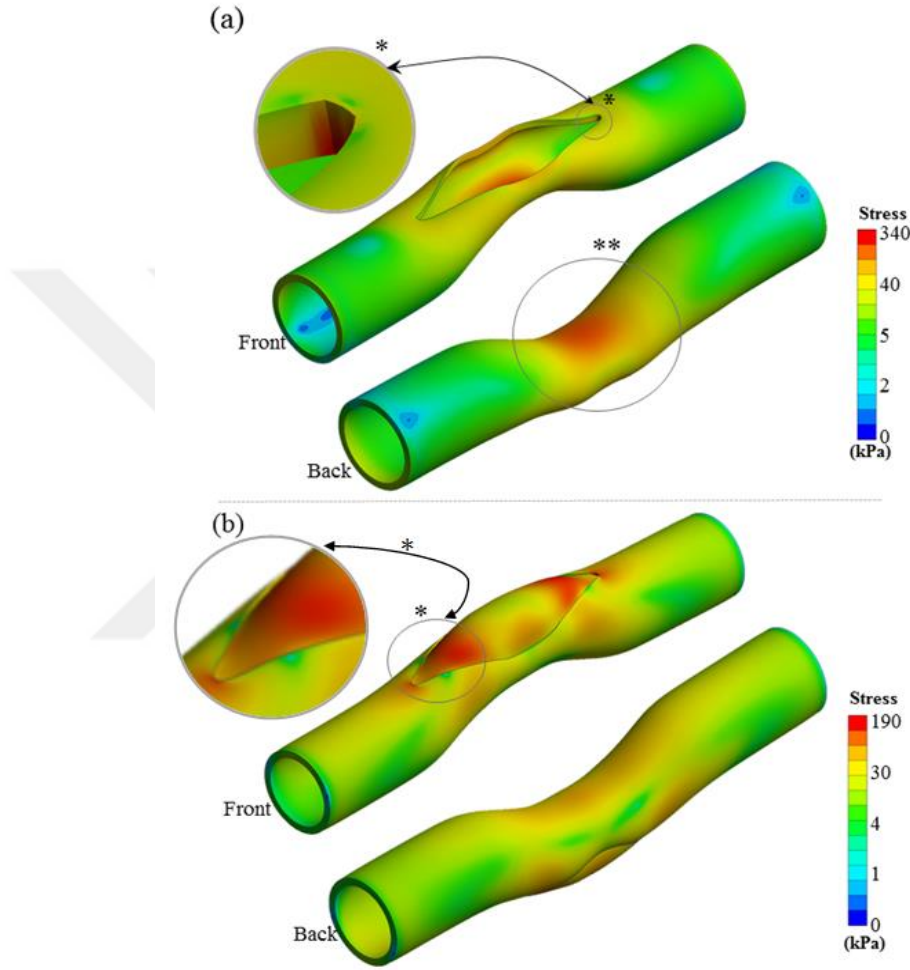


Figure 2.2: (a) Equivalent stress distribution on the artery during the opening of slit in surgery. * indicates the highest stressed region of the main pulmonary artery, which also observed symmetrically at the opposite side of the vessel. ** highlights the relatively moderate stressed regions. (b) Equivalent stress distribution on the patch and artery after pressurizing to post-operative blood pressure level. * shows the stress concentration regions on the patch and the artery. Stress gradient maps are shown in logarithmic scale to highlight the vessel and patch connection region's stress contours in various colors.

Simulation results for two novel patch configurations, which are not used conventionally in clinics, are presented in this section (Figure 2.4). The first patch configuration is obtained through an oblique cut at the stenosis region (Shape_1). The 3D

tangent patch generated for this case is more distorted in post-op state compared to the standard straight cut case (Baseline). Stress level on the patch was found to be 80% higher for case Shape_1 compared to the case Baseline, while the patch surface area decreased 16%.

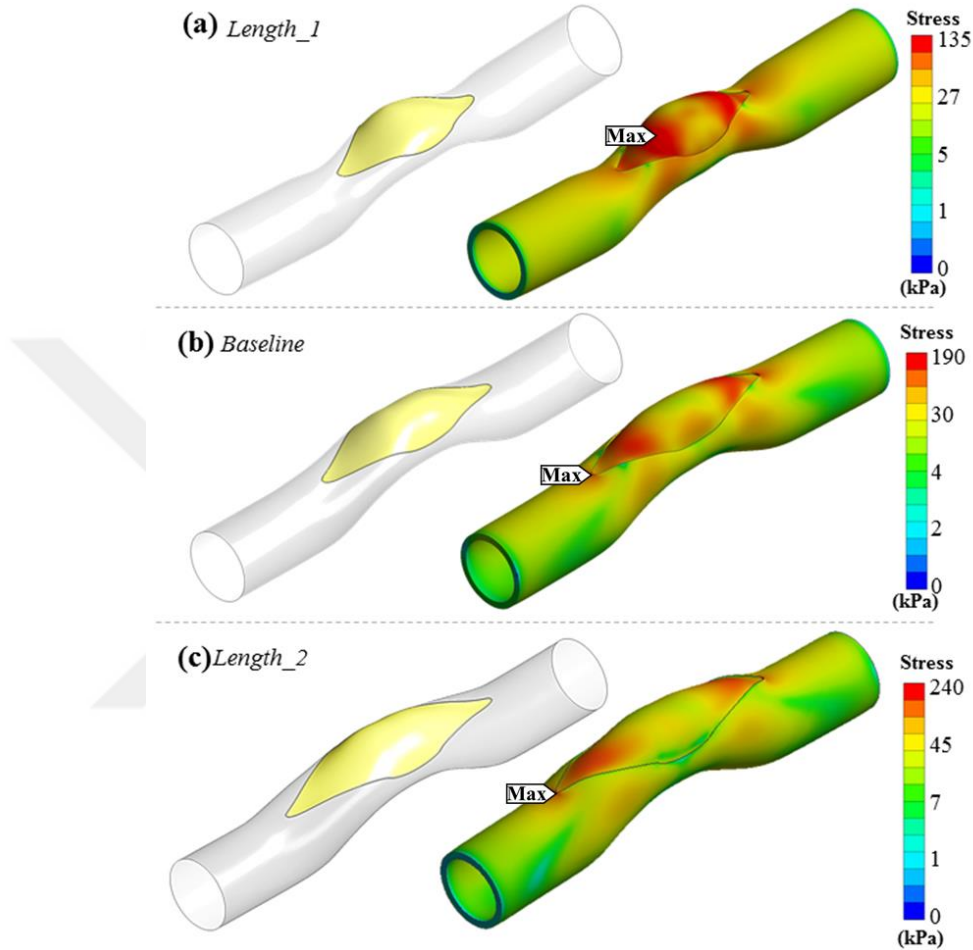


Figure 2.3: Comparison of von-Mises stress distributions on patched models having different surgical incision lengths. Left column shows the generated patch for three different cases - right column shows equivalent stress distribution on patch and artery, considering post-operative blood pressure. (a) 20% shorter cut than stenosis length (Length_1). (b) Stenosis length same as the cut length (Baseline). (c) 20% longer than stenosis length (Length_2). Stress gradient maps are shown in logarithmic scale to highlight the vessel and patch connection region's stress contours in various colors.

Implementing the patch to the stenosis region by using a single vessel opening recovers the narrowing of the vessel partly and remains the second half stenosed as shown in Figure 2.2b. To overcome this residual vessel narrowing effect, one approach is to patch both sides of the vessels with two identical patches instead of one as shown in Figure 2.4c. Indeed, the resulting post-operative patch reconstructions are relatively

flatter compared to the single patch solution and are able to recover the stenosis almost fully on both sides of the artery. However, the total patch surface area increases 67% and the maximum stress on the patch rises from 119 kPa to 216 kPa. Native vessel section also bare 95% higher maximum stress value compared to the Baseline configuration.

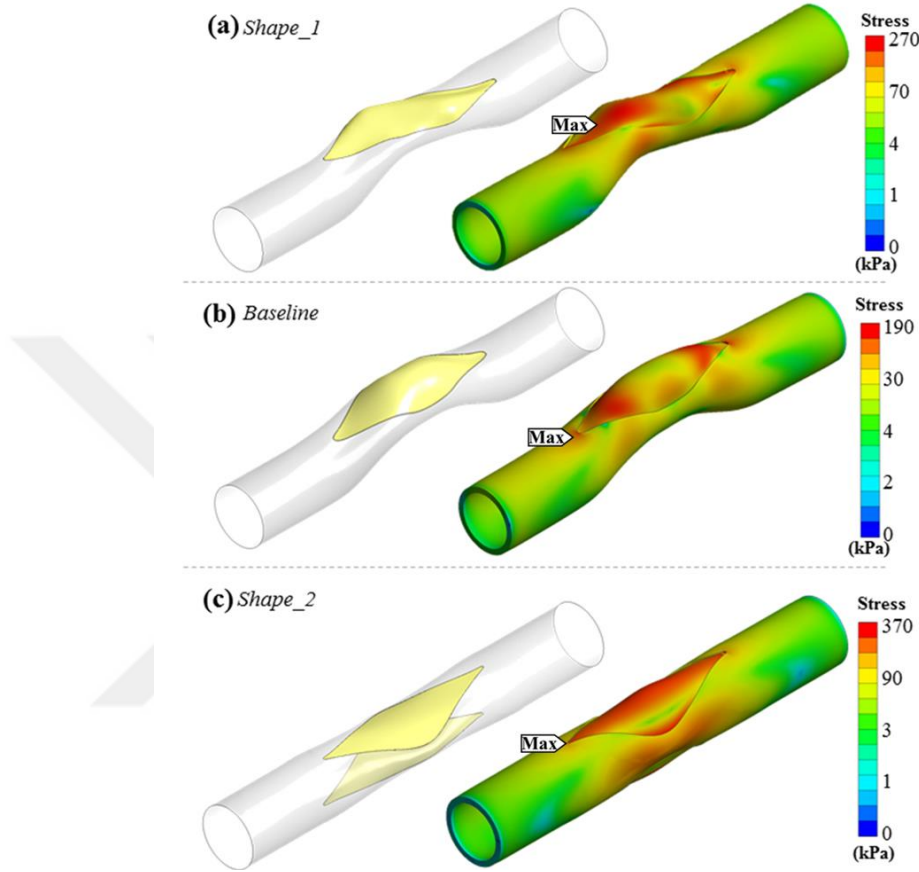


Figure 2.4: Exploring novel surgical options in main pulmonary artery patch surgery using the proposed simulation framework. (a) An oblique slit having a helix angle of 5 degree measured from center-line is introduced (Shape_1). (b) Straight cut on the artery (Baseline). (c) Implanting two similar patches on both sides of the artery (Shape_2). Stress gradient maps are shown in logarithmic scale to highlight the vessel and patch connection region's stress contours in various colors.

Simulation results for patch configurations with different materials are presented in this section. The mechanical behaviors of four different patch materials are examined. Three critical zones in terms of highest and lowest total post-operative deformation are identified in order to present the results in a compact form, as shown in Figure 2.5a.

Figure 2.5b shows the computed deformations for the case Baseline as an exemplary of all material cases. Other patch materials lead to similar total deformation distributions and the highest deformation regions are localized proximal to the ends of

the patch (Region 1 in Figure 2.5b). Although the deformation distributions are similar, stenosis recovery ratios vary for different materials: 46% (PTFE), 45% (human pericardium), 43% (porcine xenopericardium) and 41% (Dacron). Figure 2.6 shows these deformation and stress distribution.

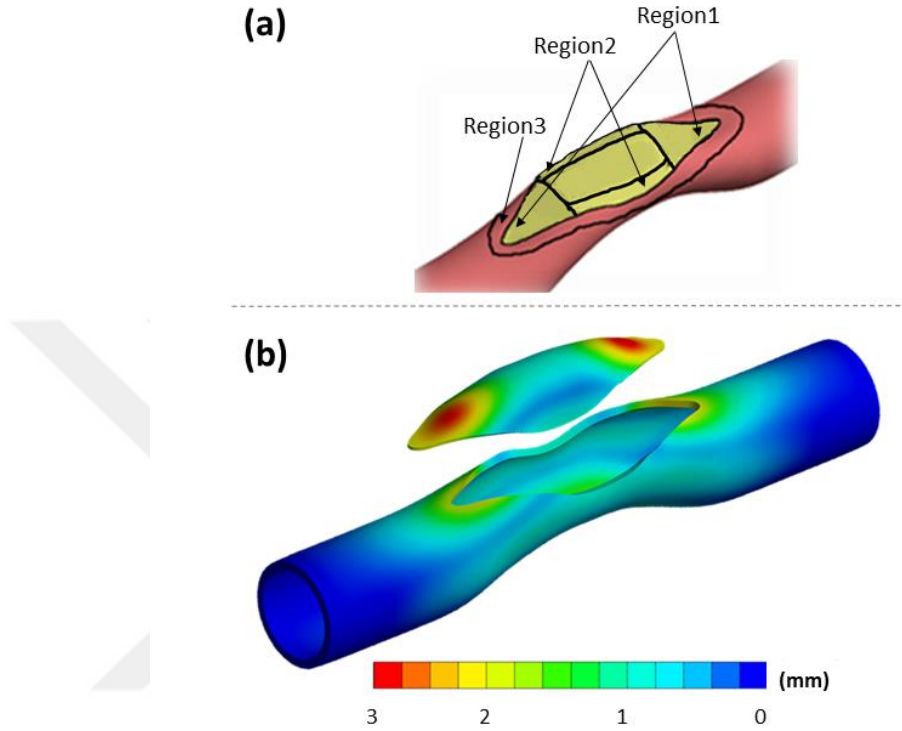


Figure 2.5: (a) Three major regions of patch and artery that experience different mechanical loading. (b) These regions are identified based on the corresponding stress patterns. For example, the total deformation on patched artery (Baseline) at the post-operative state are presented in the Figure 2.2 (patch and artery are shown separately).

Since the wall thickness of available patch materials are measured to be significantly different (Table 2.2) additional model verification studies are conducted where the sensitivity of patch thickness on post-operative mechanical loading is established. For example peak total deformation on patch corners decreases from 5.1 to 3.6 mm when the thickness of patch is increased from 0.6 mm Dacron patch (Material_3) to 0.7 mm, while peak stress on the model decreases slightly from 198 to 191 kPa. Other interesting comparison case is the modeling of human pericardium tissue with 0.4 mm thickness instead of its measured thickness of 0.5 mm. In this case, the peak total deformation and maximum stress value on the model is increased from 3.1 to 4.8 mm and from 255 to 319 kPa respectively. These simulations indicate that besides the material properties, the thickness of the patch affects total deformation values significantly that

can result in local “bumpy” regions with high deformations, proximal to patch corners as shown in Figure 2.6. These local bumps are visible in cases Material_2 and Material_3, in which a maximum total deformation of 5.7 and 5.1 mm respectively, occurs in bumpy peaks close to the patch corners (Region 1 in Figure 2.5a). For human pericardium (Material_1) and PTFE (Baseline), the post-op patch shape is entirely smooth at the ends.

Maximum equivalent stress occurs at the ends of the graft next to the stitched place (Regions 1 and 2) in all patch material cases. Both biological grafts (Material_1 and Material_2) have larger maximum stress values on the patch (255 and 325 kPa, respectively) compared to artificial grafts (Baseline and Material_3). On the other hand, first and second maximum stress values of 190 kPa and 198 kPa occur around the stitch area of the artery (region 3) in Baseline and Material_3 (artificial grafts cases), respectively.

The lowest stress difference (maximum equivalent stress) between the patch and the artery occur in the PTFE patch (Baseline), along the stitch lines, reaching 21kPa. Whereas the corresponding stress level is significantly higher (171kPa) in the porcine xenopericardium patched case (Material_2).

The post-operative cross-sectional area variation along the axial length is plotted for groups Baseline, Length and Shape in Figure 2.7. These cases employ to the same baseline surgical patch material (PTFE). Please note that the lumen area recovery characteristics for different patch materials are discussed earlier.

All cases in groups Baseline, Length and Shape display an increasing-decreasing trend where the throat corresponds to the maximum post-operative residual stenosis location, except the shorter cut model (Length_1). Interestingly, the Length_1 case displays a more complex post-operative vessel area variation. In this case, the pre-operative throat location is the most enlarged section post-operatively (9% stenosis is remaining) while the minimum lumen cross-section is observed at the patch ends where 32% stenosis is remaining. These narrow regions, make the case Length_1 disadvantageous in lumen area recovery point of view. In Figure 2.7, the green dotted line represents the longer cut (Length_2), which lies under all other lines. So, the least local residual stenosis remains for the case Length_2. A negative percentage of stenosis recovery (down to -4%), which means dilation of the artery at the patch end, is observed only for this case.

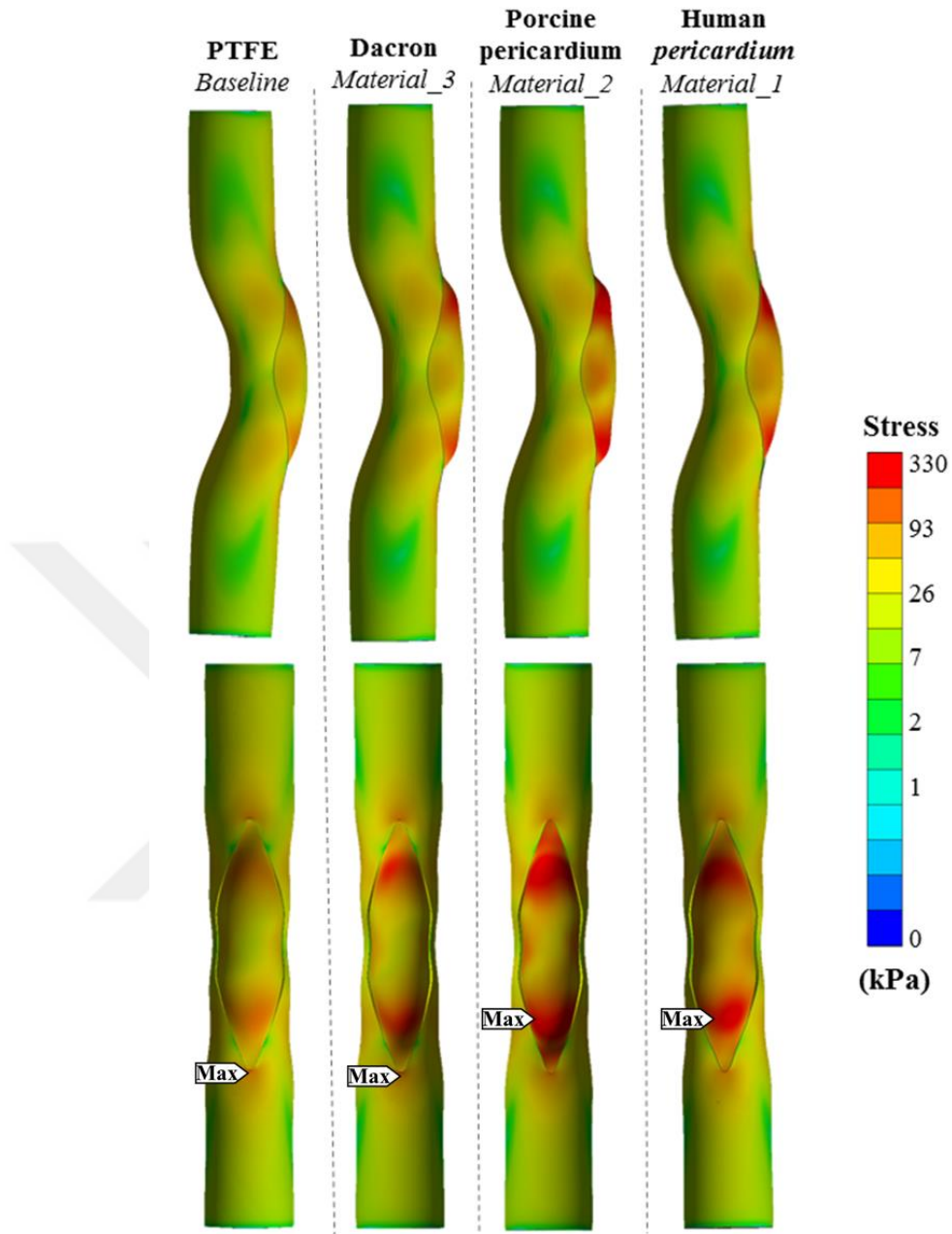


Figure 2.6: Equivalent stress distributions after patch reconstruction corresponding to the acute post-operative state, for different patch materials. Top row shows the coronal view of parametric material models and bottom row shows the corresponding sagittal view. Stress gradient maps are shown in logarithmic scale to highlight the vessel and patch connection region's stress contours in various colors.

Post-operative cross-sectional area variations are computed for the other cases, but not shown here for the sake of brevity. In both artificial and natural material grafts, there is a slight difference in cross section areas.

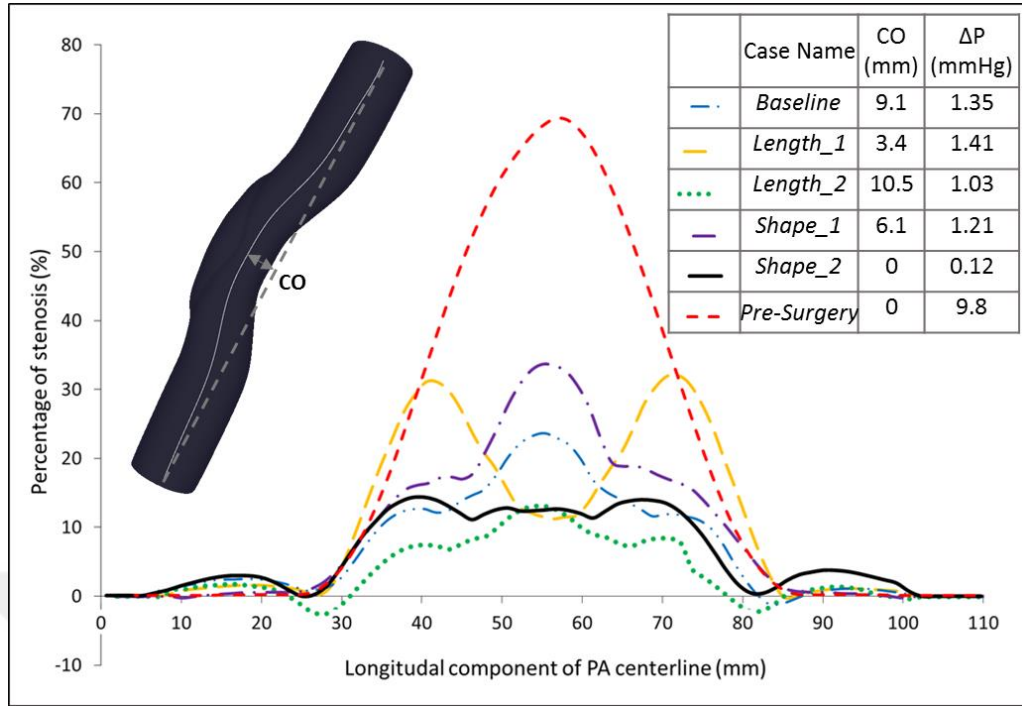


Figure 2.7: The local percentage of stenosis along the centerline is compared between pre-surgery case (70% stenosis level) and the post-operative cases. Pressure drop values and centerline offset (CO) at the throat are labeled near the case names.

The effect of pressure change on stenosis recovery is also tested in the current study. It is observed that an 80% increase in post-operative pressure (Pressure compared to Baseline) causes 29% decrease in the percentage of final post-operative stenosis as shown in Table 2.3.

Table 2.3: The performance parameters for the 10 simulated cases are summarized. Gray highlighted cells show the maximum stress value on the model.

Case name	Patch area (mm ²)	Post-operative stenosis (%)	Max arterial stress (kPa)	Max patch stress (kPa)	Average patch stress (kPa)
Baseline	610	24	189	119	40
Length_1	488	32	81	135	45
Length_2	807	13	239	140	34
Shape_1	514	34	52	268	72
Shape_2	511-511	14	369	216	104
Stenosis	535	39	176	127	42
Material_1	610	25	151	255	39
Material_2	610	27	154	325	39
Material_3	610	29	198	177	40
Pressure	610	17	457	250	81

Figure 2.8 presents the visualization of the blood flow through the patched pulmonary artery lumen in the Baseline case in terms of pressure, streamlines and velocity magnitude. A pressure difference of 1.35 mmHg from the inlet to the outlet of the vessel is computed. Due to the tortuosity of the patched conduit, the radial pressure variation is observed at the patched region. Cross sectional velocity distribution at the patched throat region of the vessel demonstrated a shift in the peak flow (~ 1 m/s magnitude). This shift persists downstream of the patch region.

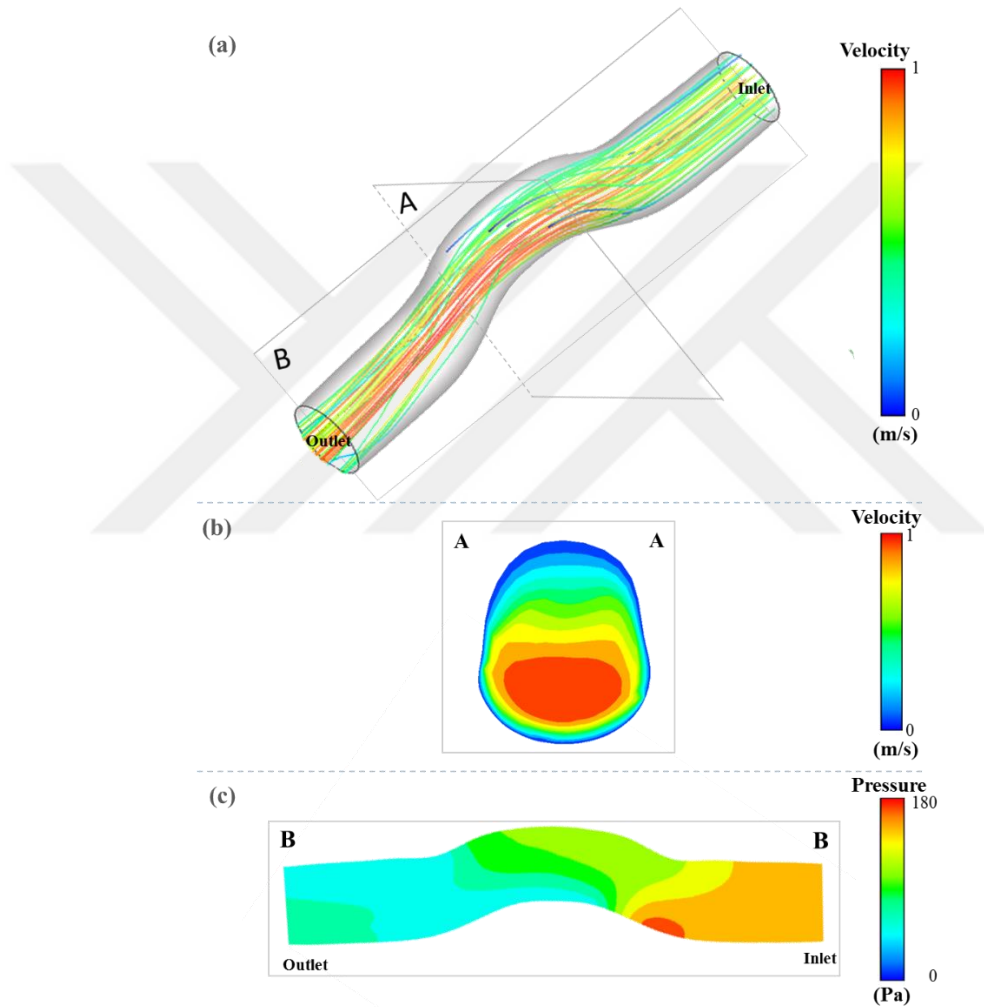


Figure 2.8: Patch hemodynamics quantified through the computational fluid dynamics analysis to compute pressure drop values. Only the Baseline case results are provided for brevity. (a) Velocity streamlines released from the inlet are colored by blood velocity magnitude. (b) Velocity magnitude contours of through the cross sectional cut of the vessel throat region (labeled by A-A). (c) Pressure distribution contour throughout the longitudinal direction at the mid-plane of the model (labeled by B-B).

Pressure drop and post-operative centerline offset values for three different slit length cases are shown in Figure 2.7. The most torturous case is the longer cut case (Length_2), which has 6.1 mm more centerline offset at the throat compared to the shorter cut case (Length_1). As expected, there are drastic changes in pressure-drop from 9.8 mmHg in pre-surgery case to 1.35 mmHg in Baseline post-operative case. In comparison between post-operative cases, pressure drop in the Baseline case decreases 0.32 mmHg when incision length is increased 10 mm in the case Length_2, while 10 mm decrease in cut length (Length_1) causes just an additional 0.06 mmHg pressure drop in the model.

It is worthwhile to mention that an extensive work is done in validating the CFD results. By running the pre-surgery case, using the k-w-STT model, the resulting pressure drop value is 30 mmHg which has a very large difference with the reported value for k-epsilon modeling result (48 mmHg). The disagreement between the turbulence models challenged us to try a “transient laminar flow simulation” which is a DNS-like simulation for all pre-surgery and post-surgery configurations. We employed this modeling strategy in our previous publications in transitional anatomical CFD models. Thus, in order to employ the same CFD model for both pre-surgery and post-surgery configurations all CFD simulations with a DNS-like CFD solver are accepted and reported in the manuscript. This approach will strengthen our confidence on the reported pressure drop comparisons made between pre- and post- geometries. The flow rate value of 4LPM according to the average MPA flow rate values in children reported in (Cheng et al. 2005a) to be precise in simulating the MPA flow in children. Table 2.4 the pressure drop values for the configurations modeled with updated boundary conditions. All results are continued until convergence of 10^{-5} residue and mesh convergence is achieved.

Table 2.4: Pressure-drop along the patched arteries with different patch shape. Results of different flow models are compared.

Q=4 LPM		Pressure drop (mmHg)			
Case name	Ave-Re	Steady-laminar	Transient-laminar (DNS-like)	K-epsilon	k-w-STT
Baseline	1638	1.24	1.35	-	-
Length_1	1732	1.13	1.41	-	-
Length_2	1531	0.94	1.03	-	-
Shape_1	1758	1.02	1.21	-	-
Shape_2	1540	0.10	0.12	-	-
Pre-Surgery	2607	-	9.8	58	45

The pressure-drop values are compared with the published results in Hojin Ha et al.'s experimental study (Ha et al. 2017). In their work, they have measured pressure drop in the stenosed pipes with the similar scale, stenosis percentage and fluid properties to our models. As shown in Table of their published manuscript, pressure drop range in experiments is in the same range with our transient-laminar flow simulation results but not the k-epsilon nor k-w-STT models results.

2.4 Discussion

2.4.1 Experience and knowledge gained in working with clinicians

Patch reconstruction is a fundamental technique employed in majority of surgical interventions of congenital heart diseases. For the surgeon, the prediction of the post-operative shape of the patch and the native tissue is a complicated task. The use of a patch design approach that provides customized, patient-specific geometries, as proposed in this paper will enable clinicians to rapidly implement a planned intervention on a 3D computer model systematically, visualize its resulting structural stresses, compute hemodynamic and mechanical performance indices and predict the 3D vascular immediate post-operative anatomical shape of their intended surgery without *in vivo* execution.

PA stenosis level in the TOF disease is widely varied from patient-to-patient; starting from mild pulmonary stenosis to pulmonary atresia with hypoplastic or absent pulmonary arteries (Jefferson et al. 1972; Kreutzer et al. 1996). In mild cases of the PA stenosis, to avoid surgical intervention, one treatment strategy could be the use of cardiac catheterization with balloon angioplasty, occasionally with an arterial stent (Gerrah et al. 2015; Pigula et al. 1999; Sugita et al.). Indeed, for mild stenosis levels, our simulations support the catheterization approach since post-operative stenosis recovery level is not high for the standard patch surgery. On the other hand, surgical intervention is preferred if the percentage of the PA stenosis is more than 50%, essentially the post-op improvement limit as shown in this paper. Most importantly, having defined the main performance parameters of patch repairs, our approach would aid the decision-making process for the borderline stenosis levels on a patient-specific basis.

The Baseline case employed in this study has been selected to represent the standard clinical operation. Briefly, a standard patch reconstruction starts with the measurement of

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main and branch PA sizes that are normalized by the body surface area (BSA) of the patient or descending aorta size at diaphragm level. Also, clinical experience implies that a pressure gradient at or above 50 mmHg through the MPA can be an indication to intervene. Then, the length of the patch is determined by measuring the length of the incision from the right ventricle to the pulmonary artery, and its width is determined by visually holding the edges of the incision open at valve level and judging the size of the roof required to create a new pulmonary annulus with a diameter no larger than three-quarters ($3/4$) the diameter of the ascending aorta (Nina 2014). The abnormal pulmonary vasculature is reconstructed in 3D using native tissue (treated or fresh pericardium) or artificial materials (PTFE/Dacron graft). Generally, a trans-annular patch should not be placed when the z-score value (Chubb and Simpson 2012) is larger than -3. Otherwise, the incision is carried across the annulus, the pulmonary valve excised, and the patch inserted (Nina 2014). Having a clinically realistic Baseline case is critical to evaluate and compare the performance of improved surgical alternatives.

2.4.2 Effect of incision length on patch performance

In this paper, both the mechanical and hemodynamics performance parameters that can be considered to optimize patch design are established. These parameters are strongly influenced through the incision length and shape, the number of cuts, patch material, stenosis level and the post-operative lumen pressure. In comparing the different cut length models, the longer cut model (Length_2) exhibits the lowest post-operative stenosis of 13% compared to 24% and 32% in Baseline and Length_1 cases respectively. Although case Length_2 has slightly higher maximum stress on the patch (140 kPa), it has the minimum average stress level (35 kPa), which makes it more favorable. The shorter cut model (Length_1) experiences the lowest maximum stress on the model (81 kPa), but from a cross-sectional enlargement point of view, stenosis is not resolved fully, particularly at the patch corners (32% stenosis is remaining).

2.4.3 Effect of incision shape on patch performance

In relation to the cut shape, the oblique cut model (Shape_1) presents unfavorable differences compared to case Baseline and forms deformation hot spots (bumps) on the patch. These distortions disturb the blood flow and may also cause folding of the patch in the long term. Furthermore, average stress (72 kPa) and maximum stress (268 kPa) levels on the patch and the post-operative stenosis (34%) are substantially higher for the oblique

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cut model compared to the straight cut model. Thus, the present findings recommend that surgeons should make the incision as straight as possible, for relatively straight vessels.

For the proposed novel patch templates, having double-cuts (Shape_2), the average stress on the patch (216 kPa) is 160% higher than the corresponding value of the Baseline case (119 kPa). However, reconstruction of the artery through this method results very good lumen enlargement and post-op rotational symmetry. Still, the small size pediatric vasculature and the difficulty in reverse side access will limit future clinical adoption.

2.4.4 Effect of patch material on patch performance

Patch material selection and its thickness influence the post-operative mechanics significantly. Among the simulated cases with different materials, the maximum stress on the patch varies significantly between 119 and 325 kPa. The PTFE material (Baseline) resulted the lowest peak stress (119 kPa) and the most homogeneous stress distribution around the stitch area compared to the other surgical material options. This is due to its high thickness and small Young's modulus of elasticity. Whereas, the porcine xenopericardium, which is the thinnest and second stiffest material, resulted multiple local bumps (5.7 mm total deformation) and the highest stress concentration on the patch corners (325 kPa). Even though the human pericardium ($E=3.40$ MPa) is stiffer than the porcine xenopericardium ($E=2.89$ MPa), it has lower stress levels due to the fact it is 0.1 mm thicker than the porcine xenopericardium. Overall, using different surgical materials for the patch results in similar total deformation distributions and the highest deformation regions are localized proximal to the corner sides of the patch (Region 1 in Figure 2.5b).

2.4.5 Effect of stenosis severity on post-operative performance

Pre-operative stenosis level also affects the post-operative patch shape, and stress level on the patch. Case Stenosis with 80% initial stenosis level is comparable to the Baseline, which has an initial stenosis level of 70%. To recover this higher stenosis level, the surgeon needs to open the slit as much as the Baseline case (16 mm gap width). This results in higher maximum stress (339 kPa compared to 881 kPa) on the artery intra-operatively, maybe due to higher curvature on the initial stenosis geometry. While the native tissue experiences this high stress level for a short duration, it could have a substantial effect for more extreme cases of stenosis. Further stretching of the tissue to open-up an appropriate gap for patch implantation would damage the native artery due to increased stress levels. Therefore, for extreme stenosis levels (higher than 80%), the

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replacement of the entire stenosis region with an artificial uniform diameter conduit can be justified for some patients -

Post-operative lumen pressure, which is typically between 25 to 45 mmHg, would influence the mechanical performance of pulmonary artery reconstruction. According to our simulations a 20 mmHg increase in post-operative pressure leads to 110% higher maximum stress levels on the patch and 7% more enlargement in vessel. These findings indicate that the post-operative pressure needs to be considered while designing the patch, especially in terms of maximum stress level rather than the stenosis recovery (Appendix C - Figure C.1).

2.4.6 Limitations

A number of important components of the present framework could be improved further. For example, determination of the initial patch shape is possible through multiple ways. For this research study, we implanted a cubic-wrapped patch with the same curvature as the surrounding native tissue and zero initial stress. This choice is reasonable since all initially planar linear elastic shells (raw patch materials) form a third-order cubic surface when subjected to bending load. Notwithstanding, the slight residual stresses are introduced when sheet patch materials are bended from flat sheets.

Likewise, simulations with initially flat and extremely cambered patches are also performed (Appendix C - Figure C.2). These simulations showed that increasing the surface curvature of the initial patch do not affect the peak stress value but it alters the location of high stress regions from the patch corners towards the lateral sides. Actually, the initial graft configuration is highly dependent on the initial slit opening area. Thus, generating equally curved patches for different surgical scenarios may not be the optimal strategy. For example, in double patch case, the initial configuration of the opened gaps constrains the use of a relatively flat “tangent” patch, since implanting two bulgy patches instead would lead to the vessel dilation for the post-operative state. Likewise, for the shorter cut case using a flat patch would not resolve the stenosis problem effectively, and a “tangent” patch (which is relatively bulgy) is preferred for this case. Therefore, in our framework by keeping the patch generating method fixed instead of the curvature level, unreasonable patch options are eliminated. This approach also allows a more unbiased comparison. It is worthwhile to mention that bulgier patches may be associated with flow recirculation and potentially flow stagnation zones.

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Another approach for determining the initial patch shape is through rapid prototyping (RP); following the registration/scaling step, the initial patch shape predicted by the FEM can be printed and the desired patch shape can be extracted directly from the printed model using a healthy RP model as a master with the help of the surgeon. This approach is partially illustrated in our experimental validation study (Appendix A). Finally, the complex 3D patch shapes predicted by the present approach can be developed through a 2D flattenization code and these shapes can be cut from the flat raw patch materials prior to implantation.

Another limitation of the current study, is the number of parameters being varied concurrently, which somewhat challenges the comparison across cases. This includes the geometrical variations in patch parameters (beyond incision shape), which challenges performance comparison across geometrical variations (Length and Shape), but also concurrent variations in mechanical properties and patch thickness. Further modeling limitations may include the use of a Newtonian blood flow model. This approach is justified in the pulmonary artery due to its large size. Furthermore, all the cases are compared within each other, thus the non-Newtonian effect is expected have relatively equal influence. Although structural and hemodynamics analysis have been performed in the current study, modeling the fluid structure interaction (FSI) has been left as a future work. This is also justified from comparative perspective and it is expected to bring roughly 10% difference in hemodynamic results.

Based on our preliminary experience with ongoing patient specific geometries the patch surgical planning would take approximately 1 week for the generation of surgical recommendations from the time of receiving 3D reconstruction of the pre-surgical MRI data. By applying the preoperative computed planning to more complex congenital cardiac reconstructive surgeries, we may reduce the early and late postoperative complication rate and thus improve mortality of the children who undergo cardiac surgery.

Chapter 3

3 VASCULAR GROWTH IN EMBRYONIC AORTIC ARCH

3.1 Introduction

Blood pressure and the vascular wall shear stress (WSS) govern the embryonic development of arterial structures as two distinct biomechanical loading modes. From a phenomenological perspective, these loading modes are associated with grossly different molecular pathways and result in distinct biological outcomes that shape the vascular morphology and augment the matrix remodeling of the embryonic great arteries. The WSS due to blood flow, is sensed through the endothelial layer, which triggers a complex time-dependent mechanogenetic network (Cansu Karakaya 2018), primarily resulting in lumen diameter increase. Taber (Taber 1998b) argues that, regardless of function, size and species, all blood vessels follow a WSS dependent energy-based optimization principle. However, these postulations do not extend to the vessel thickness, which explains why smooth muscle cell (SMC) controlling tone is not required at the initial formation of vascular beds. It is more logical for the vessel thickness to be controlled by the intramural tissue stress and/or strain due to the altered blood pressure levels. For example, for adults with hypertension, a chronic high blood pressure level is maintained during the disease progression, resulting in excessive stress levels in the tissue, sensed by fibroblasts and SMC mechanosensation. The further thickening of the artery is a result of TGF-beta related extra cellular matrix (ECM) production and fibrillar Collagen deposition (Humphrey 2008). The Collagen volume fraction is then assumed to be directly related to the mechanical strain/stress (Baaijens et al. 2010; Driessen et al. 2003), which is being regulated by the local contractile activity of the secretory cells. Given these distinct loading modes, this manuscript aims to expand our knowledge of matrix remodeling in pathological mature arterial vessels by investigating the fundamental microstructural features of embryonic aortic arch evolution *in vivo* and *in silico*, due to the step changes in the intramural stress levels and the relation with the matrix organization. Compared to our knowledge of the diseased mature vascular system, this phenomenon is less understood in developing embryonic systems due to limited research.

The embryonic development pattern of individual arch vessels exhibits a complex topological character from initial appearance around Hamburger-Hamilton stage 11

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(Stage 11) (Hamburger and Hamilton 1992) (40–45 hpf), to a relatively stable regime at Stage 27 (5 days) in the chick embryo (Wang et al. 2009). The early formation of the arch starts with endothelial cell structures connecting the primitive heart tube to the dorsal aorta (DeRuiter et al. 1993; Yablonka-Reuveni et al. 1998). A distinct aortic cell layer is formed around the endothelial layer at the beginning of Stage 12 which then leads to the creation of the second pair of pharyngeal arches (Arch II) at Stage 15 (Kolesová et al. 2008). The basic cellular process that govern the formation of the initial tube and artery formation is realized with the migration of the Neural Crest cell (NCC) derivatives through aortic arteries. In embryonic development, however, SMCs are supposed to have only a supporting role. WSS related alteration in lumen diameter is not affected by the removal of SMCs through the initial period of vascular development. Subsequently, at later stages (i.e Stage 18), the pharyngeal aortic arch structure experiences significant differentiation of the migrated NCCs into SMCs (Bergwerff et al. 1998). Thus, the supporting role of early SMC functioning now has the dominant characteristics to remodel the existing environment through the stable timing scheme between Stages 18 and 24, and beyond.

In standard growth models, growth is associated with residual stress which tends to diminish stress concentrations around lumen (Chuong and Fung 1983; Chuong and Fung 1986). Stress is a function of elastic deformation, while deformation due to growth reduces stress to the desired hemostatic level and terminates growth at that point in time (Rodriguez et al. 1994). Earlier studies show that growth laws expand to include WSS dependence and muscle contraction (Alford et al. 2008; Taber 1998a), where stress normalization and homeostasis occurs through SMC growth and SMC-mediated ECM deposition. In our previous studies the hemodynamic WSS loading at the embryonic arch arteries have been quantified (Kowalski et al. 2013; Wang et al. 2009). However, the WSS based pathological conditions were not clear from a mechanistic perspective and non-linear relation between WSS and lumen growth can only be explained through a more complex mechanosensitive gene expression network (Cansu Karakaya 2018). For example, we recently implemented a simple proportionality model to test the ability of WSS field computed from Computational Fluid Dynamics (CFD) analysis in forecasting the downstream shear-mediated three-dimensional pharyngeal arch artery growth (Lindsey et al. 2015). Despite some degree of linear lumen growth, this analytical approach did not produce predictions that agree with *in vivo* measurements since the WSS

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exhibited a definitive increasing-and-decreasing trend from Stages 18 to 24. Recent studies (Ryvlin et al. 2019) also support that WSS is not a “direct” driver of PAA vessel wall remodeling but likely to mediate lumen size increase through a nonlinear dependency (Celik M. 2019). The main point from that earlier research that created the impetus for the present study is that unlike WSS, the mechanical tissue stress caused by blood pressure demonstrates a continuously increasing trend during embryonic stages. In order to complement our earlier hemodynamic studies, we applied a loading mode with Collagen localization trend around the lumen through a finite element model (FEM), which provides new insights into the complex growth and remodeling process of soft tissue in the embryonic aortic arches. The embryonic soft tissue mechanical stress levels at these stages vary significantly, which correlate with the dynamic microstructural configuration of embryonic arch vessels, but at an unknown degree. In the present phenomenological approach, the concentration of strain around the aortic arches is simulated as a driving factor for further maturation of the tissue. Thus, dilatation like enlargement of the lumen periphery due to the localized strain increment is modelled as a phenomenological growth response with an accumulated growth stretch. This approach describes the signaling mechanism in general terms without analytical details.

In order to understand the fundamental relation between cellular production and the continuum mechanical environment of the aortic arch structure, the spatial distribution of major microstructural proteins, embryonic pressure load and the vessel strain/stress levels were measured *in vivo* at consecutive developmental stages. The spatial and temporal effects of a steadily increasing pressure level through Stages 18 to 24 is investigated in a recent study (Lindsey et al. 2018). In the present work, it is hypothesized that vascular stress levels are correlated with microstructural organization, which then trigger the remodeling events in the vessel wall during the early embryonic development of arch. While a strong correlation between these parameters are evidenced in this paper, the most exciting contribution of present research is the phenomenological computational description of microstructural protein production and the capability to simulate the arterial embryonic growth mechanism. In the future, the successful use of this analytical approach can lead to the simulation of the entire evolutionary process, reduce the need for complex animal models and predict the prognosis of complex arterial malformations. The present avian model functions as a practical approach to validate computational growth formulations.

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In terms of Chapter organization, only the major elements of the multiple methodological approaches that require specific expertise and validation are discussed in the Methods Section 3.2. Further details are provided in extensive Appendix sections. In the Results Section 3.3, we first provide a detailed statistical analysis of the immunofluorescence recordings before presenting the finite element computation results of a representative single aortic arch and the right and left laterals of the aortic arch manifold. We conclude the Results Section with discussion of the predictive capability of growth and remodeling simulations, focusing on the precursor of mature aorta, the right Arch IV. The implications and limitations of this research study are then provided in the Discussion Section 3.4.

3.2 Methods

3.2.1 Reconstruction of 3D arch anatomy during development

Fertilized white Leghorn chicken eggs (*Gallus gallus domesticus*) were incubated (Kuhl Corp., New Jersey, USA) at 65% humidity and 37.5 °C temperature. At HH Stage 18 and Stage 24 (Hamburger and Hamilton 1992), the lumen diameter and outer tissue boundaries of the arches were acquired *in ovo* and extracted from the depressurized aortic arches providing the unloaded configuration (Cansu Karakaya 2018) through Optical Coherence Tomography (OCT) (Goktas et al. 2016; Kowalski et al. 2013; Pekkan et al. 2016). For the left lateral, embryo was flipped as in left arterial ligation (LAL) model in previous publications (Kowalski et al. 2014). Sample *in vivo* OCT images showing the arch lumen boundaries are shown in Figure 3.1. A cross-sectional sketch of aortic arch manifold is drawn manually as a representative template geometry for sample n=5, which is converted to the 3D geometry by generating a 90° sweep of the cross-section for both left and right laterals (Figure 3.1b). Arch segments including all arches were collected for immunohistochemistry (IF).

An idealized model of this arch was created for growth simulations as a quarter of the T3 tori (Figure 3.1a). The triple arch system at each lateral act as a single deforming structure under internal blood pressure and the T3 layout is preserved *in vivo* (Figure 3.1b).

At each embryonic stage there are 6 aortic arches (Figure 3.1a), which are identified in this manuscript by three labels. For example, “Stage18-IV-R” represents the right IVth

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aortic arch at Stage 18. First, the embryonic stage at either Stage 18 or Stage 24 provides the HH temporal stage information followed by the second identifier for the arch type; i.e. Arch II presents IInd aortic arch and its bilateral positing is denoted by “L” and “R” for left and right laterals respectively.

3.2.2 Immunofluorescence and confocal imaging of existing aortic arches

Aortic arch tissues were extracted from the embryo and were processed in 4% paraformaldehyde solution at 4°C. For IF staining of the Collagen Type I (COL-I) and vascular endothelial growth factor (VEGF), the following antibodies were used: Anti-COL-I antibody (ABCAM, ab19807); rabbit anti-VEGF polyclonal antibody (BIOSS, bs-1665R) followed by goat anti-rabbit IgG H&L (Alexa Fluor® 488; ABCAM, ab150077) as the secondary antibody. As negative controls, sections with PBS rather than the primary antibody were incubated for each staining. Skin and great vessels of the heart from Stage 37 chick embryos were stained as positive controls. Primary antibodies were incubated overnight at 4°C and secondary antibodies were incubated for 2 hours at 37°C. In addition, Hematoxylin and Eosin staining was done as a control.

For qualitative assessment of IF stains, fluorescence images were captured with a Nikon AZ100 confocal microscope. DAPI (excitation 403 nm, emission 400-450 nm) and Alexa Fluor® 488 (excitation 490 nm, emission 525 nm) fluorescence were captured using sequential acquisition to give separate image files for each. Intensity values within and around each aortic arch wall were measured with ImageJ v3.91 software (Rueden et al. 2017). At least 10 sections from different samples (n=10) were averaged in order to eliminate the effect of longitudinal gradients in the staining intensity. Additionally, for the individual arch wall intensity measurements, any fluorescence signal generated by the red blood cells (i.e. erythrocytes in the vessel lumen) was excluded. Sample IF panels are provided as Appendix D - Figure D.1.

Arch pairs at Stage 18 and Stage 24 are also classified as 3 types; (i) Disappearing arch pairs (such as Arch II at Stage 18 which does not exist in the next stage), (ii) Persistent arch pairs (Arch III and Arch IV that exists in both Stage 18 and Stage 24), and (iii) Emerging arch pairs (Arch VI that first appears at Stage 21).

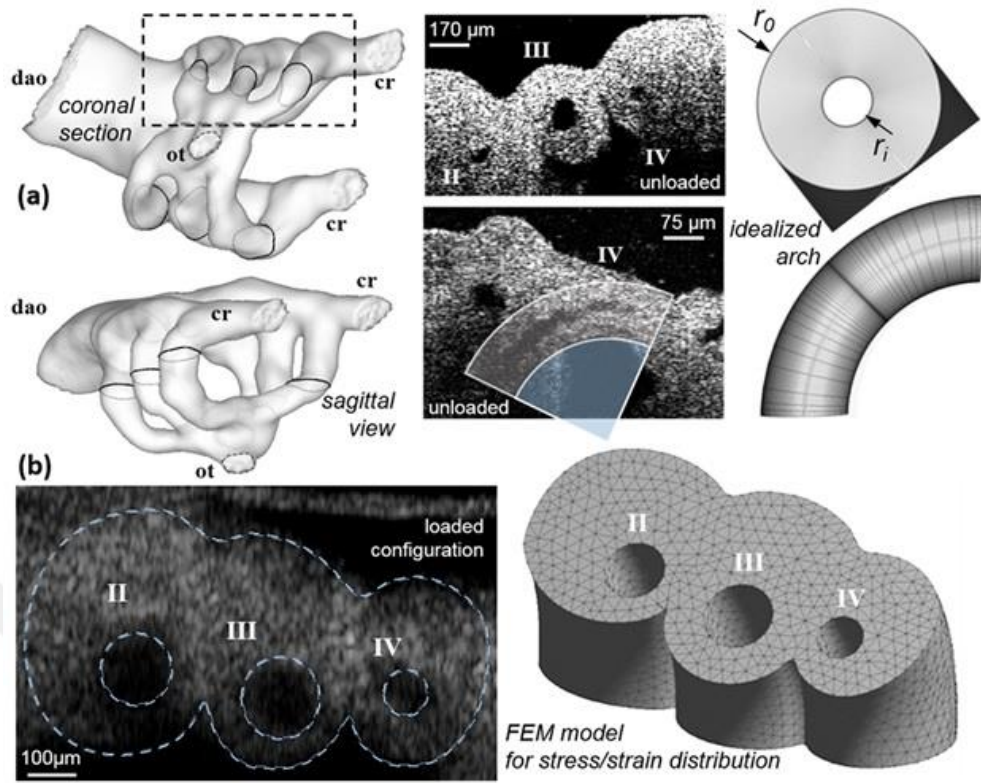


Figure 3.1: Coronal and sagittal views of the 3D reconstruction of the aortic arch manifold at Stage 18 is presented together with typical *in ovo* OCT image sections. OCT images correspond to the “unloaded configuration” where the systemic pressure is reduced to zero via a vitelline artery cut. For Arch IV, the geometric complexity of a paired arterial system is idealized as a cylindrical structure initializing the growth simulation at Stage 18. The prescribed 90-degree curvature is compatible with the sagittal OCT view as displayed on the raw OCT image. **(b)** The BOTTOM ROW displays a representative *in vivo* OCT image showing all three arches at Stage 18 at the loaded configuration. The corresponding segmental 3D finite element model of the aortic arch manifold for coarse tetrahedral mesh is presented. dao: Dorsal Aorta, ot: Outflow Tract, cr: left and right cranial arteries.

3.2.3 Space-time registration and normalization of IF images

Although the geometry of the arches under pressure resembles a circular shape, the paraffin-based embedding slightly distorts the arch geometries (Figure 3.2a). Therefore, we applied a multistep mapping procedure on IF images. Firstly, all images were “background subtracted” using ImageJ v3.91 software toolbox (Rueden et al. 2017). Then, a spatial mapping procedure (G) was applied on initial aortic arch geometries to obtain a non-dimensional circular version of intensity representations (Figure 3.2b). The underlying deformed grid layout in Figure 3.2c indicates that the registration is performed in elastic manner. In the next step, elastically registered images were transformed to the Cartesian form spanned by the polar (r, θ) axis via mapping procedure (T). T operator

consists of a polar transformation followed by a complementary registration procedure based on boundary mapping with soft landmarks (Figure 3.2d). Detailed information, including verification cases, of the mapping procedure is provided in Appendix E. Cross section of the idealized arch geometry used in the growth simulation is equivalent to the mean cross section of Arch IV-R measured from IF images of 5 test samples.

3.2.4 Statistical Analysis

Once the IF images are normalized it is possible to test the overall fluctuation of the intensity values with high spatial resolution. Therefore, each transformed sample was mapped on to a 720×400 pixels Cartesian grid to normalize the lengths by pixel numbers so that all statistical analysis is based on these registered (r, θ) sample sequences. This database includes grayscale value of each pixel which depicts quantitative intensity levels. We compared two fundamental intensity features of matrix proteins; (i) the mean level at each radial slice and (ii) the shape (S) of the radial intensity variation (Figure 3.2e).

In order to first calculate the mean level at each radial slice (one pixel width), the data was averaged over circumferential direction ($I(r)$). This quantity, without loss of generalization, can be used in statistical tests directly for pairwise comparison of arches. The testing design consists of a total of 10 comparison arch pairs that were devised as 3 arch types (disappearing, persistent and emerging) for further comparisons and intensity tests. The comparisons were carried out via parametric testing of the null hypothesis H_0 which states that samples do not differ significantly in terms of their intensity levels. For comparison procedures, the parametric two-sample t-test was used ($n = 5$) under the assumption of normality. In all cases, the results for the non-parametric two-sample Kruskal-Wallis test has been shown to track any significant difference between samples, as an additional supporting argument for the parametric test results. The normality of the individual arch sample groups were tested using the Shapiro-Wilk test.

Secondly, the shape of the protein distribution along the radial direction was then investigated. The position of the peak levels of protein distribution and its radial trends were determined, including the way it descends towards the wall and the level at which it finalizes a steady state end condition. The functional layout of the Collagen deposition is well characterized by a double-exponential decay function having a single peak. To compare the shape of the radial intensity variation, unlike Collagen level tests, we defined

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the quantity S which does not depend on the level of intensity layout due to normalization (Figure 3.2e). Even though each arch vessel sample has a different diameter and inner/outer lumen contour, this analytical methodology allowed the scaling of each sample to map all samples to the same unit size. This allowed us to statistically compare the microstructural intensity at each radial location. Thus, the normalized vessel thickness was divided in to 10 radial blocks in which Collagen intensities were computed. Each block includes 40 radial slices. Thus, the normalized radial distance (rd) from the lumen ranges from 0 to 1 where each 0.1 width segment specifies the borders of one radial block. These statistics were tested by parametric t-tests (setting $\alpha=0.05$) to evaluate the null hypothesis H_0 , which states that two arch blocks do not differ significantly (are similar) in terms of the slope magnitude.

The intensity levels and the slope (S) statistics were measured taking into account the fact that geometric distortions have effects on the registration procedure. Reported statistical analyses were performed on ($N = 5$) samples of each arch.

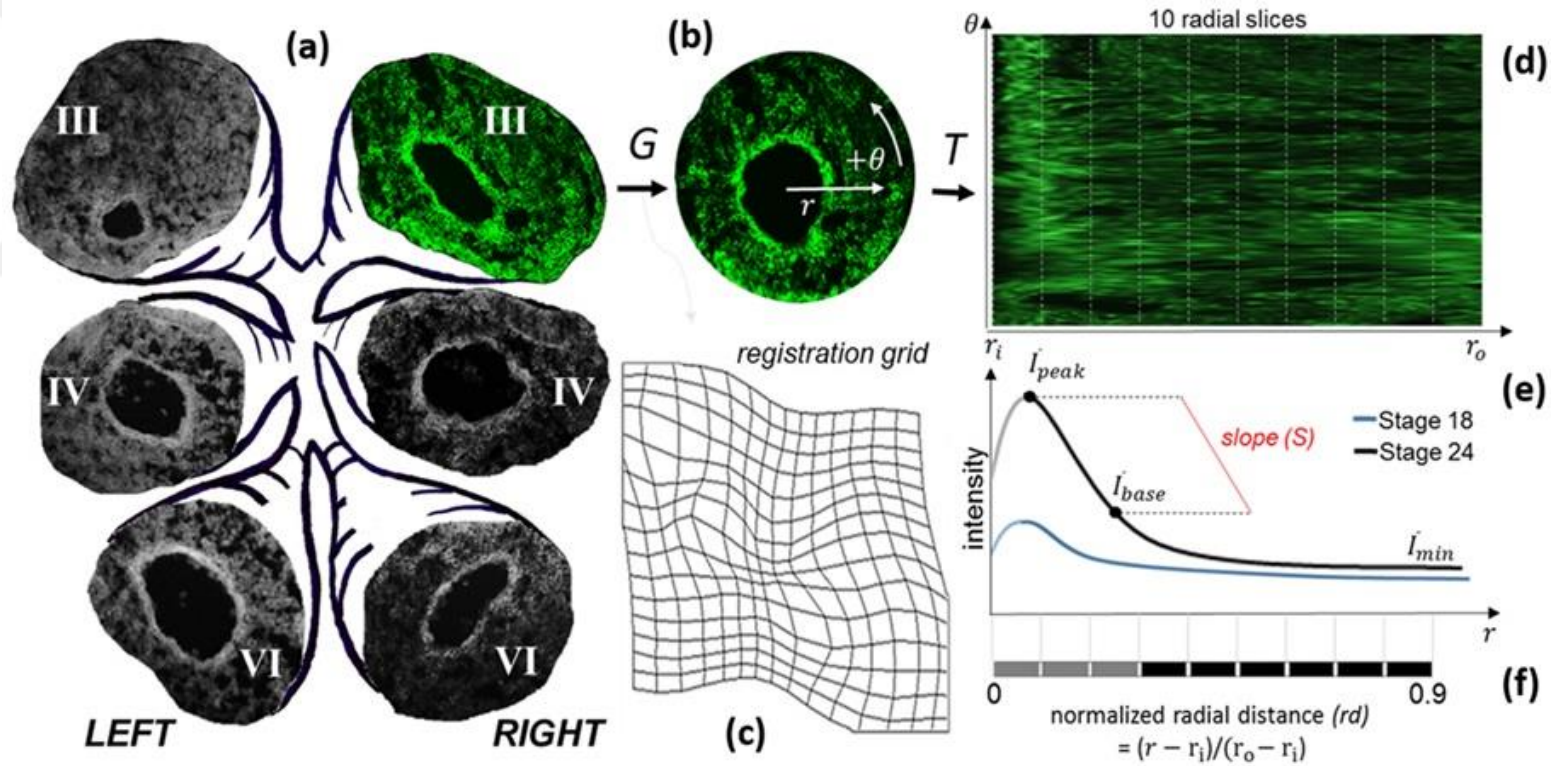


Figure 3.2: (a) Zoom confocal microscopy IF image of COL-I displays the cross-sectional slices of all 6 aortic arches at Stage 24. (b) An elastic spatial mapping procedure (G) is applied on IF image of Stage24-III-R to obtain a circular registered version of COL-I intensity representation. (c) The underlying deformed grid layout of the image shows the resulting elastic deformation of the registration. (d) An invertible polar transformation (T) is then applied to provide a dimension-free Cartesian representation of COL-I distribution spanned along the polar (r, θ) axis. For each case, 10 statistical radial blocks are identified on the image along the radial direction of each vessel. (e) Representative graphs of the average intensity over circumferential direction, $\bar{I}(r)$, for Stage 18 and Stage 24, positioning from the inner radius, r_i to the outer radius, r_o . Slope S is identified as the rate of intensity decrease. (f) The null hypothesis of “equal level of deposition” (identified in GRAY color) is tested against significant difference in collagen deposition levels (identified in BLACK color) on radial block segments. Radial regions highlighted in BLACK indicate significant differences in “intensity level”.

3.2.5 Tissue growth and remodeling formulation

Single-parameter material models of long chain polymers were used for our experimental observations. This particular model has potential to include more complex situations when anisotropic properties are determined (Figure 3.3). We characterized this behavior through an isotropic Neo-Hookean material model with a single shear modulus parameter (μ), which is customarily dependent on the volume fraction of stiff material embedding. The elastic modulus of the tissue increased twice over time. The production of stiff materials was assumed to be activated around lumen periphery first, based on the same experimental observations.

Since the modulus of the tissue is not preserved but constantly increasing, it is possible to link the net changes in modulus magnitudes to the cellular production of more stiff materials. The cellular production is assumed to be dependent on the mechanical stretch level sensed by the organism via a deterministic feed-back through a mechano-transduction pathway. Compressibility is assumed to model the interaction between the newly created material inside the extracellular matrix and its surrounding tissue.

Under these circumstances the model framework is given as follows. First, we introduce the basic kinematic quantity, the deformation gradient $\mathbf{F}$ which is defined as the tangent of the nonlinear deformation map $\boldsymbol{\varphi}$,

$$\mathbf{F} = \nabla_{\mathbf{x}} \boldsymbol{\varphi} \quad (3.1)$$

According to the multiplicative decomposition theorem, total deformation gradient tensor $\mathbf{F}$ in this model can be decomposed into,

$$\mathbf{F} = \mathbf{F}_e \mathbf{F}_g \quad (3.2)$$

where $\mathbf{F}_g$ represents the growth-related deformation gradient tensor and $\mathbf{F}_e$ is the elastic part of the tangent mapping that is used to obtain the elastic stress accumulated inside the domain (Rodriguez et al. 1994). The growth deformation can be given by the multiplicative decomposition with a single parameter v_g ,

$$\mathbf{F}_g = \mathbf{I} + (v_g - 1) \mathbf{f}_0 \otimes \mathbf{f}_0 \quad (3.3)$$

that defines the amount of permanent elongation in the direction of the fabric vector $\mathbf{f}_0$. The fabric direction is determined by the growing material flow controlled by the stimulus function of elastic stretch level λ_e inside the tissue. This flow direction is selected to be co-axial with the maximum principal stretch $\lambda_{\max}$. The growth stretch λ_g satisfies the

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condition $\lambda_{\max} = \lambda_g \lambda_e$. The stimulus function $v_g(\lambda_e)$ has been defined in the same form in previous research ((Göktepe et al. 2010), (Rausch et al. 2011))

$$\dot{v}_g = k_g(v_g) \eta_g(\lambda_e) \quad (3.4)$$

and

$$k(v_g) = \frac{1}{\tau} \left(\frac{\lambda_{\max} - \lambda_g}{\lambda_{\max} - 1} \right)^\gamma, \quad \eta_g(\lambda_e) = \lambda_e - \lambda_h \quad (3.5)$$

For a kernel nonlinearity parameter γ . We hypothesize that the embryonic structures have an unlimited growth kernel where the tissue is assumed to grow towards multiple orders of its original magnitude, a limit constraint for the weighting kernel function k_g is carried out. In succinct terms, it is $k_g = 1/\tau$. Then the evolution of the grown stretch depends on the critical homeostatic stretch λ_h and the critical time τ . The growth process is activated when the elastic stretch exceeds λ_h and the speed is determined by τ . The source of the mass increase is related to the internal stretch change and consistent hardening. The elastic part of the second Piola-Kirchhoff stress function $\mathbf{S}_e$ is defined as,

$$\mathbf{S}_e = (K \ln(J_e) - \mu) \mathbf{C}_e^{-1} + \mu \mathbf{I} \quad (3.6)$$

For the Lamé parameter $K = \nu E / ((1 + \nu)(1 - 2\nu))$, where $E = 2\mu(1 + \nu)$. The stress function does not include a hydrostatic pressure term $\kappa(J - J_g) \mathbf{I}$ representing the phenomenological bulk growth (Ateshian et al. 2012) and tissue interaction (Machyshyn et al. 2010). Instead the growth is achieved via the flow rule.

The time dependent increase in shear modulus is explained by the newly created stiff material product which is in contact with the existing matrix content. The change in matrix content effecting shear modulus can be related to the stress/strain field in a differential form. So far, computational remodeling theories were able to predict the collagen architecture in the studied cardiovascular tissues and investigated the effect of mechanical stimuli on fiber reorientation and tissue remodeling. Here we hypothesize that collagen fibers aligned with principal strain directions and stiff material content increases with the fiber stretch (please see (Baaijens et al. 2010) for detailed information). Thus, in the implemented model, the supporting properties of inter-cellular molecular forces including adhesion and cytoskeletal contractility dominate the mechanical characteristics in controlling the fiber production.

The relationship between the time evolution of arch's shear modulus and the fiber content is described by the young modulus (and bulk modulus) effecting the matrix

environment. It has been shown that the stiffness of the matrix materials, in terms of shear modulus magnitude, has a linear relationship with Collagen fiber content in very soft tissues (here, $\mu < 200$ Pa) (Reinhardt and Gooch 2018). Here we define the evolution of growth stretch in a second order A-stable explicit update algorithm (Ramos 2007), from time step t_{n-1} to current t_n by

$$\lambda_g(k_g, \eta_g, t_n) \approx \lambda_g(k_g, \eta_g, t_{n-1}) + 2\Delta t k_1 \frac{1}{\tau} \eta_g(\lambda_e) \left(2 + \Delta t k_1 \frac{\lambda}{\lambda_g^2 \tau}\right)^{-1} \quad (3.7)$$

which is known to solve stiff processes. The shear modulus is modeled to describe the stretch-based activation of the stiff polymeric substance to enforce the very soft lumen proximity for higher surface tensions observed in later stages. The shortest form is given by the linear update,

$$\mu(k_g, \eta_g, t_n) \approx \mu(k_g, \eta_g, t_{n-1}) + \Delta t k_1 \eta_g(\lambda_e) \quad (3.8)$$

Hence, the value of matrix stiffness parameter k_1 is controlled by the transduction-based biological activity which is set at constant for the entire simulation process. Consequently, the evolution of material stiffness is related to an increase in load bearing nano-fiber content including Collagen (and elastin). These regions are defined as the growing regions, where new material is being created and in contact with the existing matrix.

We kept the material production parameters fixed through the simulation process, where the internal blood pressure is linearly increased from Stage 18 to Stage 24. The Collagen production and degradation rates in spatial domain was set to specified values for all simulation cases. These values were determined via some numerical trials in accordance with the experimental magnitudes of the Stage 18 modulus level and lumen enlargement at Stage 22, as shown in Figure 3.3. The evolution of the matrix modulus around lumen is correlated with matrix growth, volumetric expansion.

3.2.6 Numerical Implementation

We simulated the evolution in aortic arch composition by using the plugin framework of FEBio open source software (Maas et al. 2012b). The in-house plugin class functions were supplied to obtain the field results. This plugin was constructed to couple a displacement based implicit nonlinear solver with an explicit (Euler-like) second order stable iterator for the growth evolution law. The mesh convergence was evaluated by means of the saturation of growth stretch (λ_g) and the maximum principal strain in the

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specified mesh. Then, the saturation point was taken to be the optimal element number for presenting the results. Considering the complexity of simulation cases, $\Delta t \leq (t_{HH24} - t_{HH18}) \times 10^{-2}$, $t \in [0,1]$ was required for the time convergence. The simulations were performed in a shared memory cluster machine. An in-house script based on FEBio 2.5 transformed these results to compatible analysis files with Tecplot software (Bellevue, Washington) for further post-processing. To obtain mesh convergence, 8-node hexagonal elements with reduced integration property were implemented. The mesh sensitivity study was accomplished by increasing the number of elements to 32 k to reach less than 3% change in the results. The plane-strain axisymmetric arch model is used to initialize the curved arch growth simulation for faster convergence and decreasing the computational time.

In addition to evolution models of Arch IV - R, quasi-static finite element models were carried out on the aortic arch manifold models of Stage 18 and Stage 24 for the right and left laterals separately. The aim of doing these complementary simulations was both to verify single arch growth simulation results and to obtain stress and strain distributions for the entire aortic arch mesenchyme tissue. The sensitivity of results to different boundary condition schemes were tested to replicate the *in vivo* embryonic aortic arch characteristics. Accordingly, the simulations were performed by fixing the base and end cross-sectional planes in the plane normal directions. Embryonic residual stresses were introduced to the unloaded configuration, as a finite intramural pressure corresponding to the estimated *in vivo* residual stress distribution, ~0.05 mmHg (Donmazov et al. 2015). In order to simulate the *in vivo* loading condition during circulation in the embryo, three arches of each model were pressurized to the same *in vivo* measured arterial blood pressure levels. The same in-house computational model (FEBio software plugin) was implemented in these models while the growth and remodeling was not activated. In these simulations, the same hyperelastic Neo-Hookean material parameter values were assigned for Stage 18. Computational material stiffening predictions were used for Stage 24 models. High-quality tetrahedral elements were used in the model. Mesh convergence runs were performed with edge lengths of 5 to 15 μm and a relatively finer grid-size (10 μm) was chosen.

3.3 Results

3.3.1 Pressure loading and embryonic material properties

The material properties of the arch domain and initial geometric magnitudes were obtained via a procedure described briefly in earlier research (Gürsan Çoban 2018). The data in Figure 3.3 is essential since it lets us to define the basic evolution parameters and an evolutionary model that can be used to extrapolate Stage 22 data by starting with Stage 18 material parameters. To model Stage 18 to Stage 22 transition (Arch IV-R), an axisymmetric-cylinder with plane strain condition was used. The shear modulus parameters for both Stage 18 and Stage 22 were obtained by a non-growing hyperelastic model fit. Furthermore, the entire blood pressure vs. inner radius path in Figure 3.3 was predicted by the growth model proposed in this manuscript.

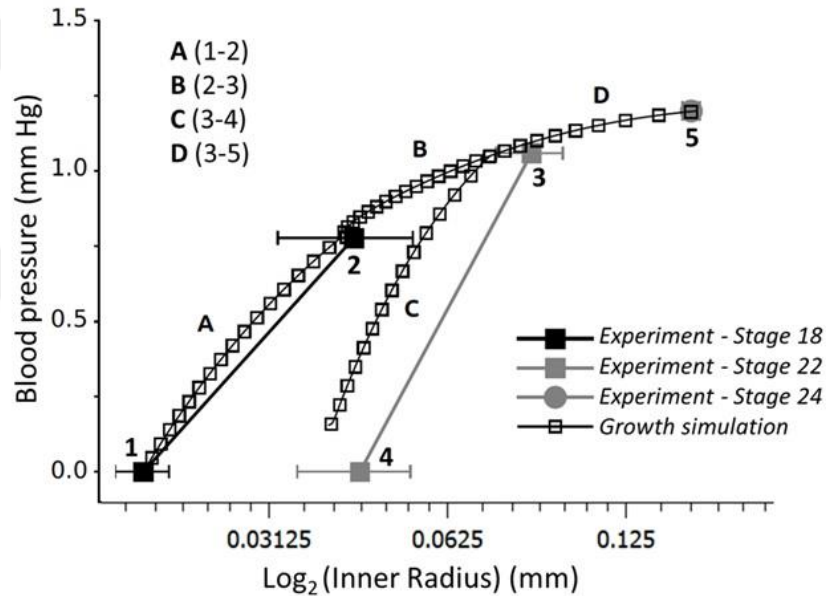


Figure 3.3: *In vivo* validation of computational (G&R) simulations is presented in this Figure. Experimental OCT data for the change in inner radius with respect to the applied internal blood pressure for the Arch IV-R at Stage 18, Stage 22 and Stage 24 are shown ($n = 5$). Following the pressure measurements at the *in vivo* “loaded configuration”, the vitelline artery is cut providing the unloaded vessel diameter. During this time, a continuous diameter/pressure recording was not possible since the cardiovascular system prioritized to maintain the systemic pressure level under a plethora of blood loss. On the other hand, the details of depressurization (Segment C) were acquired from our FEM growth and remodeling (G&R) simulations displaying a nonlinear trend and correlate well with experimentally measured end points. The diameter increase during embryonic development from Stage 18 to Stage 24 under linear physiological pressure increase that was obtained from the G&R FEM model is also displayed (Segments B and D). At Stage 22 the depressurization (Segment C), also shrinks to a radius very close to the experimental data obtained at this stage.

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The internal blood pressure experienced by the aortic sac is assumed to be the mean of the dorsal and ventricle cardiac- cycle averaged. The pulsatile dorsal and ventricle pressures were obtained using a challenging servo null technique, as available in the literature (Clark and Hu 1982; Zahka et al. 1989). These values were confirmed by our in house OCT-guided pressure measurements as well (Goktas et al. 2016). Although there is a nonlinear trend in pressure levels beyond Stage 26, the trend between Stage 18 and Stage 24 can be approximated by a linear curve efficiently (Hu and Clark 1989; Zahka et al. 1989). The pressure levels are 0.34 ± 0.02 mmHg for the average value of the ventricular and dorsal diastolic and 1.22 ± 0.06 mmHg for the (average) systolic pressure at Stage 18. Therefore, mean pressure values for Stage 18 is set as 0.78 ± 0.03 mmHg which increases linearly to 1.06 ± 0.03 mmHg at Stage 22 and 1.21 ± 0.05 mmHg at Stage 24 by means of linear least squares.

Internal radius measurements (r_i) under pressure were first carried out on freely beating *in vivo* embryos (Gürsan Çoban 2018). Initial loaded and final unloaded configurations were able to supply adequate information for a single parameter hyperelastic domain consisting of long chain polymeric substance. Experimental measurements of unloaded inner radius and thickness are respectively 19 ± 2 μ m and 81 ± 12 μ m for Stage 18. Arch thickness increases to 105 ± 11 μ m at Stage 22 and the unpressurized inner radius is measured to be 44.5 ± 11 μ m at this stage.

The arch material was described by the hyperelastic Neo-Hookean material model with Poisson's ratio $\nu = 0.475$ showing slight compressibility. In order to estimate the Neo-Hookean shear modulus parameter, a representative plane strain axisymmetric-cylinder finite element model of Stage 18 - Arch IV - R was generated due to this arch's clear visibility in both unloaded and loaded OCT tracks.

Finite element estimates the evolution path of the pressure-radius curves as presented in Figure 3.3. The starting initial lumen radius at Stage 18 is $r_i = 19$ μ m where the wall thickness is $t = 81$ μ m. Pressure increase at that stage yields a lumen radius of $r_i = 43.5$ μ m. The hyperelastic material model has a single stiffness parameter and observing the simulation path from the unloaded to loaded curve Segment (A) without activating the internal material evolution yields a shear modulus of $\mu \approx 0.1$ kPa. The second Segment B in Figure 3.3 includes additional linear pressure increments as well as growth and remodeling due to internal strains. The evolutionary parameters are detailed

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in Section 3.3.4. In this case, the final internally loaded configuration at Stage 22 supplied sufficient information to determine a shear modulus parameter for that stage when a final depressurization process (Segment C) was applied. In succinct terms, we computed $r_i = 44 \mu\text{m}$ (and $t = 101 \mu\text{m}$) for the unloaded configuration and $r_i = 85.6 \mu\text{m}$ when the pressure load was applied. Matching the final points of simulation with experimental observation also let us to determine the shear modulus parameter for Stage 22 as $\mu = 0.186 \text{ kPa}$. Computed inner radius for Stage 24 in loading condition is $r_i = 185 \mu\text{m}$.

From our experimental observations, the circumferential strain (stretch) around the lumen was observed to be preserved over time. Our experimental test observation data records the ratio between loaded and unloaded inner radius magnitudes. These magnitudes were similar at both Stage 18 and Stage 22 being close to 2 (2.28 and 1.95 respectively), which is a strong indicator of a growing permanent stretch that dilates lumen periphery over time, in order to maintain the ratio around 2.

3.3.2 Statistical analysis results of aortic arch immunohistochemistry

To investigate the relationship between radial COL-I deposition levels and the mechanical information propagating through the literature, we transformed the random scattering of fluorescent areas in histology into comparable statistical quantities. These statistical results are presented in two sub-sections. First, we discuss the mean Collagen intensity level results and then the second the intensity peak positioning and radial trend statistics.

As explained in Section 3.3.2.4 above, we used statistical tests to make pairwise comparisons between existing arches in studied stages. We devised 10 comparison pairs as listed below to interpret our statistical results:

- Left and right pairs of Arch II, Arch III and Arch IV at Stage 18 (3 comparison pairs) e.g.; Stage18-II-L vs. Stage18-II-R.
- Left and right pairs of Arch III, Arch IV and Arch VI at Stage 24 (3 comparison pairs) e.g.; Stage24-IV-L vs. Stage24-IV-R.
- Stage 18 is compared with Stage 24 in left (L) lateral of persistent arches, Arch III and Arch IV (2 comparison pairs) e.g.; Stage18-IV-L vs. Stage24-IV-L
- Stage 18 is compared with Stage 24 in right (R) lateral of persistent arches Arch III and Arch IV (2 comparison pairs) e.g.; Stage18-IV-R vs. Stage24-IV-R.

Arch based intensity comparison results

The test results are briefly summarized in radial block format in Figure 3.5. Corresponding detailed graphical plots of all intensity variations are provided in Appendix F.

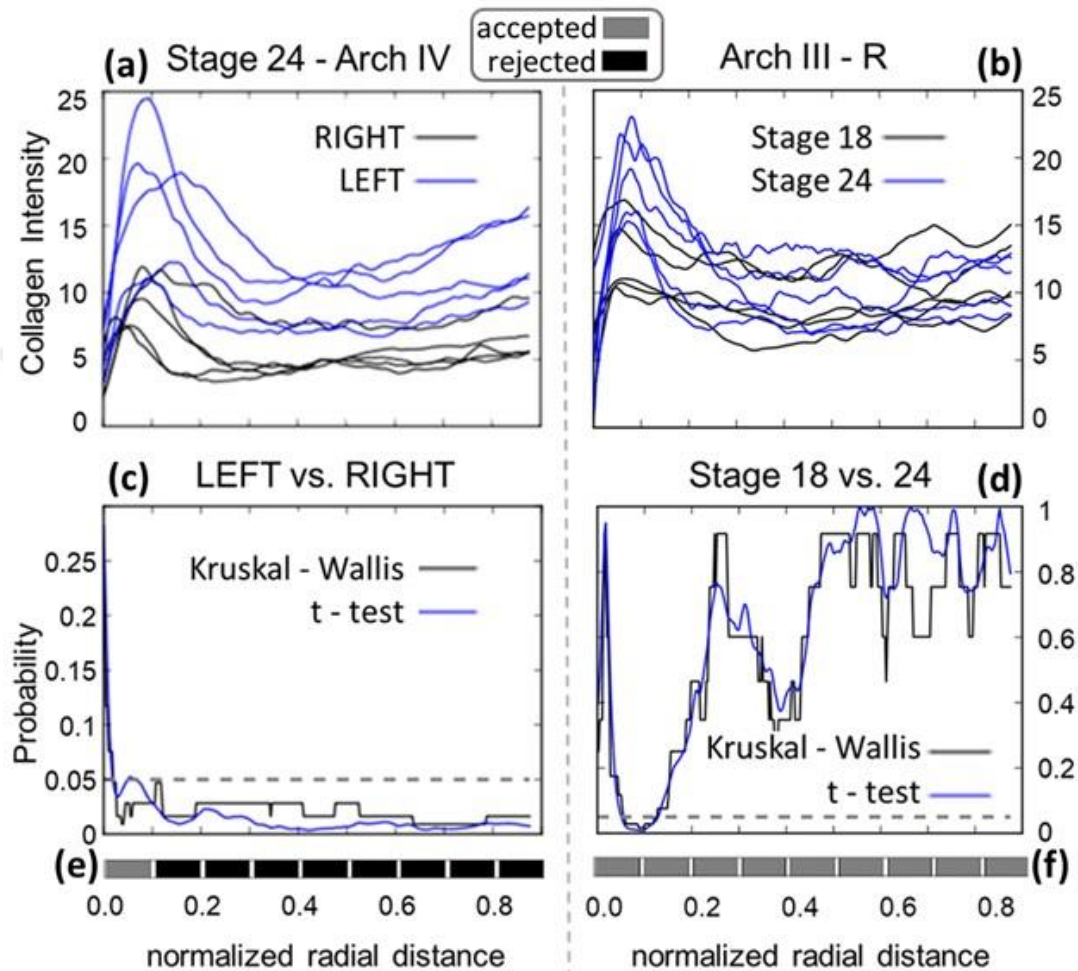


Figure 3.4: The normalized Collagen Type I intensity plots along the radial direction are presented in the TOP ROW for two pairs of arch vessels; (a) Stage24-IV-L vs. R and (b) Arch III-R-Stage 18 vs. Stage 24. Intensity plots are averaged circumferentially and all samples are plotted ($n = 5$). The corresponding probability statistical test results for these pairs are plotted in the MIDDLE ROW (c-d) for testing the null hypothesis of “equal level of deposition” in radial direction for each arch pair. Probability tests are performed using both the Kruskal-Wallis and t-test methods. The parametric test results are summarized by labeling the accepted and rejected radial regions in different colors in cross-comparisons in BOTTOM ROW (e-f). Acceptance of the null hypothesis of “equal level of Collagen deposition” is associated with a t-test probability of higher than 0.05 which is identified in GRAY color. Rejected regions are identified in BLACK, which indicate a significant difference in Collagen deposition levels in the compared arch pair at that specific normalized radial location. (All other paired arch comparisons are provided in Appendix F in this format).

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Persistent - symmetric Arch III: For Stage18-III-L vs. Stage18-III-R, there was significant statistical difference between the left and right arches inside the region $0 < rd < 0.3$, just near the lumen. An initial differentiation region was stabilized to cover the whole radial direction at Stage 24. Case Stage24-III-L vs. Stage24-III-R had insignificant regions around the lumen which fluctuated around confidence line $\alpha = 0.05$ (level line for acceptance and repentance). The rest of the radial blocks differed significantly. The differentiation process that commenced at Stage 18 around the lumen proximity evolved into covering the entire wall thickness. Thus, a significant difference in the left-right Collagen deposition levels was observed for all the radial slices covering the entire vessel thickness. Although there was a difference in the bilateral position of Arch III, a significant difference was not observed for Stage 18 vs. Stage 24 comparisons. The comparisons of Stage18-III-L vs. Stage24-III-L and Stage18-III-R vs. Stage24-III-R both exhibited a layout of a (convex) pattern with a minimum acceptance probability around the lumen periphery (first block). Both test group samples can be considered similar due to their probability scores (similarity in trends). Comparatively, Arch III did not show any statistically significant change in Collagen intensity levels over time, whereas there was a high probability of significantly different block around the lumen.

Persistent - asymmetric Arch IV: The Stage24-IV-L vs. Stage24-IV-R comparison identified complete differentiation of left and right arches at Stage 24. The preliminary evolution at the beginning of the formation at Stage 18, shows us that the differentiation in Arch IV also started from lumen proximity ($0 < rd < 0.1$) and around $0.5 < rd < 0.6$. Even though the lumen proximity was again evident at the initial differentiated region, the accepted regions were not wide in this case. Thus, a delayed time evolution in COL-I production activity of Arch IV was observed where a total indifference evolved into a total differentiation over time. The time evolution of the intensity levels from Stage 18 to Stage 24 did not show any significant differentiation of blocks around the lumen for the same bilateral positions (Figure 3.5). For Arch IV-R, there was no significant difference between right and left arches from Stage 18 to Stage 24 inside the region $rd < 0.65$. As in the Arch III-R, the probability of H_0 acceptance was lower around the lumen proximity, which did not yield any significant differentiation. Similarly, for Arch IV- L, there was no significant difference between right and left arches from Stage 18 to Stage 24 through the thickness of the artery. As in Arch III - R, the probability of H_0 acceptance was lower around the lumen proximity, which did not yield any significant differentiation.

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Disappearing Arch II: For Arch II which is a disappearing arch pair, there was no difference between left and right at Stage 18.

Emerging - symmetric Arch VI: Stage24-VI-L vs. Stage24-VI-R comparison shows that there was a significant difference between left and right Arch VI at the lumen proximity for < 0.3 . For $rd > 0.3$ the comparison results fluctuated around the confidence level line.

Resulting similarities between arch based intensity comparison

The temporal evolution of COL-I intensity results shows that between Stage 18 to Stage 24, the evolution appeared in a way that preserved the COL-I levels between stages. The last radial range for this particular test case (Stage18-IV-R vs. Stage24-IV-R) did not show similarity with the other 9 cases. Instead, there was a significant difference for the approximate region of $rd > 0.65$ and there was no definable region for a differentiation event. However, the differentiation probability increased around the lumen proximity for both Arch III and IV bilateral. In some tests, there were differentiated intervals around the lumen, while the length of these intervals was not wide (as in Stage18-III-R vs. Stage24-III-R).

All observations indicate that the probability of acceptance around the lumen was lower in all tests except Stage18-II-L vs. Stage18-II-R comparison. It can be understood that there is a positive tendency in COL-I production around the lumen proximity, based on a common observation for Arch III, IV and VI. There was also a totally left-right differentiated region around the lumen for Arch III at Stage 18 and Arch VI at Stage 24. Thus, the differentiation region of III and VI was similar in terms of H_0 acceptance, and the source of the differentiation was purely cellular activity around lumen.

3.3.3 Shape analysis (localization) of microstructural protein distribution

As discussed in the section above, the differentiation of COL-I level has a differentiating region around the lumen, at least for the bilateral arches of Arch III at Stage 18 and Arch VI at Stage 24. Furthermore, the probability of differentiation increases around the lumen for Arch III, IV and VI, for all comparisons. In this section, we propose a geometric “slope” statistic to classify arches by means of the radial protein localization (COL-I) shape. Full statistical results are given in Appendix F.

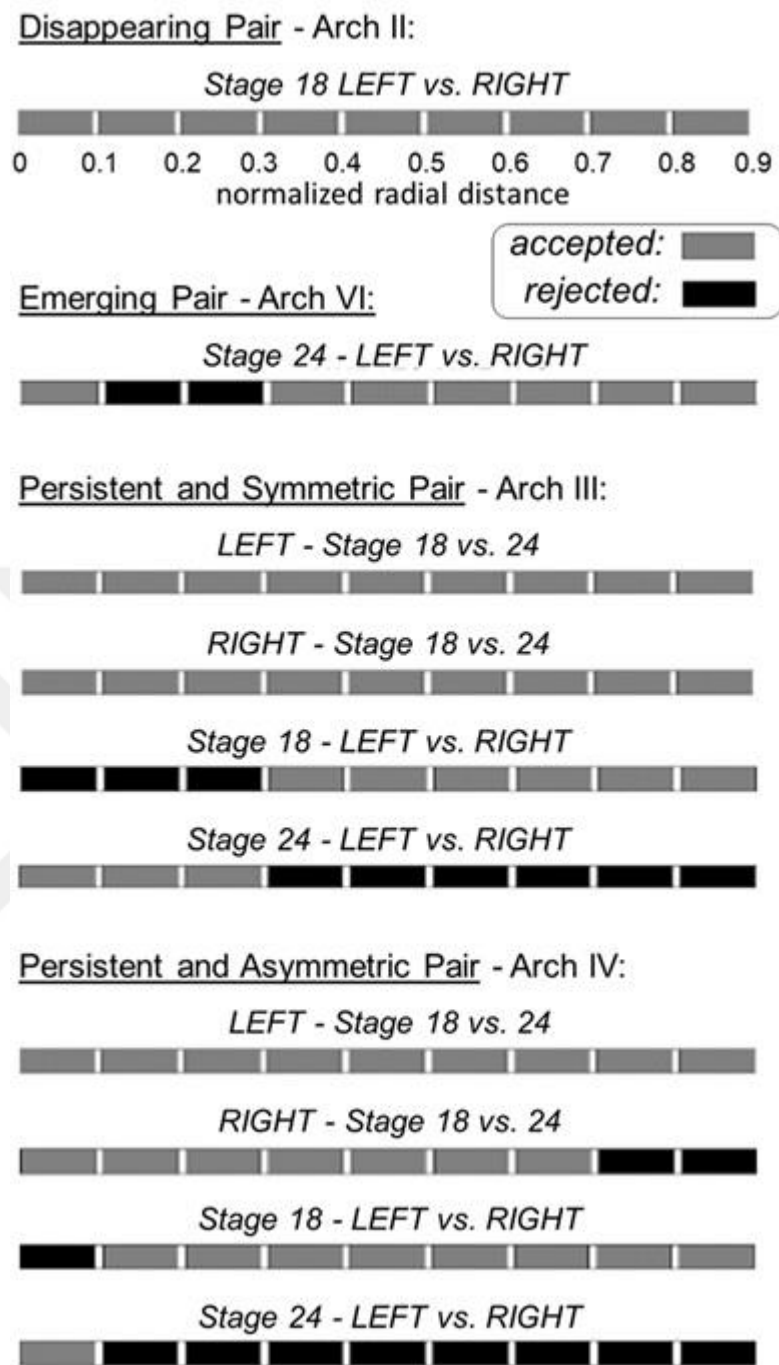


Figure 3.5: Parametric test results of all sample groups are summarized in this Figure by labeling the accepted and rejected radial blocks for paired arch cross-comparison cases. Acceptance of the null hypothesis of “equal level of Collagen type I deposition” is identified in GRAY color. Rejected regions are identified in BLACK color, which means that there is significant difference in collagen deposition levels in the compared arch pair at that specific normalized radial location. Only one test case Arch III-stage18-L vs. R is shown here by its nonparametric (Kruskal-Wallis) comparison. (As in Figure 4, all corresponding normalized and circumferentially-averaged intensity images in Figure 5 are provided in Appendix F).

We tested the equality of the proposed slope levels with both nonparametric and parametric representations and present the results for the normality tests for the investigated samples in Appendix F. The initial scattering of observations gives an impression of a stage-based difference rather than an arch-based differentiation (Figure 3.6a and 6b). This interpretation is made clearer in the cross-tabular statistical results given in Figure 3.6c. The checkerboard style test results for 12×12 groups can be merged into 6×6 samples, where 6×6 cross-comparison gives rise to a 2×2 binary scheme (Figure 3.6c). Statistically, there were no slope differences observed inside the pooled sample of Stage 18 (and Stage 24). However, there was significant statistical difference between Stage 18 and Stage 24 slope levels, when arches were combined (pooled) according to their temporal stages. These global point patterns were distributed normally ($\alpha = 0.05$) and exhibited a random pattern on their domain. Additionally, both distributions accumulated around their mean slope levels, which are independent from the arch types. According to the random scattering of data, there was no differentiation in arch slope coefficients where mechanical effects are considered to be dominant. These differentiation patterns in arch slope coefficients are related to the intramural pressure and volume of the blood inside arteries. Although the Collagen production mechanism demonstrated a differentiated pattern between the bilateral positions of the same arch types according to the parametric test results, we observed that the slope (S) of the Collagen deposition levels did not show such layout in sample space.

3.3.4 Phenomenological relation of growth and remodeling with COL-I deposition

We compared the results of the intensity distribution patterns with the predicted mechanical variables using the implemented growth model based on the permanent transversally isotropic extension in growth stretches. Simulation results of plane-strain axisymmetric model are matched with the experimental data and the same boundary conditions is used for the idealized 90° sweep model representing Arch IV.. Computed distribution field of shear modulus μ , growth stretch (λ_g), elastic stretch (λ_e) and maximum principle stress were shown for a cross section of the model at Stages 18, 21 and 24 (Figure 3.7a to 7c). The corresponding graphical layouts are based on the material evolution parameters summarized in Table 3.1. The stiffening in parallel to the growth event is necessary since the predicted pattern in Figure 3.7b can only be achieved by means of a modulus increase, where the material is close to its inflation-instability region

(Gürsan Çoban 2018). There was a strong correlation between the radial distribution of the mechanical stress magnitudes and estimated shear modulus values (Figure 3.7a to 7c).

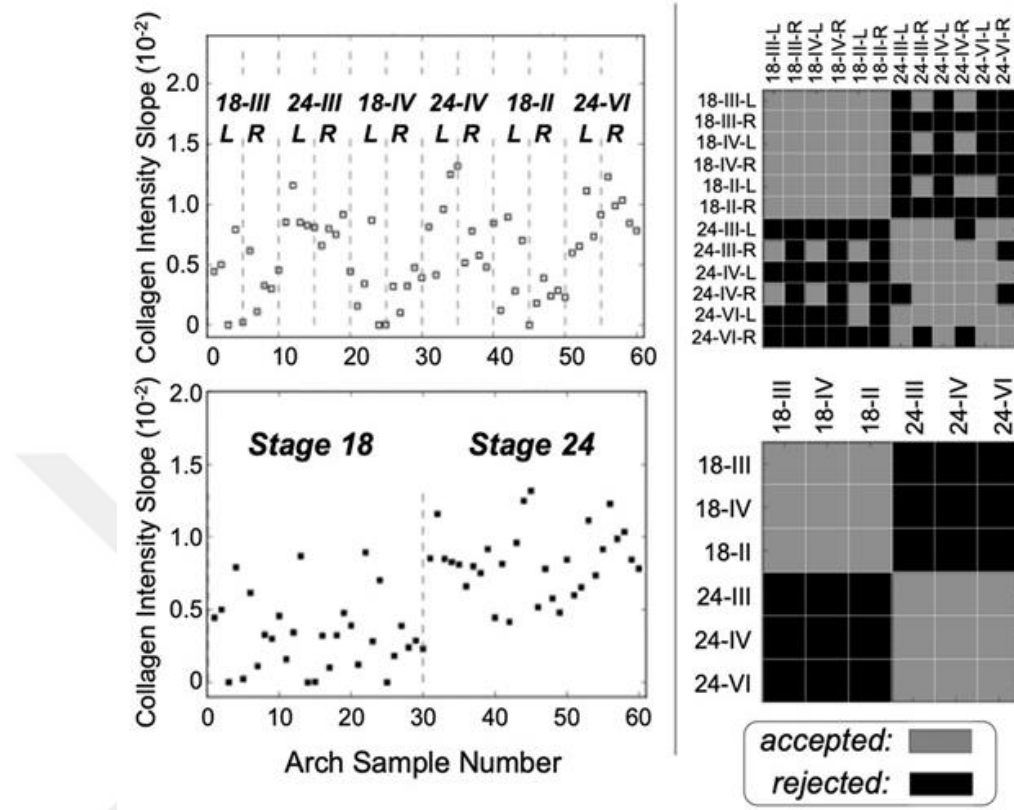


Figure 3.6: Localization statistics of Collagen Type I proximal to the inner radius from Stage 18 to Stage 24 are summarized in this Figure. Collagen intensity peak is represented by the decay rate of the collagen intensity along the radial direction that is quantified by the decay “slope” magnitude. The overall distribution layout for all arch groups observed in Stage 18 and Stage 24 are displayed on the TOP-LEFT. The level shifts are clearly observed at Stage18-II and Stage24-VI collagen degradation slopes. When the pooled samples ($n = 5(\text{samples}) \times 6(\text{arches}) = 30$ for each arch) are grouped according to their embryonic stage information as in the TOP-RIGHT, a clear pattern emerges proving that the mean decay slope in Stage 24 arches is significantly higher than Stage 18. The matrix layout of the cross-testing results (parametric t-test with unequal variances) is displayed in the RIGHT COLUMN by considering the left and right arch distinction between arch groups (12x12 cross comparison). Acceptance of the null hypothesis of “equal slope magnitude” is identified in GRAY color. Rejected regions are identified in BLACK which means that there is a significant difference in the decay slope magnitude for the compared arch pair. The matrix layout of the cross-testing results with merged left and right distribution clouds (6x6 cross comparison) indicates a clear accumulated pattern according to the stage information rather than the spatial (left or right) position of the arch or the aortic arch type.

The data from a single node selected on the surface of the inner lumen shows that the elastic stretches λ_e are bounded by the gray region (Figure 3.7d) such that $1.6 < \lambda_e < 2$. In these periods, the total stretch λ increases nonlinearly. The growth in tissue is so

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stable that λ_g increases linearly, whereas λ_e exhibits an upward convex pattern. Despite the transversally isotropic growth around the circumferential direction to preserve the elastic stretches bounded, λ_e still increased nonlinearly which gave rise to a stress increment beyond Stage 21 (Figure 3.7b and 7e). The main result in our observations is that the elastic stretches are bounded in a well-defined region, keeping in mind that this model was evaluated on a slightly higher shear modulus evolution parameter k_1 . The evolution of volume in terms of growth stretch, which is assumed to have effects on the local stiffness of the media, demonstrated exponential decay trends on the radial direction similar to the COL-I level observations presented in Appendix F.

The characteristics of the stress levels and stiffness of the environment was similar to the exponential decay in the COL-I layout (Figure 3.7e and 7f). In all simulated stages, stress was localized around the lumen. The simulated stress levels for Stage 24 decreased sharply from a maximum value of 0.64 kPa in the lumen to 0.1-0.15 kPa around the midpoint between the outer boundary and the lumen side. These results are similar to the Stage 21 outcomes, while decay slope was 2 times less than Stage 24. At Stage 18, stress levels were less than Stage 21 and the maximum stress value was 0.21 kPa at this stage. While the stress trend closely followed the stress distribution pattern at Stage 21, its stress localization was not as intense as at Stage 24. Base line stress level demonstrated an increasing trend from 0.7 kPa at Stage 18 to 0.19 kPa at Stage 24 (Figure 3.7e). These results also match with the recently growing regions where stiff material production is expected to occur (Figure 3.7f). Maximum stiffness values recorded at the lumen increased from 0.1 kPa at Stage 18 to 0.3 kPa and 0.5 kPa at Stage 21 and Stage 24 respectively.

Table 3.1: Material evolution parameters used in the computational simulations tabulated. Where τ is the adaptation speed of the growth. λ_h identifies the homeostatic stretch levels. k_1 is the material stiffening parameter. Neo-Hookean material parameters including shear modulus (μ_0) and Poisson's ratio (ν) are given as well.

τ (1/days)	0.651	
λ_h (-)	1.1	
k_1 (kPa)	Stage 18 to 22	0.65
	Stage 22 to 24	0.5
μ_0 (kPa)	Stage 18	0.1
	Stage 22	0.186
ν (-)	0.475	

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3.3.5 Quasi-static FEM simulation results of entire arch tissue domain

Our experimental immunohistochemistry data clearly shows a trend that forms a diffuse microstructural protein distribution at Stage 18 towards a more localized fiber distribution at Stage 24. We hypothesize that this statistically significant evolution could be related to the mechanical load. The dynamics of matrix proteins and reported radial localization of structural proteins close to the inner vessel walls prompted us to quantify the evolution of vascular stress and tissue deformation levels in the aortic arch laterals.

The maximum principal stress and elastic strain distributions due to pressure loading in the left and right aortic arch laterals are computed in Figure 3.8. Maximum principal strains alter in the 0.5 to 1 range around the lumen for different models. This range of strain variation correlates well with our time-lapsed OCT observations. The most significant finding from these observations is that the first principal strain was maintained between Stages 18 and 24, which verifies that strain-based growth algorithm is a more applicable methodology to describe arch evolution. (We tested both stress and strain-based growth models, but only the strain-based approach is explained here as more applicable to our experimental results).

The quasi-static simulations showed localized stress patterns around the arch lumen. Maximum stress values of 0.28 kPa and 0.58 kPa occurred in the lumen at Stage 18 and Stage 24 respectively and reduced to stress free regions in the outer walls at both stages. Comparative analysis results show that stress was 2.2 times more localized around the lumen in Stage 24 compared to Stage 18. As expected, the quasi-static computational results correlate well with single-arch growth model results presented earlier. Only 10-15% less maximum principal stress was observed in quasi-static model at Stage 24. The drop in the computed stress level in the triple-arch model at Stage 24 may be attributable to geometrical difference in the loaded configuration. The configuration changed from a single arch to three arches in these simulations and the tissue between the arches experienced the intramural blood pressure from two adjacent arches simultaneously. The other possible reason for the mentioned difference can be the radial distribution of stiffness modulus in growth model at Stage 24, while the mean value of it is assigned to the entire domain in the quasi-static finite element model.

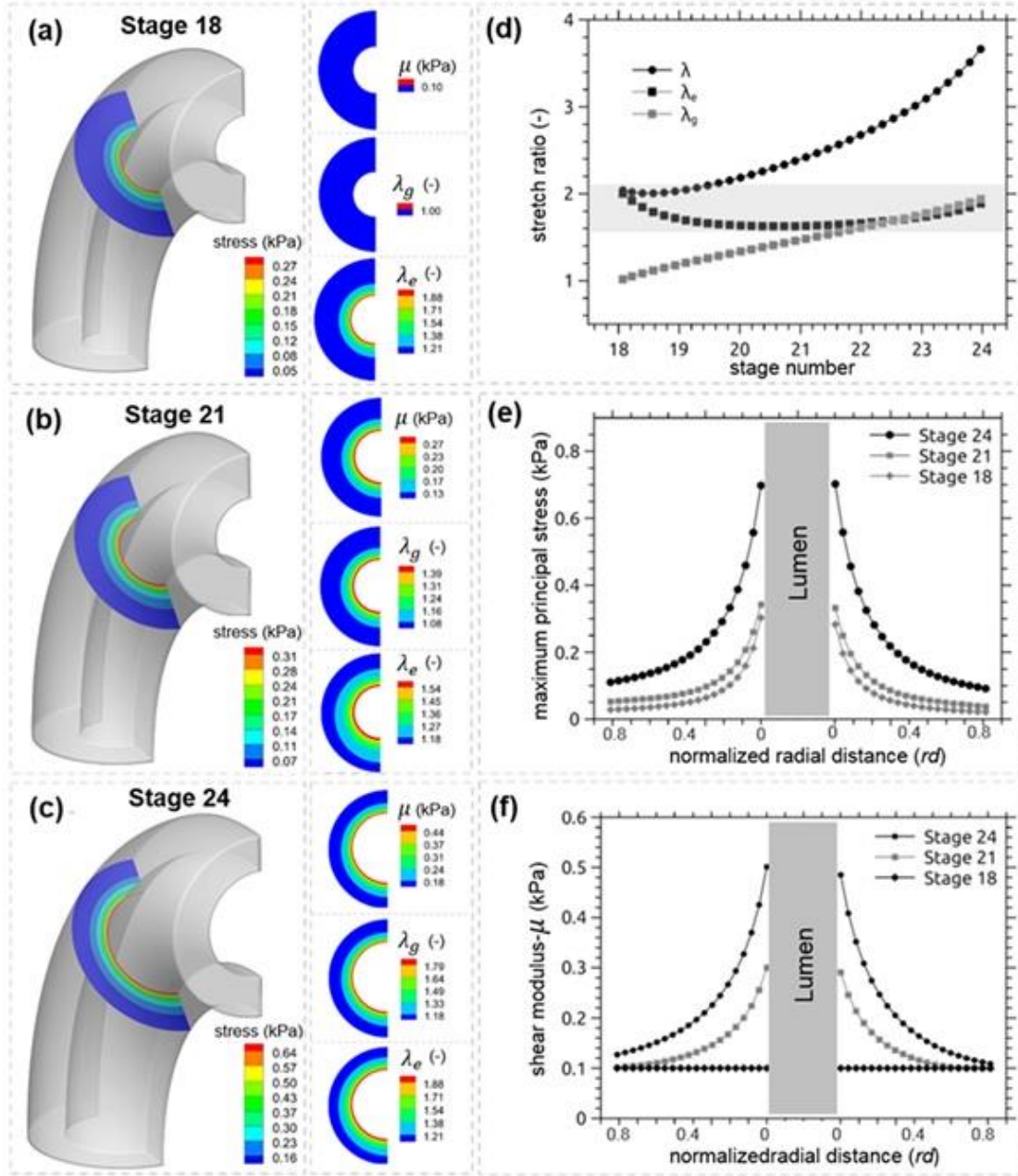


Figure 3.7: The growth and remodeling (G&R) computational results at Stage 18, 21 and 24 are presented in (a), (b) and (c) corresponding to the radial distributions of shear modulus (μ), growth stretch (λ_g), elastic stretch (λ_e) and maximum principal stress for the idealized IVth right Arch. In Figure (d) data extracted at a point on the inner surface lumen shows that the elastic stretch values (λ_e) are bounded in the gray region. Growth is extremely stable and λ_g increases linearly. Consequently, the total stretch (λ) increases nonlinearly. The radial distribution of stress levels and stiffness (μ) of the environment indicates an concave upward decreasing around the lumen as plotted in (e) and (f).

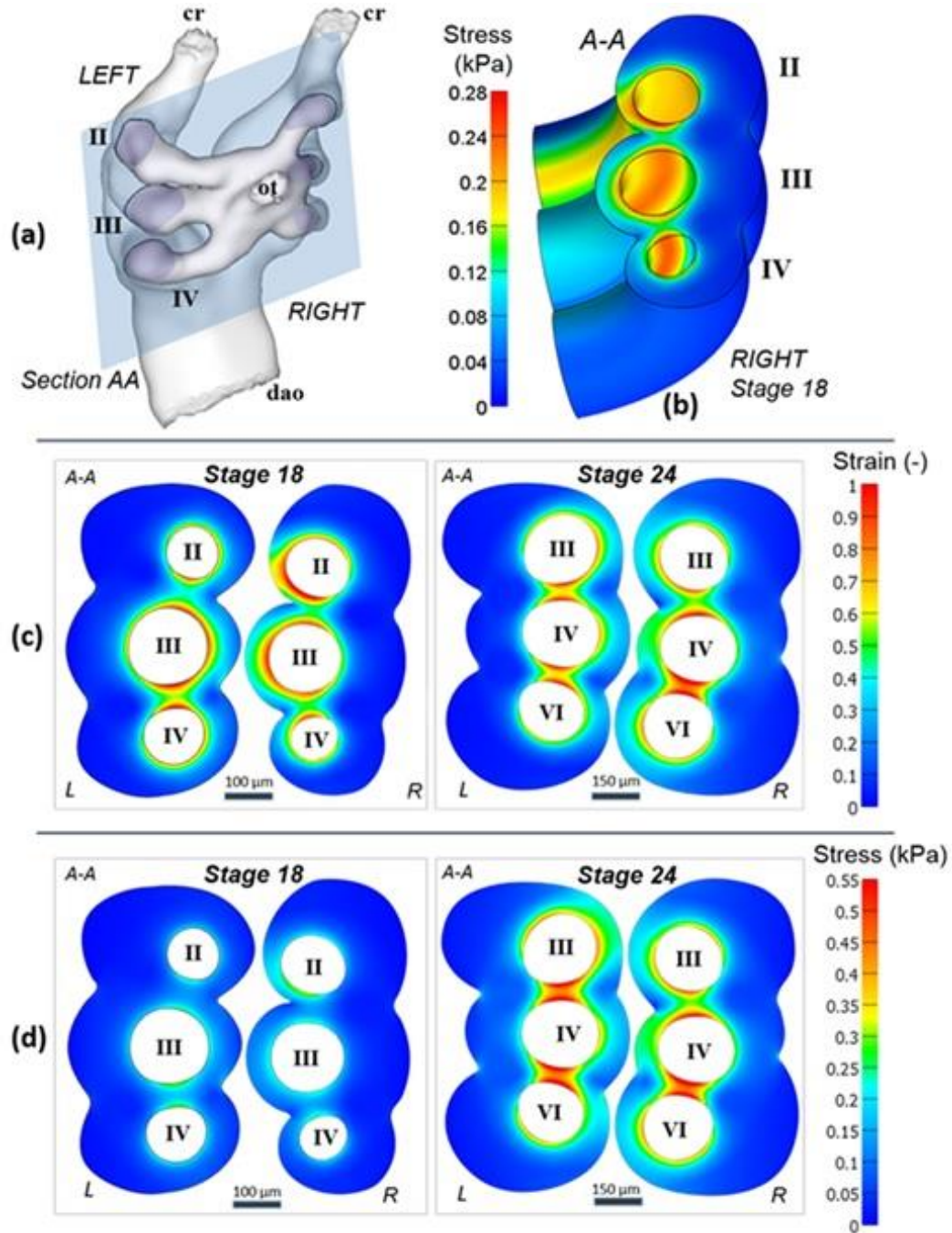


Figure 3.8: Quasi-steady stress and strain distributions obtained by FEM model of each arch lateral at the embryonic Stage 18 and 24 considering the stage-specific intramural blood pressure and measured loaded arch configuration. (a) Displays the 3D reconstruction of the complex arch assembly at Stage 18 and the central cross-section (Section AA) where the simulation results are plotted. The first principal stress distribution at Stage 18 for the RIGHT (R) aortic arch manifold is presented in (b) in three dimensions for the entire FEM model. For both embryonic stages the maximum principal elastic strain distribution along Section AA are plotted in (c). The corresponding first principal stress distribution for both embryonic time points are presented in (d). Stress level and concentration around the lumen is significantly elevated at Stage 24 compared to Stage 18. dao: Dorsal Aorta , ot: Outflow Tract, cr: Left and Right Cranial Arteries.

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The data presented in Figure 3.8 and Appendix D - Figure D.1 allows us to make a qualitative comparison between stress levels with COL-L fiber density, VEGF expression and cell density. Interestingly at Stage 24, we observed that the high tissue stress regions (around the inner walls) corresponded to the high Collagen staining intensity, high VEGF expression and high cell density (DAPI). In comparison, the earlier Stage 18 proteins and cells were dispersed in the whole arch domain and no observable localization was formed in the stress concentration regions.

3.4 Discussion

3.4.1 Significance of right arch IV evolution

Among the three pairs of aortic arch vessels, the evolution of right IVth arch is particularly interesting on the basis that it becomes the adult aorta as a persistent great artery. In addition, the outflow track is directed towards this arch during the period of interest, reducing the complex influence of WSS. Thus, an idealized model of this arch was created for growth simulations.

3.4.2 Stiffening in aortic arch evolution

The simulations revealed that for the observed lumen radii evolution, the shear modulus parameter in the Neo-Hookean model should also increase over time for appropriate fitting. Although not fully discussed in this manuscript for brevity, our initial observations through pipette-aspiration experimental sessions on the same arch domain also indicate that it was not the effective shear modulus of the domain, but rather the nonlinear stiffening of the tissue that progressed over time. Consequently, the shear modulus increment corresponds to the nonlinear stiffening over time, due to deposited polymeric material. We note that our main aim in material properties estimation of aortic arch is to characterize and utilize the stiffness of the material consistent with initial observations, rather than its anisotropic properties. Although fibrous components can be embedded in the polymeric substance of the extra cellular environment, the stiffness of the tissue is regarded to describe the overall character of this mixture. To summarize, nonlinearity in the stiffening of the embedded material could play a role in the stress-strain descriptions.

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3.4.3 Isotropic vs. composite material models

Even though different origins of aortic arch tissue may require different composite models, a global material determination approach is used to overcome this complexity. The early development of the pharyngeal aortic arch structure, beginning at Stage 18 for example, experiences significant differentiation of the migrated cardiac NCCs into SMCs (Bergwerff et al. 1998). Thus, the supporting role of the early SMC function now has the dominant characteristics to remodel the existing environment through the stable timing scheme between Stages 18 and 24 and beyond. Despite the lack of research on the material properties of the aortic arches, the cellular characteristics dominate the behavior of the material environment and the stiffness is in the range of a few hundred Pascals, which is appropriate to describe as a gel-like, very soft embryonic structure.

3.4.4 Dilatation growth vs. material thickening model

The lumen enlargement of Arch IV through Stage 18 to Stage 22 is close to 100% in terms of inner radius. The increase in the radial thickness of tissue was around 24% which is comparatively 4 times smaller than the lumen enlargement. These conditions resemble a dilatation-like phenomenon, which is known as a pathological situation in mature body due to ‘volume overload’. Thus, in our modeling perspective, we determined the maximum principal stretch value to be the homeostatic stimulus for the material evolution in time. Due to the fast evolution of this growth process, we modelled a stretch-based shear modulus evolution algorithm where accumulation of newly produced materials locally stabilized the environment for additional pressure increment in the following embryonic stages. Our main concern was that volumetric expansion and stiffening creates an additional limiting barrier to eliminate the progressing effect of continuous hypertension during these periods. The observed dilatation-like transversally isotropic growth also supports this hypothesis; the pressure increases between these periods, which is sensed by the lumen periphery, may not only be related to the pumping capacity of the heart tissue, but also due to the volume overload of the fluid. The reaction of the arch structure inserting additional fluid volume into the circulation system first occurred with the area expansion of the lumen, and internal stretch levels beyond the threshold are believed to govern this process. On this basis, the exact reason for early circumferential growth of the aortic arch structure is crucial to understanding the mechanism and its effects on internal stress evolution.

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3.4.5 Strong dependency on stiff material production

The constructed model does describe the experimental data well and our additional experiments reveal that the production of stiff chemicals is related to the increase in blood-pressure levels. Therefore, the functionality of the matrix content distribution is attributable to the mechanical forces rather than arch type. In the following discussion, we set out our support for the dependency of stiff material production on mechanical magnitudes, based on comprehensive statistical analysis.

3.4.6 Biomechanical activity at lumen proximity

Previous observations on the accumulation pattern of growth-related materials reveal that the lumen proximity could be main source of mechanobiological activities yielding further growth and remodeling of the aortic arch structures (Plein et al. 2015; Ruhrberg et al. 2002). Qualitative examination of immunohistology results at different embryonic timepoints lead us to hypothesize that, lumen periphery should be the main activator for stiff material deposition due to growth. Therefore, circumferential incremental growth stretches around lumen should show decreasing trend in the radial direction. Furthermore, the same trend for material stiffening is expected. Preliminary observations on COL-I intensity levels follow a similar trend with stress distribution around the arches. The distribution pattern also matches with the spatial distribution of well-known growth enzymes (Kolesová et al. 2008). Thus, these findings have the potential to be generalized to other growth enzymes which show high florescence intensity in their lumen proximity. As explained in the Results Section 3, the functional form of the protein distribution patterns for each arch type has a unique character represented by an exponential decay trend in a radial direction, which evolves over time.

3.4.7 Correlation of material deposition and stress distribution

The stiff material production concept involves accumulation of the ECM materials over time, which can be described by phenomenological stress/strain based governing stimulus functions (Baaijens et al. 2010). In this case, stress production can be related to basal matrix production (or degradation) rates in addition to the rates that are controlled by the mechanical magnitudes. Both our servo-null pressure measurements (Goktas et al. 2016) and the literature (Clark and Hu 1982; Zahka et al. 1989) show that the mean blood pressure in the aortic arch between Stages 18 and 24 increases linearly. The COL-I distribution is remodeled to change the mechanical properties of the media as it progresses

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in proportion to the pressure. The linearly increased blood pressure in these time steps is perceptively similarly around the lumen for each arch. Our experimental findings confirm that the slope coefficients s (determiner for the shape of material deposition) significantly increase from Stage 18 to Stage 24, independent of the aortic arch type. Thus, intense COL-I localization around lumen is associated with material stiffening. This functional character was observed in simulations via localization of stress around the lumen as well.

3.4.8 Importance of arch bilateral positioning in protein intensity levels

The comparison of nominal intensity levels between same arch types at a specific stage informs us about the importance of bilateral positioning of arch in differentiation of arches. Our research shows that the probability of accepting H_0 (null hypothesis of equal COL-I intensity levels) reached to a local minimum for $rd < 0.2$, except for the statistics for Arch II in Stage 18. Thus, there is a tendency of differentiation for the lumen proximity in that narrow region. Otherwise in Arch II, the material accumulation level was not different for the right and left bilateral domain for the entire radial direction. In comparison (e.g. Stage24-IV-L vs. Stage24-IV-R comparison), the H_0 statistic remained below the 0.05 confidence band, and this trend was maintained throughout the entire radial direction. In some cases, the probability of acceptance increased after a decrease (i.e. Stage18-III-L vs. Stage18-III-R) around the lumen. The trend line of H_0 acceptance scores for the right and left difference in Arch III at Stage 18 was very similar to the right and left difference for Arch VI at Stage 24. A significant differentiation of $rd < 0.3$ was observed between the right and left laterals of both Arch III and Arch VI. Accordingly, the distribution of Stage24-VI replicated the trend of Stage18-III, where Arch VI was a younger formation than Arch III. Based on the assumption that COL-I evolution does not follow an extremely chaotic path, it is observed here that Collagen deposition initialized before Stage 18 around the lumen and progressed faster for the Arch III right more than the left. The progression covered the entire radial direction until Stage 24.

3.4.9 No temporal change in protein intensity levels

If we look at the time-dependent intensity levels at Stage 18 and Stage 24, there is no significant difference in COL-I levels, in the radial direction, for both the left and right laterals of Arch III and Arch IV between Stages 18 and 24. The exception is the significant difference for $rd > 0.65$ in the Stage18-IV-R vs. Stage24-IV-R comparison. In general, the intensity levels of arches are relatively stable during the time course for each arch.

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This particular case of stability shows the existence of a sensitive mechanism of COL-I production, which can be termed as a "scale balance". In accordance with this mechanism, the production imbalance that started and spread between the left and right laterals of Arch III and Arch IV stabilized with another unknown mechanism for the long term, allowing the production to be set in a limited, but permanent condition. This equilibrium state was established in a critical manner for all Stage 18 to Stage 24 comparisons and Arch II right vs. left comparison.

3.4.10 Internal clock hypothesis in aortic arch evolution

Our observations of early COL-I differentiation of left and right laterals of Arch VI reinforces our age-dependent hypothesis that the source of evolution is an activation around the lumen periphery that triggers a process of COL-I that progresses over time. Below we summarize our most important determinations for Arch IV. Although there is some similarity in terms of the initial trigger region of accumulation between Arch III and Arch VI, the same phenomenon was not clearly observed for Arch IV. On the other hand, there are some similarities for H_0 acceptance statistics for Arch III and Arch IV. When the results of Appendix F are taken into consideration, similar features are observed for the fluctuation of H_0 in the right and left bilateral tests for both Arch III and Arch IV based comparisons. Although the evolution of Arch III precedes Arch IV in terms of aging, it is interesting to note that the complete radial differentiation of laterals of Arch IV was completed by Stage 24. It is also significant to note that this differentiation was still primitive at Stage 24-VI. Although there was some similarity between the comparative test results for Arch III and Arch IV at Stage 18, this similarity was not as clear as the comparison at Stage 24. For example, the Arch III lateral comparison at Stage 18 shows that $\text{Prob}(H_0) < 0.05$ for $rd < 0.3$ was followed by an increase in H_0 for $0.3 < rd < 0.5$, a decrease in H_0 for $0.5 < rd < 0.7$, and then a final increase. A similar trend was observed with a shift in the increasing and decreasing intervals for lateral comparisons for Arch IV at Stage 18. The reason for this shift is presumed to be due to the difference in ages between the two arches (Arch III vs. Arch IV), and the observed similarities are due to differences in the speed of the "internal clock" that manages the mechanisms for production. This internal clock functions with the concept of "characteristic remodeling time" as perceived in the computational community, and we evaluate this internal clock as being a part of the epigenetic mechanism driving the process of COL-I.

3.4.11 Possibility of an intrinsic time-scale in arch aging and order

When analyzing the test results for all arches, there appears to be a possible delayed evolution of the left and right arches, with the left arch deposition appearing to be slower compared to the right one in terms of an evolutionary internal clock. If we consider the aging of the artery system, it can be concluded that a (hypothetical) internal clock, with ongoing aging, will not be the same for all arches and this genetic behavior is believed to trigger the production mechanisms depending on the relative time sequence. Arches can be classified according to their embryonic lifetime (Kowalski et al. 2013). Less than 25 percent of the total lifetime is considered as a “young” arch and more than 50 percent of lifetime can be counted as “old” arch. Thus, between young (Stage18-III, Stage18-IV and Stage24-VI), pre-mature (Stage24-IV), mature (Stage24-III) and old arteries (Stage18-II), there can be a level of difference in terms of deposition, which depends on the production efficiency of the cellular compartments. Thus, the aging ordering can be coded by means of its intrinsic time scale as,

"VI-Stage24"

≈ "III-Stage18" ≈ "IV-Stage18" < "III-Stage24" ≈ "IV-Stage24" < "II-Stage18"

We also postulate an intrinsic time scale for the left and right age ordering as,

Left arch < Right arch

We note that this ordering is due to the production efficiency of the artery as there is no age difference in left and right of the arteries. In terms of the Collagen levels, a beginning-rising and peak-declining life-cycle is possible for the Collagen deposition. Statistical results indicate that the levels start to differentiate for Stage24-VI (the youngest) and Stage18-III (the previous youngest). When the temporal maturation is observed, the left and right levels start to differentiate (such as the laterals of Arch III and Arch IV at Stage 24) and progress in the following stages. The differentiations are then expected to decline to a low base level with aging, where the left and right levels are equalized at the end of the cycle (Stage18-II). Since Arch II is a relatively old, mature arch at Stage 18 and is the predecessor of other arches, we can claim that the evolution of biological factors is stabilized for both laterals of Arch II over time. The statistical results of this study correlate well with this hypothetical construction, however more detailed research is required for a complete understanding of the underlying mechanisms.

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3.4.12 Limitations

While the major findings presented in this manuscript are statistically reliable and provide important insights into the remodeling of embryonic aortic arch, there are several technical improvements that can advance the proposed computational model. In particular, a very detailed material characterization study of the embryonic aortic arch is currently progressing in our laboratory, which will allow us to use hyper-elastic material model parameters. In order to supply the correct mechanical information to these models, we initially constructed an idealized form of a representative arch geometry with phenomenological description, which is still a common approach in computational modeling of very soft embryonic structures. Likewise, 3D optical coherence tomography (OCT) scans can be employed to reconstruct a full 3D model of the aortic arch manifold in which our computational approach can be directly implemented. Furthermore, assigning pulsatile pressure distribution throughout the arteries enables quantitative comparison of vessel diameter changes to be obtained from OCT, which can correlate with the measured COL-I synthesis. Although the phenomenological shear modulus increase is modelled on the newly grown material, this mechanical evolution process was not strictly measured by our experimental observations (due to the experimental challenges with micron size arteries). Due to the bridge formation and coupled movement of the arches, a possible description of the internal evolution of aortic arches is simplified through analyzing the single Arch IV, which recently appears around Stage 18, and it is also mature enough to be computationally modeled. The only exception for the stable formation for Stages 18 to 24 is that Arch II exhibits a transitory scheme with Arch VI formation, due to the disappearing and appearing of the lumen, which may be problematic for a consistent unique description.

3.4.13 Future work

To suppress the convergence of the computational model, we investigated low levels basal matrix production, which affects volume growth. The material description and ECM component production functions used in these simulations can also be used to test the final shape of the accumulation. This research approach is able to provide the bounded levels of COL-I production with an exponential-like distribution associated with local stiffness change in the extra-cellular matrix. Future research requires more complex geometries and more accurate precursor parameter estimates with the possible anisotropic character of the arch structure, which is unknown. Given that the matrix production

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mechanisms in question are structured around a complex equilibrium, further studies of advanced high-dimensional interpolation for the detection of parameter sensitivities are needed.



Chapter 4

4 COMPUTATIONAL MODELING OF GROWTH IN ARTERIAL PATCH RECONSTRUCTIONS

4.1 Introduction

In Chapter 2, a pre-surgical computer-aided surgical patch design framework for stenosed pulmonary arteries was developed for Tetralogy of Fallot (TOF) patients (Lashkarinia et al. 2018). While lacking the present essential growth and remodeling (G&R) component, this surgical planning approach enables surgeons to incorporate the effect of intramural pressure in 3D surgical patch design. More specifically, the computational design framework is able to predict the structural optimization of the patched region and the effects of stenosis grade, the 3D shape of the surgical incision and the material properties of the patch. In the present study, we were able to exploit the advancements of this research to examine the growth of native tissues in the long-term 3D anatomy of the surgical site.

Continuum level growth models are based on either constrained mixture (Humphrey and Rajagopal 2002) or kinematic (Rodriguez et al. 1994) theory. The computational implementation of micromechanical constrained mixture theory (Ateshian and Humphrey 2012; Valentín et al. 2013) is usually associated with higher computational costs. In comparison, the kinetic theory model used in this study is more cost-efficient for surgical-planning purposes that involve complex anatomies. While there is a variety of finite element-based numerical models of cardiovascular growth (Chen et al. 2000; Göktepe et al. 2010; Himpel et al. 2005; Kroon et al. 2009; Kuhl et al. 2007; Lubarda and Hoger 2002; Taber and Eggers 1996), patient-specific studies are still limited (Alastrué et al. 2010; Grytsan et al. 2015; Saez et al. 2014; Zeinali-Davarani et al. 2011). The growth formulations used in the present study are based on Göktepe et al. (Göktepe et al. 2010), Saez et al. (Saez et al. 2014) and our recent work on modeling vascular G&R of embryonic aortic arch (Lashkarinia et al. 2020), which reveal micromechanically motivated assumptions for the growth tensor of cardiac tissue.

The predictive growth tool developed by this study will advance state-of-the-art patient-specific surgical planning technology with its capability to predict 3D vascular G&R. The practical outcome is that our proposed planning system will enable clinicians

to rapidly implement a patch reconstruction strategy based on a patient-specific 3D computer model, which can visualize its resulting long-term growth pattern without *in vivo* execution.

4.2 Materials and Methods

4.2.1 Arterial Tissue Growth and Remodeling

Pulmonary artery lumen size increase during the pediatric stages is defined by irreversible growth mechanics. In this scenario, the basic kinematic quantity is the deformation gradient ($\mathbf{F}$). It is presented as the tangent of the nonlinear deformation map ($\boldsymbol{\varphi}$). According to multiplicative decomposition theorem (Rodriguez et al. 1994), the total deformation gradient tensor $\mathbf{F}$ is decomposed into $\mathbf{F}_g$ and $\mathbf{F}_e$:

$$\mathbf{F} = \mathbf{F}_e \mathbf{F}_g \quad (4.1)$$

where $\mathbf{F}_g$ is the growth deformation gradient tensor and $\mathbf{F}_e$ is the elastic part. The growth deformation tensor is defined by the following equation (Göktepe et al. 2010; Saez et al. 2014):

$$\mathbf{F}_g = \mathbf{I} + (\vartheta_g - 1) \mathbf{n} \otimes \mathbf{n} \quad (4.2)$$

that governs the amount of permanent elongation in the direction of the fabric vector $\mathbf{n}$. The fabric direction is determined by the growing material flow. The growth direction resembles the elongation of the endothelial and the smooth muscle cells change from globular shape to fusiform in the pulmonary artery during growth (Rabinovitch 1992). The direction is selected to be co-axial with the maximum principal stretch ($\lambda_{\max}$) in the tissue and the growth stretch (λ_g) satisfies the condition $\lambda_{\max} = \lambda_e \lambda_g$. Growth tensor is characterized through a single growth multiplier (v_g) which is set equal to growth stretch ($v_g = \lambda_g$)(Göktepe et al. 2010). The evolution rate of growth multiplier ($\dot{v}_g$) has been defined in the same form as in our recent embryonic growth model (S. Samaneh Lashkarinia 2020):

$$\dot{v}_g = k(v_g) \eta_g(\lambda_e) \quad (4.3)$$

where the limiting function $k(v_g)$ and growth stimulus function $\eta_g(\lambda_e)$ are identified as follows:

$$k(v_g) = \frac{1}{\tau} \left(\frac{v_{\max} - v_g}{v_{\max} - 1} \right)^Y, \quad \eta_g(\lambda_e) = \lambda_e - \lambda_h \quad (4.4)$$

$v_{\max}$ is a high threshold value for growth stretch. This threshold represents the maximum extent allowed for pathological smooth muscle cell stretch. Adaptation speed of growth (τ) specifies the required time for the activation of the growth process. Non-linearity of the growth process (γ) adjusts the shape of the adaptation curve. The driving force for growth is the maximum principal stretch sensed by tissue ($\lambda_{\max}$). The growth process is activated when the elastic stretch (λ_e) exceeds the homeostatic stretch level (λ_h).

The elastic behavior of native tissue in response to internal blood pressure is determined by an isotropic single parameter neo-Hookean material model with slight compressibility ($\nu = 0.475$). The stiffening of the arterial wall in a growing child due to an increase in the microstructural constituents (e.g. Collagen) in tissue is modeled by internal elevation of stiffness modulus (μ) during the growth.

The elastic part of the second Piola Kirchhoff stress function $\mathbf{S}_e$ is defined as in (S. Samaneh Lashkarinia 2020) as:

$$\mathbf{S}_e = (K \ln(J_e) - \mu) \mathbf{C}_e^{-1} + \mu \mathbf{I} \quad (4.5)$$

where the Lamé parameter (K) and young modulus (E) are given by:

$$K = \nu E / ((1 + \nu)(1 - 2\nu)), \quad E = 2\mu(1 + \nu) \quad (4.6)$$

In the numerical modelling, the biological activity rate which leads to material production and stiffening is assumed to be constant for the entire simulation process. Hence, parameter (k) which controls the rate of growth and stiffening in the model is kept constant. The evolution of growth stretch is given by a second order stable explicit update algorithm:

$$\lambda_g(k_g, \eta_g, t_n) \approx \lambda_g + 2\Delta t k \frac{1}{\tau} \eta_g(\lambda_e) \left(2 + \Delta t k \frac{\lambda}{\lambda_g^2 \tau} \right)^{-1} \quad (4.7)$$

The shear modulus is updated linearly:

$$\mu(k_g, \eta_g, t_n) \approx \mu(k_g, \eta_g, t_{n-1}) + \Delta t k \eta_g(\lambda_e) \quad (4.8)$$

The aforementioned elastic-growing material model was generated through an in-house code and imported as new material model plugin to FEBio (Maas et al. 2012a).

4.2.2 Calibration of growth parameters for human main pulmonary artery

To calibrate the vascular growth parameters for the strain driven growth in pediatric PA tissue, a clinical database that provides the dimensions and pressure loading in a healthy human from birth to 18 years old was used (Parasuraman et al. 2016; Pettersen et al. 2008). To first identify the homeostatic stretch level (λ_h) in human main pulmonary

Chapter 4: Computational modeling of growth in arterial patch reconstructions

artery (MPA), a cylindrical vessel model was pressurized to 12 mmHg, which corresponds to the healthy adult-stage MPA mean pressure level in a quasi-static simulation. The shear modulus parameter for the neo-Hookean material parameter is considered as $\mu = 280$ (kPa) for mature PA tissue (Van den Abbeele et al. 2015). The maximum principal elastic stretch in this simulation was set as the homeostatic stretch level (λ_h) for the growth simulations.

Idealized healthy human MPA having initial vessel dimensions compatible with the MPA of a newborn was used in the growth simulation model which starts from birth to 18 years old. The model was first pressurized to 42 mmHg pressure, which is the physiological pressure level for newborn MPA. Pressure loading was then decreased gradually to 12 mmHg at 18 years old when growth diminishes at this age. Growth parameters were adjusted to capture the diameter-pressure curve obtained from clinical data and shear modulus of $\mu = 280$ (kPa) at adulthood. Accordingly, the initial value of the shear modulus (μ_0) and growth parameters ($\lambda_{max}, \tau, \gamma, k$) for the human PA tissue G&R was obtained from this simulation.

4.2.3 Growth model of idealized MPA patch reconstruction

The idealized model of a 70% stenosed pulmonary artery for a 10-year-old child was repaired through a typical patch reconstruction surgery by means of our computer-aided pre-surgical patch design framework (Lashkarinia et al. 2018) (Figure 4.1a). The artificial patch material used was expanded polytetrafluoroethylene (ePTFE). The material properties of the ePTFE patch were obtained from our bi-axial tests, which can be faithfully modeled as an elastic linear-isotropic material ($E=1.4\text{Mpa}$, $\nu=0.31$) for the operating pressure range (Lashkarinia et al. 2018). Simulations started from the 10-year-old child's pre-surgery dimensions and mechanical loading (22 mm-Hg) and continued until the age of 18 years when somatic growth gradually stops.

4.2.4 Patient-specific pulmonary artery reconstruction

A newborn male TOF patient with severe stenosis in right pulmonary artery (RPA) was recruited for cardiac MRI retrospectively through the approved IRB protocols of Koc University and Medipol University. The sequence of surgical operations and patch generation along the narrowed arterial segment was performed interactively through an anatomical editing tool (Geomagic Inc, NC, USA) (Figure 4.1b), as described in detail in

a previous study (Lashkarinia et al. 2018). Post-operative pressure loading condition started from 2 months and gradually rose to the age of 18 years (42 to 12 mmHg) for this patient (Figure 4.2).

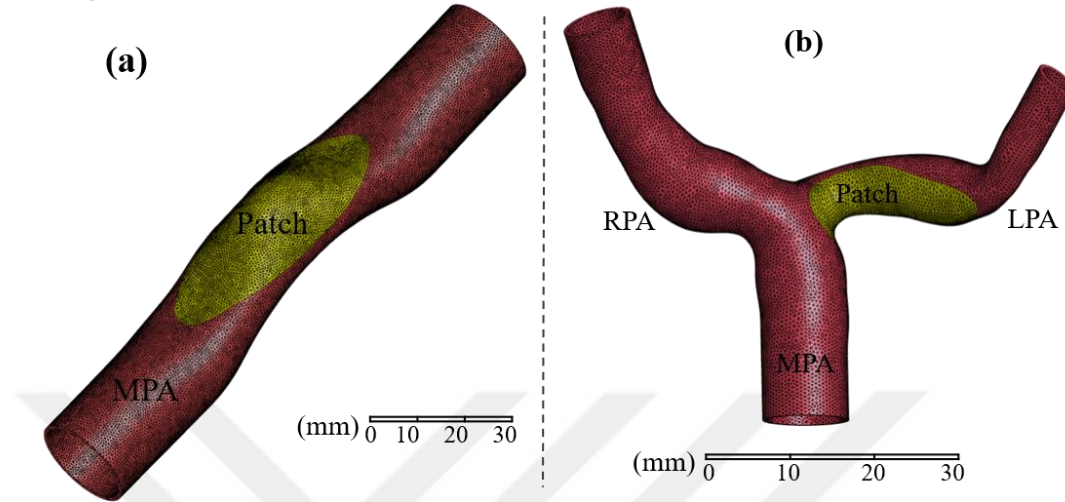


Figure 4.1: (a) Idealized patched main pulmonary artery (MPA) with 70% pre-surgery stenosis in cross-section corresponding to a 10-year-old child (b) Patient-specific pulmonary anatomy of a one-week-old newborn with severe stenosis at the left pulmonary artery (LPA). Both configurations are plotted in their unloaded configurations overpotted with the computational mesh.

4.2.5 Numerical implementation

Finite element simulations were performed on a 5 node HPC-cluster with 72 cores per node, using the plugin framework of FEBio open source software (Maas et al. 2012b). Each simulation took around 3-4 hours. The plugin was constructed to couple a displacement-based implicit nonlinear solver with an explicit second order stable iterator for growth simulation. Second-order tetrahedral mesh elements were generated on both the patch and the artery in one layer across the wall with a thickness of 1mm. Smooth mesh size transition was achieved on the boundaries of both the patch and the artery, and this welded contact condition functioned as the surgical stitch in this region. The mesh convergence was tested by means of the saturation of growth stretch (λ_g) in the specified mesh. A mesh sensitivity study was concluded by selecting a grid edge size of 0.35 mm to achieve less than 5% change in the results. Pre and post processing analysis were also performed in the FEBio software suite.

4.3 Results

4.3.1 Growth parameters for healthy pediatric pulmonary artery aging

Diameter enlargement for the healthy MPA configuration during vascular growth was obtained and compared to the clinical data. Pressure-diameter changes acquired from the growth simulation and clinical data are shown in the same plot in Figure 4.2. The numerical curve stays in the experimental mean curve $\pm$ standard error region. The maximum error of numerical estimation from the experimental curve was 7%. Growth parameters were also calibrated through the healthy MPA aging simulations. These parameters are summarized in Table 4.1.

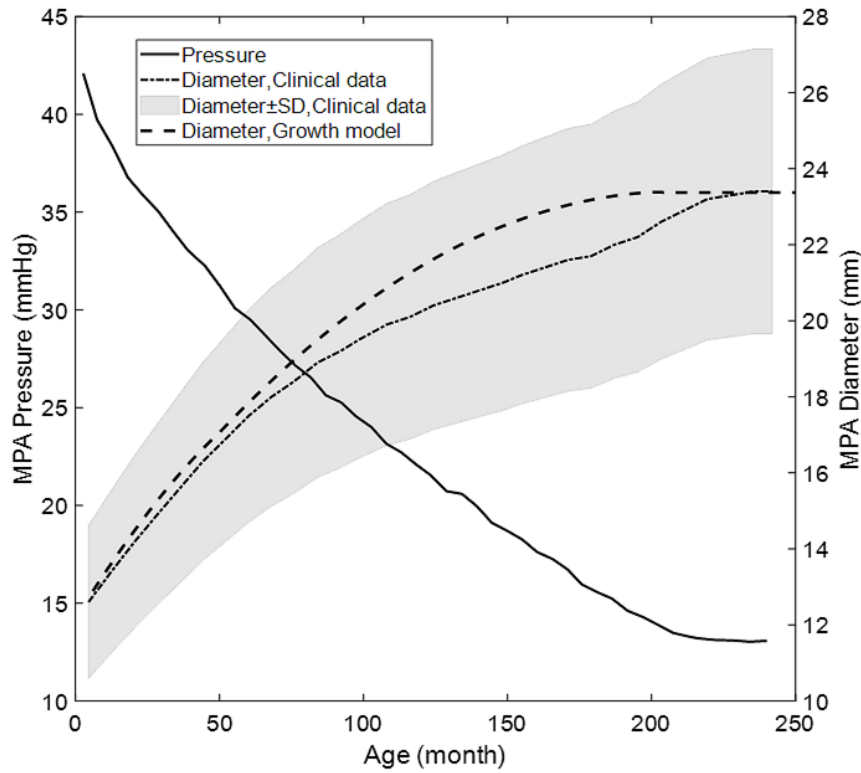


Figure 4.2: Healthy main pulmonary artery lumen diameter increases in human from birth to 18 years old. Corresponding computational growth simulation results under physiological blood pressure loading are compared with this clinically measured dimension trend.

Table 4.1: Material evolution parameters used in the computational simulations are tabulated. The maximum threshold for growth ($v_{\max}$), adaptation speed of growth (τ), non-linearity of growth process (γ), the homeostatic stretch level (λ_h) and the initial shear modulus (μ_0) are given.

$v_{\max}$	2
τ (1/days)	1
γ	3
λ_h	1.04
μ_0 (kPa)	160

4.3.2 Evolution of growth in the idealized patched MPA

Growth at the age of 18 years was computed in the idealized patched MPA model (Figure 4.3). The growth demonstrated a non-homogeneous pattern at the throat. While non-growing regions ($v_g=1$) were observed in this region, the maximum growth of $v_g=1.24$ primarily occurred at the arterial tissue close to the patch corners.

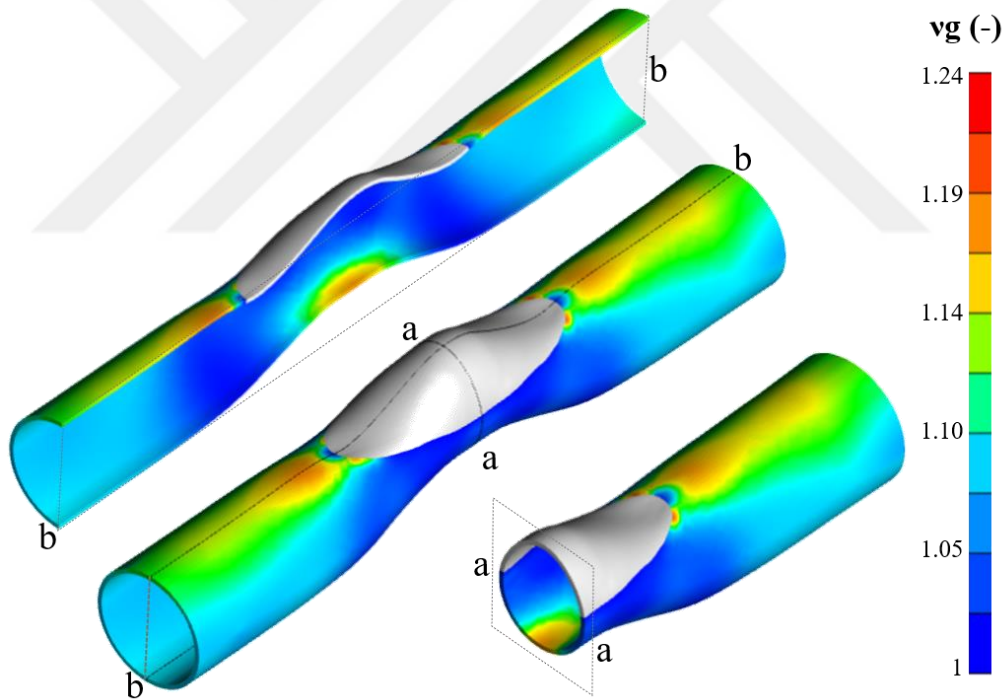


Figure 4.3: Final growth map in the idealized patched main pulmonary artery of an 18-year-old patient who underwent surgery at the age 10. Two representative planes in longitudinal and transverse directions are displayed. Growth is heterogeneous and it is higher on the arterial tissue close to the incision corners and throat.

The idealized model simulation started with a homogeneous shear modulus level of 200 (kPa) on the entire domain. At the end of simulation, highly stressed portions of the tissue experienced a 50% increase of the shear modulus (Figure 4.4).

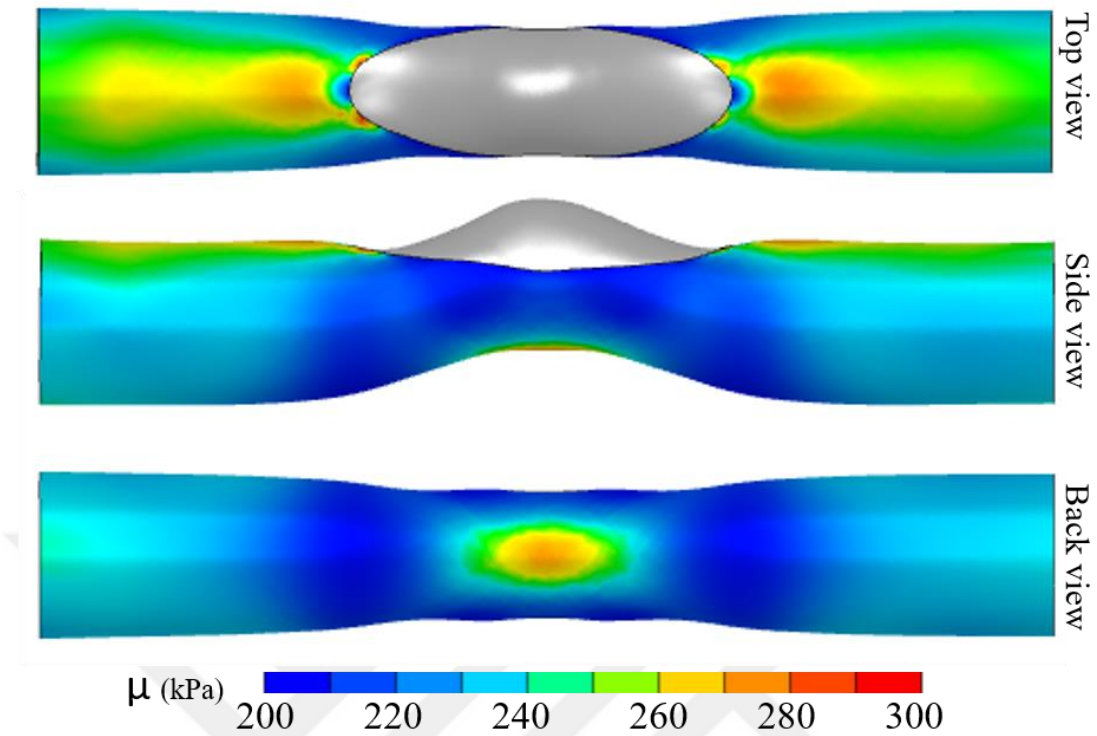


Figure 4.4: The predicted shear modulus map on the arterial tissue is plotted at the age of 18 years after surgery at 10 years old. Top, side and back view of the model is shown. The most stiffened regions of the arterial tissue are the incision corners and throat (stenosis section). Arterial tissue near the longitudinal sides of the patch does not stiffen during aging.

As presented in Figure 4.5, the highest value of maximum principal stress on the arterial tissue was decreased from 55 to 13 (kPa). The ellipsoidal corners of the patch remained in a high stress range of 35-65 (kPa), while the average stress level on the patch dropped from the value of 40 to 15 (kPa). The maximum principal elastic stretch on the artificial patch did not exceed the value of 1.06 during the growth simulation, while the maximum principal stretch on the live tissue reached the maximum value of 1.30 at the throat and incision corners.

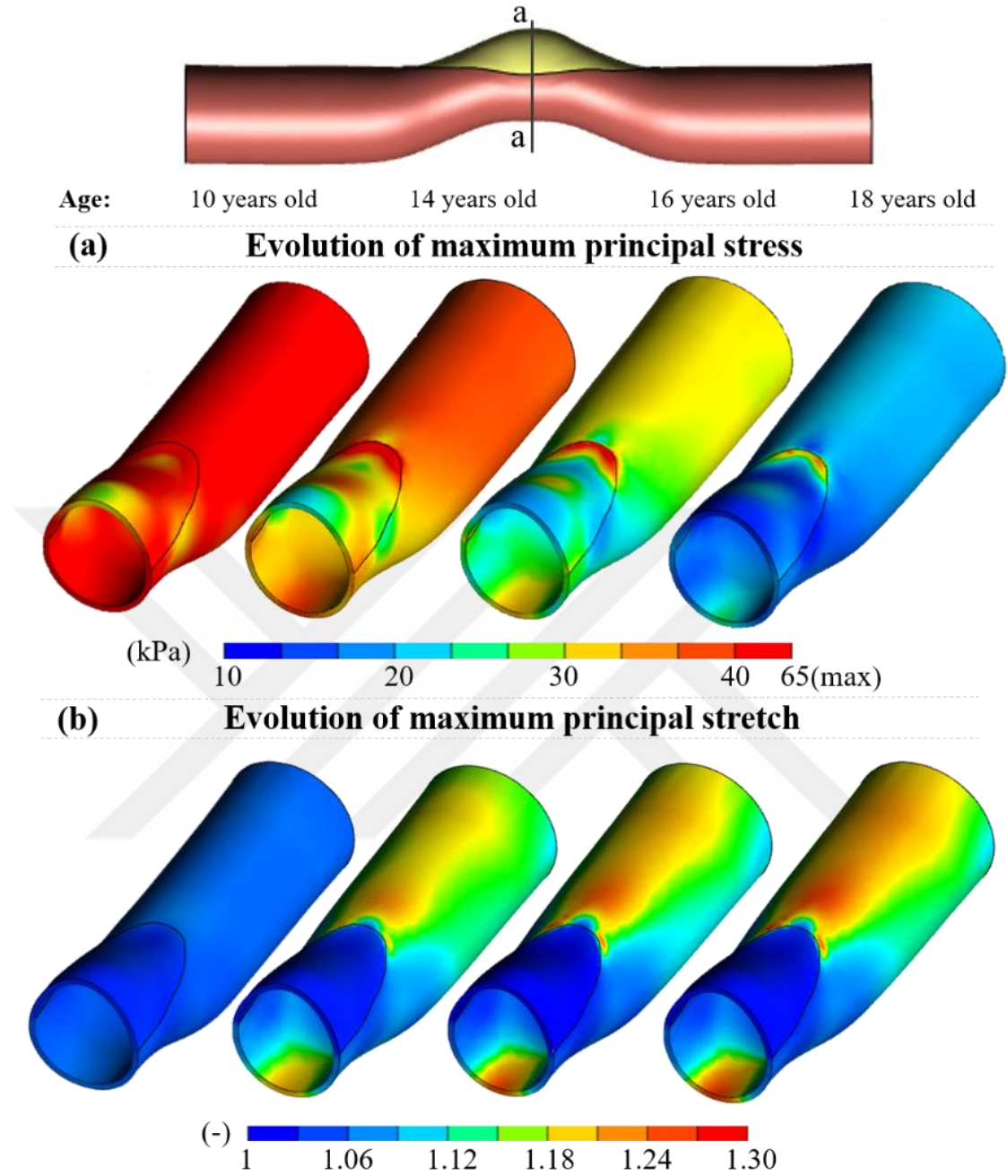


Figure 4.5: Long-term time-lapsed post-operative response of MPA. In (a) and (b) model is visualized using a cut from the section aa shown in the top figure. Half of the model is shown due to the model symmetry. The evolution of max principal stress in an idealized model of patched pulmonary artery under post-operative blood pressure is shown in (a). Pressure decreases from 22 to 14 mmHg gradually from 10 years old to 18 years old as an input to the simulations. The evolution of maximum principal stretch on the model is shown in (b). This plot indicates superposition of elastic and permanent stretch on the arterial tissue, while only the elastic stretch is observed on patch material during the evolution.

4.3.3 Evolution of growth in the patient-specific patched model

While the distal regions of the left pulmonary artery (LPA) in the patient-specific model did not grow ($v_g = 1$), the proximal regions experienced the highest growth of $v_g = 2.5$ at the age of 18 years, as presented in Figure 4.6.

The maximum level of elastic stretch on the tissue was observed at infancy ($\lambda_e = 1.16$), which gradually decreased and was compensated by growth stretch as time progressed (Figure 7a). At 18 years of age, the highest value of the maximum principal elastic stretch on the entire domain dropped below the homeostatic stretch level ($\lambda_h = 1.04$), as growth gradually stops at this age. Since growth stretch is equivalent to growth multiplier ($v_g = \lambda_g$) in growth formulations, Figure 4.7b represents the spatio-temporal evolution of both the growth stretch and growth multiplier. The bifurcation regions and some portions of the patch stitch region grew non-linearly and experienced the maximum principal growth stretch value of 1.24, 1.93 and 2.13 at the ages of 6, 12 and 18, respectively.

The maximum principal stress distribution on the native tissue in the patient-specific model showed a decreasing trend. The average value of maximum principal stress on the arterial tissue dropped by 26%, 58% and 75% at the ages of 6, 12 and 18, respectively (Figure 4.7b). Likewise, the stress levels on the patch tissue demonstrated a decreasing trend. The maximum value of maximum principal stress on the patch tissue at the age of 18 years was 60 (kPa), which was 38% higher than this value on the arterial tissue. It is also important to note that the maximum stretch level on the patch did not exceed the value of 1.16 during growth, while the peak value of total maximum principal stretch on the arterial tissue reached 2.48 at the end of the growth period.

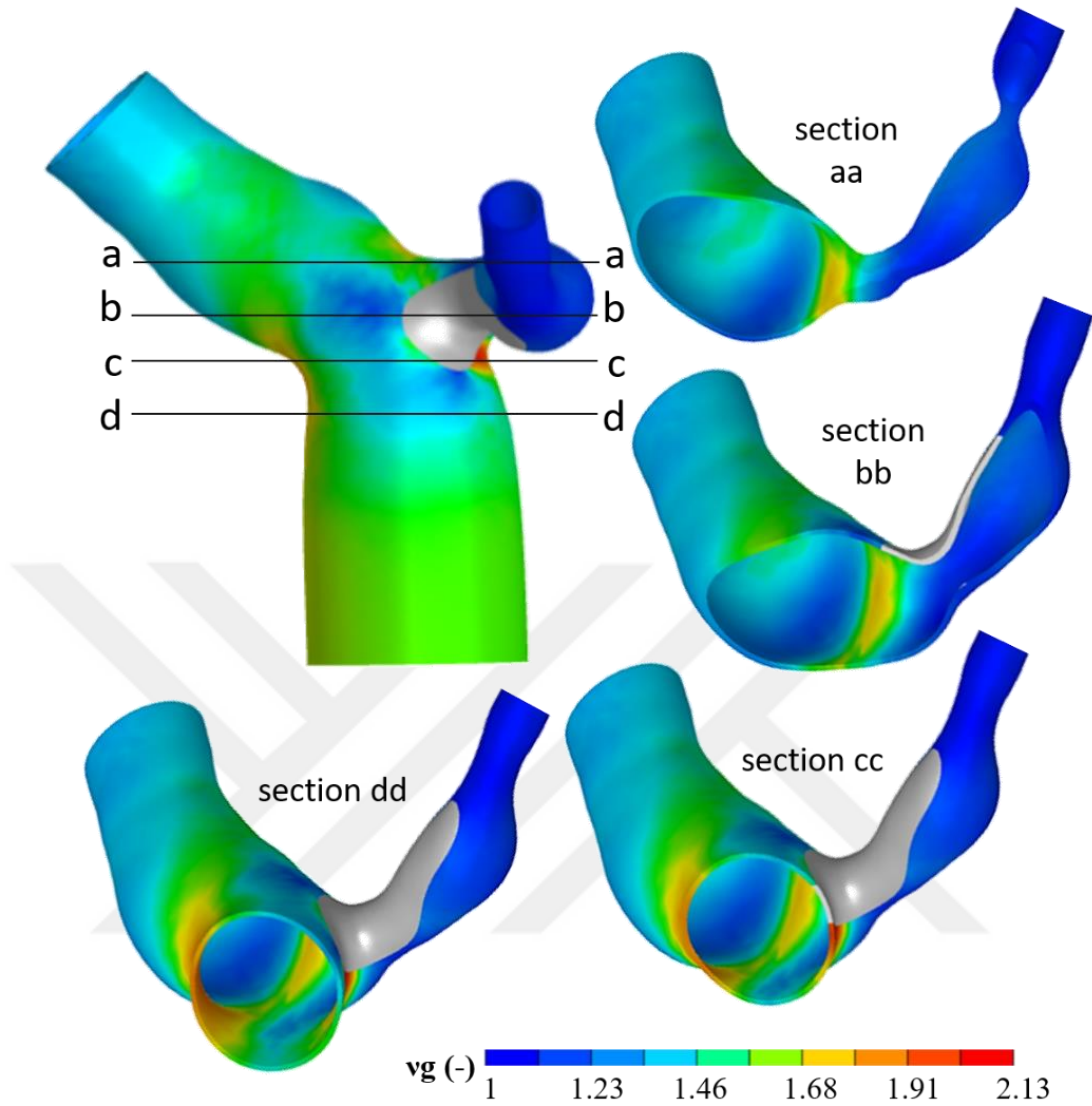
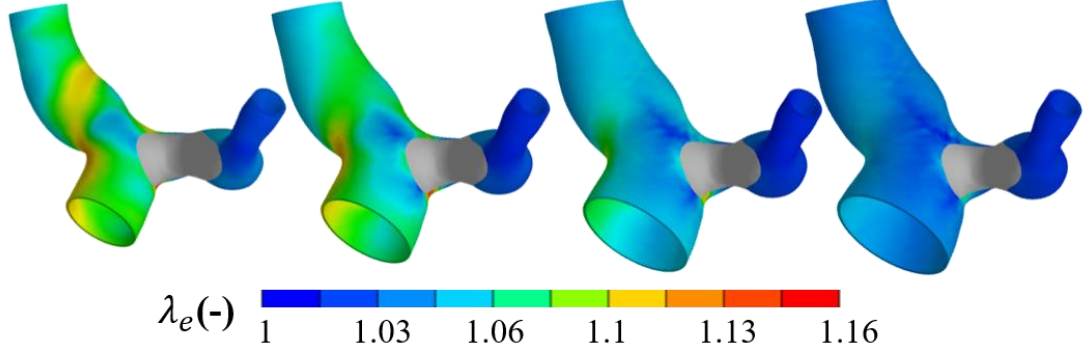


Figure 4.6: Patient-specific model results. To display the entire growth gradient on the 3D model, four representative sections are shown. The contour plots are displayed on the deformed configuration after 18 years of growth. Some portions of PA bifurcation indicate elevated growth level. While MPA and RPA experienced considerable levels of growth, the distal parts of the LPA demonstrated reduced growth.

As shown in Figure 4.9, the stiffening of arterial tissue due to growth was significant at the age of 18 years. The contour map of the shear modulus is similar to the growth map and highly stiffened regions are defined as the bifurcation portions, where 125% stiffening of the tissue was observed. In the distal regions of the LPA, growth was not triggered extensively and did not experience any stiffening.

Age: 2 weeks old 6 years old 12 years old 18 years old

(a) Evolution of maximum principal elastic stretches



(b) Evolution of maximum principal growth stretches

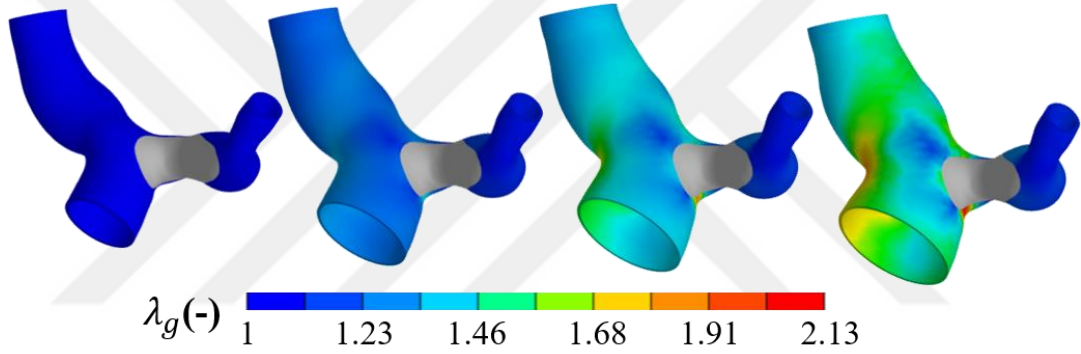


Figure 4.7: (a) The time-lapsed evolution of maximum principal elastic stretch on vascular tissue is plotted at six-year intervals from birth to 18 years old. (b) Evolution of maximum principal growth stretch is shown on the domain which compensates for elastic stretch and provides permanent vessel enlargement (cut section by plane (dd) in Figure 4.6 is shown).

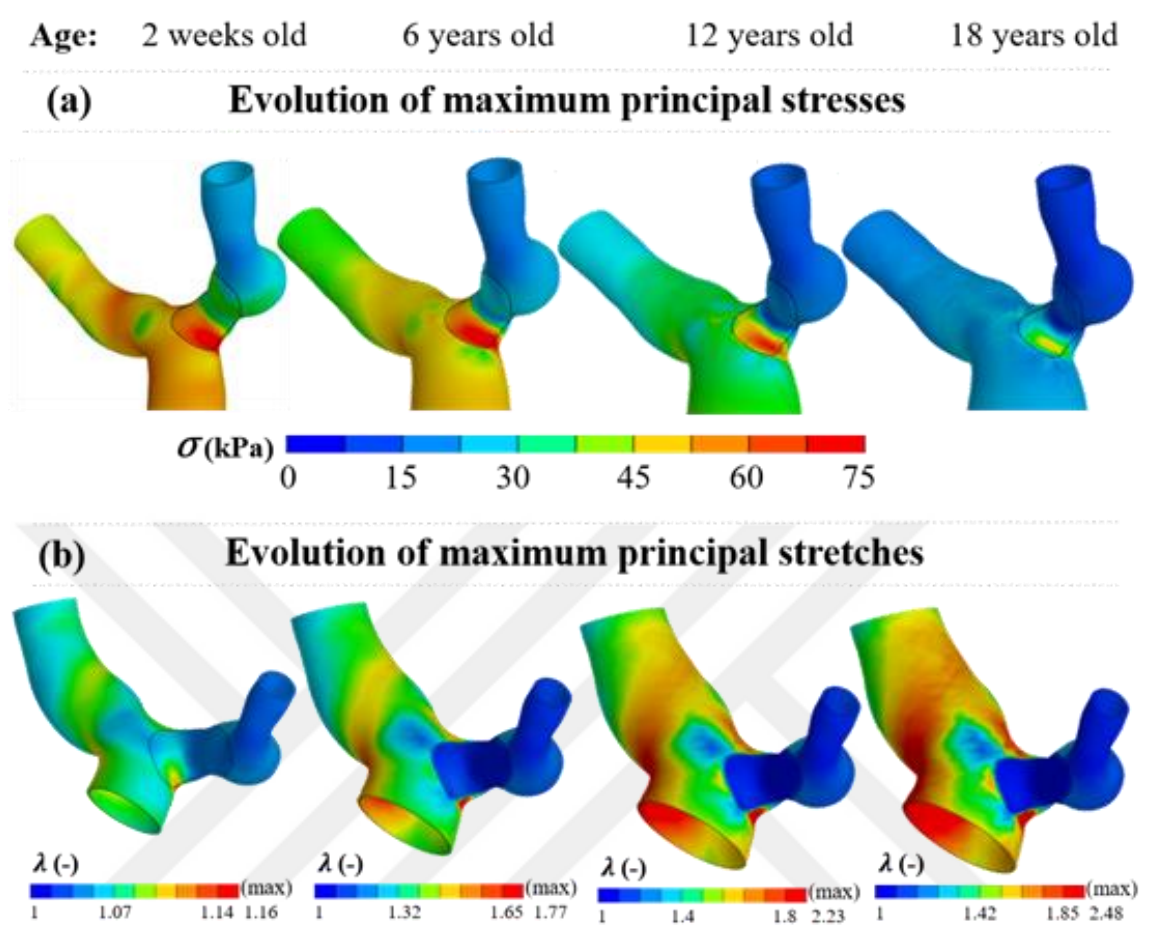


Figure 4.8: (a) Time-lapsed evolution of maximum principal stress on both the patch and live tissue is shown at 6-year intervals from birth to 18 years old. (b) Evolution of maximum principal stretch is plotted on the domain (cut section by plane (dd) is shown). A separate legend is assigned for each contour plot in this part for better visualization of the gradient maps on both patch and tissue.

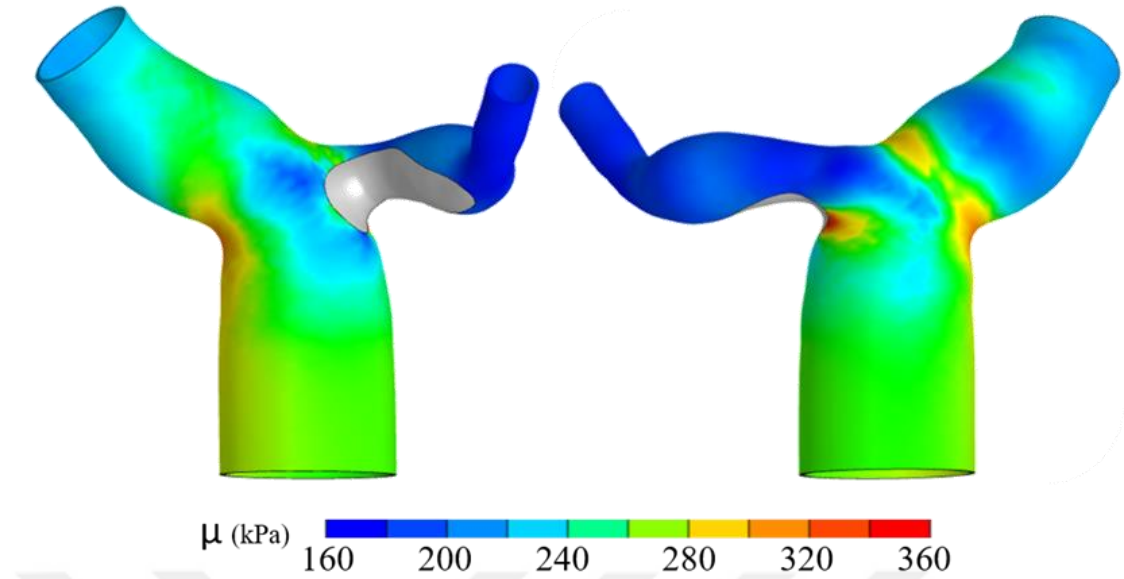


Figure 4.9: Predicted map of the shear modulus on the patient-specific arterial tissue at the age of 18 after surgery at infancy. Front and back view of the model is shown. Most stiffened regions of the arterial tissue are the portions of bifurcation and turnings in the PA anatomy, while the distal parts of the LPA do not stiffen.

4.4 Discussion

In this study we analyzed the long-term prognosis of surgically corrected TOF patients with the use of *in vivo* pediatric PA growth data and its relatively simple 3D topology, which is equally applicable to more complex aortic arch reconstructions (Haas et al. 2000). The main impetus for this research is that surgical treatments that involve the placement of a transannular patch more frequently require reoperation (Ylitalo et al. 2014). The high risk for morbidity and late complications associated with right ventricular dysfunction and re-stenosis of the reconstructed neo right ventricular outflow tract and branch PA in these patients (Oechslin et al. 1999) further underline the importance of this research approach to more precisely plan for patch reconstructive surgeries based on simulation analysis. However, patient-specific models are not a standard of care in clinical practice because assessment of the predictive capability of these models needs to be applied on a large patient cohort (Neal and Kerckhoffs 2009). For the first time in literature, we were able to investigate the post-operative response of the native PA as the growing domain came into contact with the non-growing patch domain. To address the complexity of patient-specific anatomies, material remodeling was embedded in the growth formulations and the neo-Hookean shear modulus, which were updated at each iteration in order to simulate the material stiffening associated with growth (Cheung 2010;

Savant et al. 2014). This approach enabled us to predict the long-term outcomes of patch reconstructive surgeries and improve state-of-the art surgical strategies that can mitigate undesired anatomical changes during growth.

Microstructural cardiovascular adaptations due to altered mechanical load represent a complex mechanism (Celik M et al. 2020). Hypertrophy of SMC and endothelial cells in the pulmonary arteries during pediatric pulmonary growth emerges from the elongation of these cells (Rabinovitch 1992). In relation to the growth formulation used in this study, the assumption is that these cells are load-bearing structures which are being re-aligned during the growth period to bear maximum principal stretch. The biological response of tissue to increased loading is volume increase and stiffening to decrease the elastic strain/stress levels. This can be observed from the results of the simulation for both idealized MPA (Figures 4.3 and 4.4) and the patient-specific model (Figures 4.6 and 4.9). The high growth level is associated with highly stiffened regions to diminish the stress and elastic strain gradients on the arterial tissue to provide a homogenous stress/strain distribution on the arteries.

Growth can be expressed as tissue response to disturbed homeostasis in the native tissue. While it is possible that vascular growth can be triggered in response to a variety of hemodynamic, hormonal, and pathologic stimuli, the disturbance can also be caused by pressure-over load due to the increase of blood pressure applied to the wall or volume-overload due to flow increase in the vessel (Hunter and Chien 1999). The drop in pulmonary vascular resistance within minutes of birth, which is due to the recruitment of peripheral arteries, leads to PA pressure decrease in post-natal life (Rabinovitch 1992). The decrease in pressure implies that there is no stress elevation caused by pressure, which could be considered as the driving force for physiological PA growth. On the other hand, blood flow increase in the PA is associated with cross-section enlargement and dilation-like growth in the vessel, which can be expressed by strain-based growth formulation (Göktepe et al. 2010). Our recent elastin-collagen intermittent load sharing approach can be used to model lumen growth due to wall shear stress changes (Celik et al.). In the simulation model used in this study, the mechanical stimuli for growth was selected to be strain (stretch) based. This model was able to capture the physiological pulmonary artery diameter enlargement from birth to adulthood, which showed good agreement both qualitatively and quantitatively, as shown in Figure 4.2. It is important to note that since clinical state-of-the-art imaging protocols do not provide accurate vessel

thickness information, the strain-based directional growth model used in this study only resembles the diameter enlargement regardless of vessel thickness changes during growth.

In both the idealized MPA and patient-specific PA models, non-uniform distribution of growth was observed around the stitch line along the arterial tissue. This implies that material differences between the PTFE patch and live PA tissue do not significantly affect the anatomy of stress/strain formations around the stitch line during growth. The maximum principal stress/stretch distribution in Figure 4.3 shows that the stress value around the stitch line on live tissue varies between the 30-65 (kPa) range immediately after surgery, which then drops to 10-25 (kPa) at the age of 18 years. Also, by observing the stress/strain distribution around the surgical stitch in the patient-specific PA model (Figure 4.8), it can be concluded that the high gradient of stress/strain on live tissue in this region is mainly related to geometrical variations. These findings highlight the critical importance of the patch shape for optimal postoperative outcomes. For the specific patient characteristics examined in this study, even though a severe stenosis of 90% was successfully repaired with a PTFE patch, the distal part of the LPA still remained 4 mm narrower than the RPA in diameter. Since the pressure loading applied to the model was equal in all domains, any narrowness in vessel radius is associated with lower elastic stress/strain levels on the tissue (Hoefer et al. 2013). With decreases in blood pressure loading, strain levels remained under the homeostatic level of $\lambda_h = 1.04$ and consequently, growth was not triggered in the distal parts of the LPA, even around the stitch line. In comparison, the proximal part of the LPA patch experienced high stress levels, which led to high growth.

In the idealized MPA model, the highest levels of maximum principal stress in spatiotemporal evolution occurs in the arterial tissue immediately after surgery, but as time goes by and tissue grows, the extra stress is compensated and degraded by 61% at the age of 18 years. While growth does provide stress relief for live tissue, patch tissue also experiences higher stress because of the appearance of excessive arterial tissue at the adjacent arterial region over time. Therefore, despite decreases in applied pressure load leading to a 27% drop in maximum principal stress in the patch, the highest stress regions move from the arterial incision corners towards the patch corners during the spatiotemporal evolution (Figure 4.5). A similar trend was observed in the evolution of maximum principal stress in the patient-specific PA model. As shown in Figure 4.8, the

Chapter 4: Computational modeling of growth in arterial patch reconstructions

maximum value of maximum principal stress dropped by 67% on the arterial tissue and 35% on the patch and the highest stress level was observed on the patch at the end of the growth simulation.

Despite the promising potential of this study in predicting the long-term post-operative outcomes of patch reconstructive surgeries, we would like to highlight the limitations of this emerging research approach. The clinical calibration of growth parameters is performed by using a healthy pulmonary artery database. However, several studies have proven the dominant role of genetic disorders in malformations of the cardiac diseases (Gelb and Chung 2014), which can significantly influence the material response of tissue. Furthermore, the postoperative pathology of the vasculature (Van Praagh and Visner 1976) is likely to induce some fibrosis in the wounded tissue around the surgical stitch (Hinderer and Schenke-Layland 2019), which can create a different material response compared to healthy tissue. Another issue is that in order to simplify the numerical model, the average physiological pressure loading at MPA is applied to the whole domain uniformly. However, this pressure naturally varies in MPA, LPA and RPA due to blood flow. This analytical weakness can nevertheless be overcome through the use of a one-way coupled FSI model. The calcification of PTFE is also an important problem that deteriorates the function and long-term durability of the patch and the computational modeling of this study is unable to predict this destructive phenomenon. Angiography can only provide limited information regarding the postoperative condition of patches as synthetic materials (Hayabuchi et al. 2011) and there are few computational studies that can account for the effects of synthetic material calcification in post-operative complications (Weinberg et al. 2009). Despite these limitations, research findings obtained from the idealized model are compatible with the patient-specific model. Hence, various geometrical configurations with several bio-prosthetic and synthetic materials can be tested in the idealized simpler geometry as a benchmark model to detect and highlight the role of patches in post-operative growth patterns in arterial tissue.

Chapter 5

5 CONCLUSION

Surgical patch reconstruction of pulmonary artery stenosis is a complex procedure. This task is carried out skillfully during cardiopulmonary bypass, without blood flow inside the vessel lumen. The unpressurized stage of surgery makes it particularly challenging to predict the best post-operative patch size and shape to reconstruct the stenosed vessel zone. While there are conventional rules of cardiovascular surgeries, computer simulations may also enable us to test novel designs and provide a mechanism for creativity through virtual surgeries without any harm to the patient. In this thesis, we present a framework to demonstrate the post-operative performance for a number of surgery parameters; cut configuration of the artery, patch material and hemodynamic indices. Based on these results, a longer cut with PTFE patch material appears to be the preferred case for real surgeries compared to other cases presented in this study due to its better stenosis recovery function, especially for vessels with very high stenosis level. Straight cut is preferred to oblique cuts, which cause relatively larger bulbous regions and result in lower stenosis recovery. Another critical finding relates to the thickness of the patch and how changing the thickness of the patch significantly affects the post-operative performance of the patch more than the material parameters. The patch material property is of secondary importance and it seems more suitable to use a patch with a lower stiffness, but not lower than the vessel tissue. Although it might cause higher maximum stress, our novel double patch configuration appears to be useful for cases of very high stenosis, where a single cut and single patch might not be enough to recover the stenosis level.

In a parallel study, the evolution of 3D vascular stress distribution was computed during a critical period in embryonic (pharyngeal) aortic arch development. A theoretical model that explains the growth path of real data through embryonic Stages 18 to 22 is constructed. In addition, the basic dynamic features of the spatial distribution of COL-I immunofluorescence data is determined and explained that the strain-based evolution hypothesis of the intensity distribution is satisfied for all six arches. The slope statistics parameter can classify Stage 18 and 24 arches efficiently, and an exponential decay for COL-I degradation pattern emerges over time. Our data shows that while the protein

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distribution is diffuse and do not show a statistical radial pattern at the early stages (Stage 18), the matrix becomes more organized close to the vessel inner wall as the embryo grows. These results correlate well with the findings from *in vivo* immunofluorescence measurements. Our findings further demonstrate that the corresponding radial microstructural distribution follows this mechanical loading trend during vascular development. Firstly, major vascular proteins are not localized at Stage 18. However, starting from Stage 21, IF stain intensity of major microstructural proteins matches the spatial stress distribution in persistent embryonic aortas (such as right Arch IV). Particularly for Collagen fiber there is a strong relationship with the stress level throughout the tissue. In general, high stress levels lead to high Collagen dense regions at the later mature embryonic stages (Stage 24), which is associated with the growth and alteration of the material parameters to stiffen the tissue and preserve the elastic strain levels throughout the aortic arches. These changes can be predicted using our embryonic FEM growth model in a noninvasive way (without instrumenting on the chick embryo). Alterations in the ratio of Collagen or elastin concentration and its long-term remodeling can be modeled using the present approach and validated *in vivo* in future studies, since the predictive approach is a major step towards understanding the prognosis of congenital heart defects.

Importantly for the first time in the literature, this thesis establishes a surgical design framework for the computational modeling of vascular growth mechanics in the patch-reconstructed vessels of patients with cardiovascular disease. Specifically, our research findings show that Arterial tissue growth along the surgical stitch lines is triggered mainly due to PA geometry and blood pressure, rather than due to material property differences in the PTFE patch and native tissue. Thus, non-uniform growth patterns are observed along the arterial tissue proximal to the sutured boundaries. The most optimal materials and PA geometry of an arterial patch can now be determined for a specific patient with the ability to test different configurations using our computational model prior to the surgery, thus enabling clinicians to make the most effective surgical decisions in efficient time.

Appendix A

COMPUTATIONAL MODEL VALIDATION FOR PATCHED VESSEL

A.1 Introduction

Verification of the finite element solver used in the proposed patch-planning framework is detailed in the Chapter 2. These verification studies include mesh convergence analysis, testing different boundary condition schemes, thickness and material property sensitivity analysis. However, full model credibility, requires an experimental validation campaign, so that clinicians and scientists can confidently extrapolate the information and decisions based on the present model predictions (Henninger et al. 2010). Therefore, in this section, a novel finite element model validation approach that is based on rapid-prototyping is presented.

A.2 Experimental set-up

Initial geometry of the stenosed vessel is built by rapid prototyping (Form2, Formlabs Inc, MA, USA). 3D printed experimental main pulmonary artery (MPA) replica is manufactured from a flexible resin material (Formlabs Inc, MA, USA) having 50 μm layer thickness precision. The entire printing process takes around 9 hours. Cleaning step is performed in alcohol for 2 minutes (99% Isopropyl) in order to replicate vessel material properties. The test case is then cured under 80 mW/cm² of 365 nm fluorescent light for 15 minutes -see Figure A.1a.

The sequence of intra-operative surgical steps is performed on the rapid-prototype diseased MPA replica exactly as in the real surgery. First, the surgical incision is introduced on the rapid-prototype MPA by the pediatric cardiovascular surgeon (Dr. Ece Salihoglu) (Figure A.1b). Geometrical parameters of the incision are the same as the Baseline computational model case (straight cut – 50 mm length). A 1 mm thickness PTFE tissue (GORE-TEX Soft Tissue Patch, W. L. Gore & Associates Inc, AZ, USA) is then used for the patching operation. In order to replicate the 3D patch shape exactly as in to the computer-generated model, this patch geometry is also 3D-printed from the

Appendix A

flexible resin material and used by the surgeon as a pattern during the cutting and shaping operation of the experimental PTFE patch (Figure A.1c and d. The vessel test case is then opened (same gap as in the computational model) and the patch is fitted in to the stretched slit opening area. Body and patch are then completely bonded using Super Glue (cyanoacrylate) (Figure A.1e).

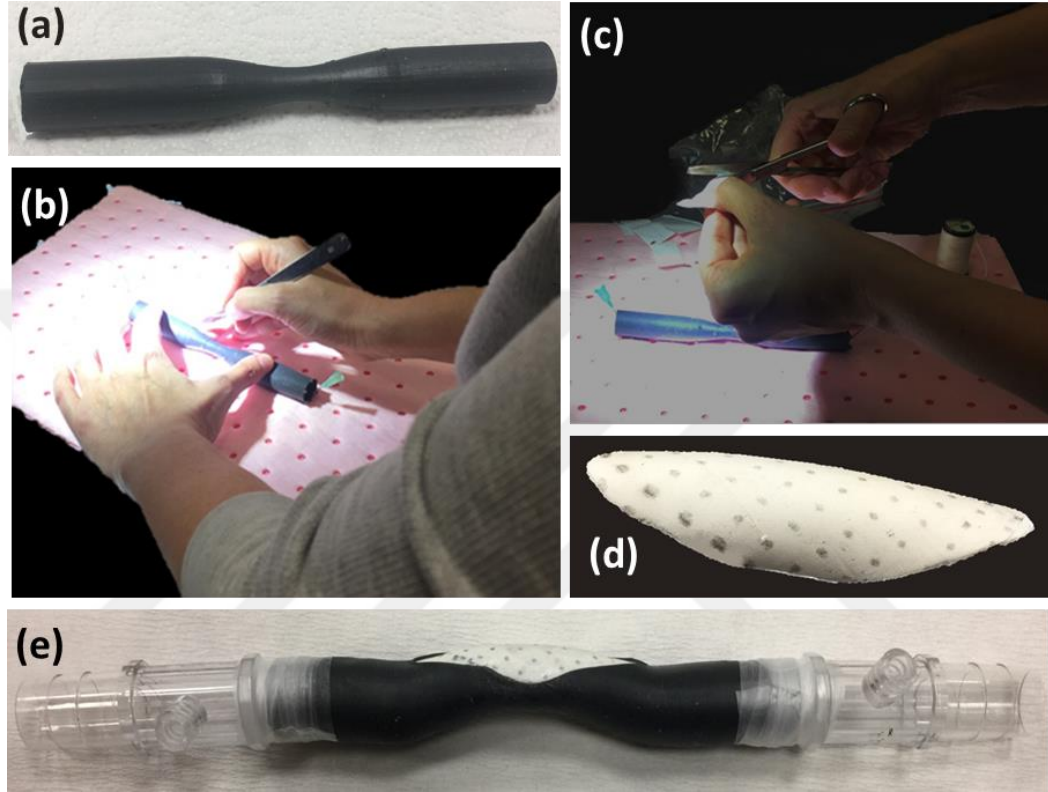


Figure A.1: (a) Shows the initial rapid-prototype of 70% stenosed main pulmonary artery model manufactured from of flexible resin material. (b) The creation of the initial suture line on the test case by a pediatric cardiovascular surgeon. (c) Intraoperative shaping of PTFE patch with respect to existing computer-generated template of patch (Baseline case). (d) The implanted PTFE patch before the post-operative pressure loading experiments. (e) The final assembled patch model. Connections are attached to both ends to fix the model in experimental set-up and supply pressurized gas.

For the static pressure test, a stopper is attached to the 3D printed and patched prototype outlet and the nitrogen gas is supplied in to the vessel from the other end. A similar set-up is utilized in a recent study that is conducted by our group (Oguz et al. 2017). Experimental measurements are acquired when the desired intramural pressure level is reached (30 to 90 mmHg pressure range). Lateral deformations of the model are recorded using a high-speed camera in 2D. The diameter of the vessel is measured using a motion analysis software (Maxtraq, Innovision Systems Inc, MI, USA).

Appendix A

The flexible resin material properties are measured in house due the strong effect of the post-curing duration. Uniaxial mechanical tests are conducted both along the tangent and perpendicular directions of the structural layout layers of the 3D printed flexible resin sheet having the same thickness as the MPA model. Stress-strain curves are obtained by sinusoidal stretching of rectangular shaped samples (10 x100 mm) up to 20% in axial directions, using two linear motor configurations in the BOSE planar test system (BOSE, Framingham, Massachusetts). Since the material properties of the resin depends significantly on the post-curing time and the time passed after printing, the experimental test sample is built and tested in the same condition and age as the test case.

The use of super-glue on the flexible resin and the PTFE tissue alters the material properties of both materials. Thus, to obtain the correct material properties at the bonded regions, thin layer of the glue is placed on the resin (10 x 100 mm) and PTFE (10 x 10 mm) samples and mechanical tests are performed. The protocol to obtain the material properties from biaxial tests are provided in Section 2.4 and employed here as well. The linear elastic material properties of the materials utilized in this experimental campaign are presented in Table A.1.

Table A.1: Linear elastic material properties and thickness of tested materials which are found in the validation test case.

Test	Material		young's modulus (MPa)		Poisson's ratio (-)	Thickness (mm)
Biaxial	PTFE - Glue		8.9		0.45	1.00
Uniaxial	Flexible resin	Tangential direction	9.97	9.71	0.45	0.7
		Transverse direction	9.45			0.7
	Flexible resin – Super glue	Tangential direction	19.96	19.51	0.45	0.9
		Transverse direction	19.07			0.9

Finite element model of Baseline case as defined in Section 2.3 of the manuscript is employed to obtain computational deformations corresponding to the experimental pressure levels. As in the experimental set-up, both end section boundary conditions are specified as fixed in all directions. Intramural pressure loading is increased from 0 to 90 mmHg. Material properties of the experimental model are assigned from the mechanical test measurements.

A.3 Results

The diameter of the patched vessel at the final loading configuration (90 mmHg) is provided in Figure A.2 for both experiments and computations. The change in deformation between the initial (0 mmHg) and final configuration (90 mmHg) is plotted in Figure A.2a. Experiments are repeated 5 times for 3 pressure load levels, and the corresponding diameters are recorded. An average diameter change of 0.82 mm, 1.8 mm and 3.12 mm corresponding to 30 mmHg, 60 mmHg and 90 mmHg pressure conditions are measured respectively. The computed deformation contour projected on the lateral side of the vessel is displayed in Figure A.2b.

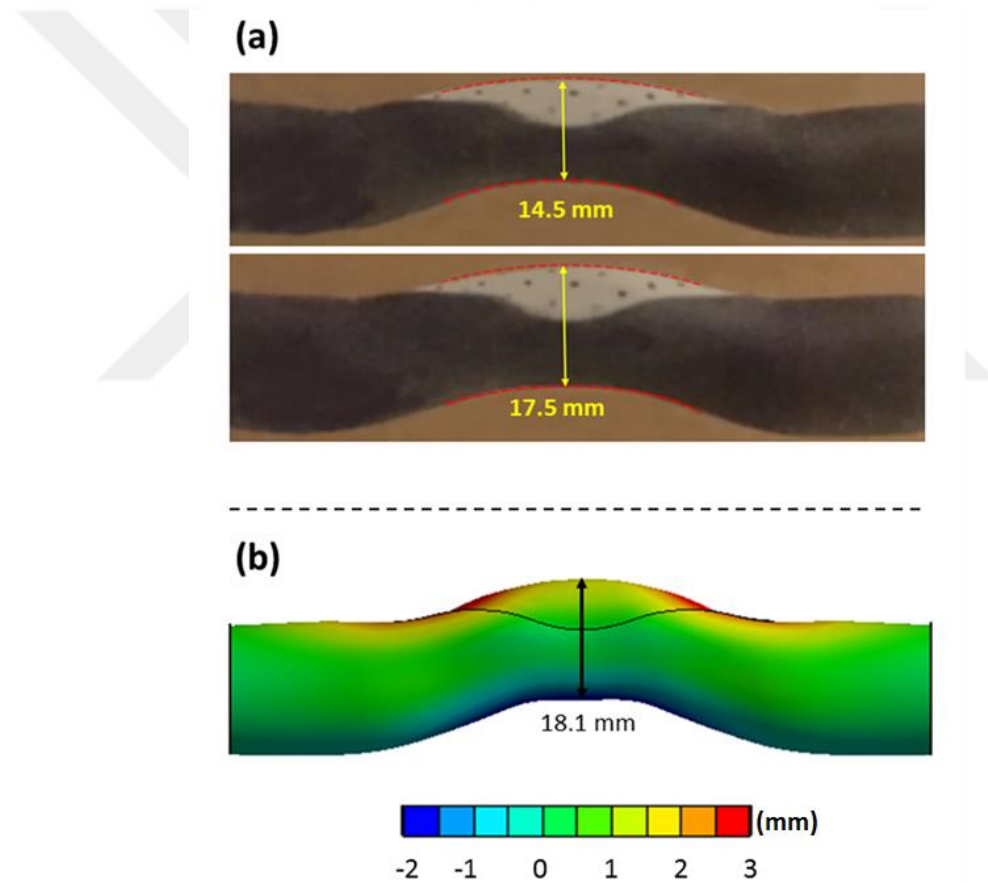


Figure A.2: (a) Upper image shows the test case in zero-pressure condition. Lower image shows the test case, which is pressurized to 90 mm-Hg loading by exerting nitrogen gas in to the vessel. (b) Distribution of the vertical deformation (y-axis) obtained from the finite-element model simulation. Boundary, initial conditions and material properties are as same as the experimental test case.

All loading states are presented in Figure A.3 where the experimental and computational average diameter values are compared. Percent error is defined as the ratio

Appendix A

of the difference between the experimental diameter and its corresponding computational model diameter relative to the experimental diameter value. According to this error description, error range is 1-3 % in all simulations.

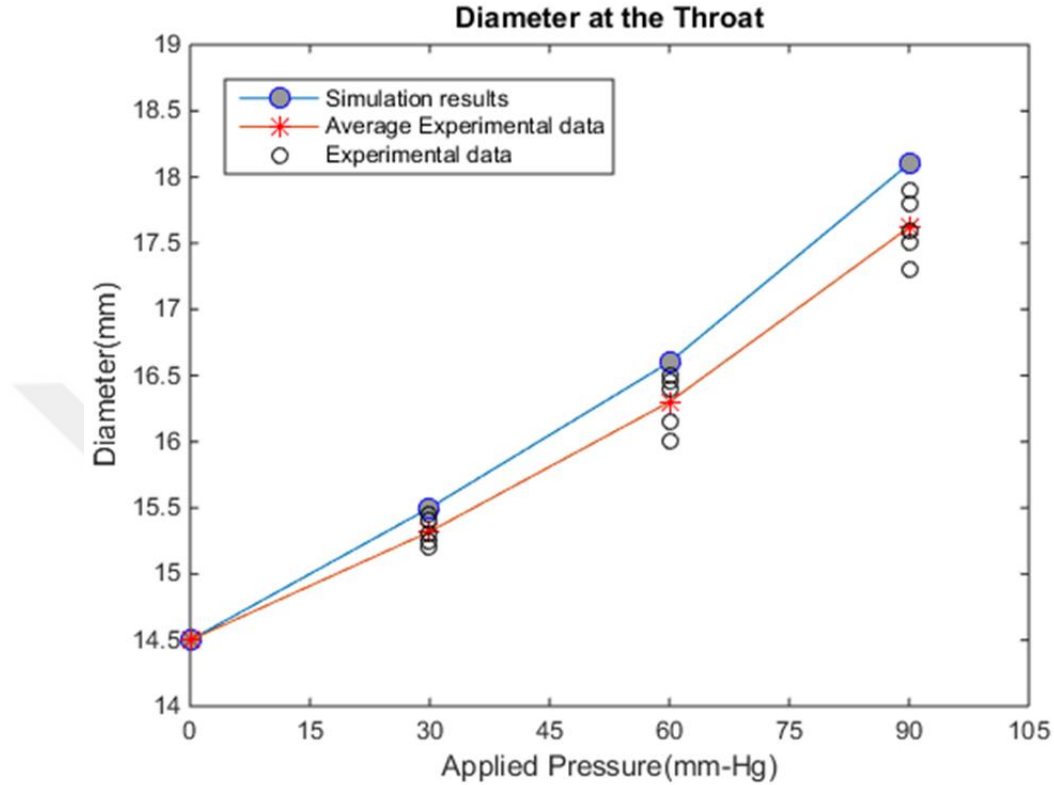


Figure A.3: Comparison of the measured throat diameter with the computational model results for three different pressure loading conditions.

A.4 Discussion

An alternative to the present *in vitro* experimental approach is to use *ex vivo* vessel segments from animals in the validation tests. In this approach it is almost impossible to obtain a diseased vessel having a stenosis. Therefore, we utilized flexible rapid prototyping to build a vessel with stenosis. While the alternative options of the appropriate flexible materials for the present validation campaign are found to be limited, the flexible resin (Formlabs Inc, MA, USA) served our purpose relatively well. One particular challenge related to the flexible resin material is its low tear resistance. This property resulted poor surgical suture retention during the stitching and caused leaks around the implanted patch. Silicone elastomer materials can be a better substitute to flexible resin and will be employed in future studies.

Appendix A

Due to the symmetry of the MPA model only the deformations from the lateral side are compared. Future studies on complex patch reconstructions in patient specific anatomies will consider capturing the 3D strain distributions using two cameras following the present computational analysis on idealized geometry. Performing fluid-structure interaction analysis will also be worth investigating in patient specific patch cases. For a comprehensive validation of the present surgery-planning framework, we have proposed an animal study to be carried out on the carotid arteries of rabbits with the use of advanced microsurgical techniques. For this study, almost 60 days old rabbits undergo patch implantation surgeries and will be monitored for surgery performance and growth of the vessel. This experimental study will help us to verify and validate the current computational study in more details.

Appendix B

MECHANICAL CHARACTERIZATION OF MATERIALS USED IN PEDIATRIC SURGICAL RECONSTRUCTIONS

B.1 Sample preparation and mechanical tests

Sections of the material specimens were cut out from the actual 20 mm diameter PTFE and Dacron conduits that are commercially available for pediatric cardiovascular surgeries. The porcine pericardium (Edward Lifesciences, CIT, STATE) in 20x90 mm size was kept in glutaraldehyde solution as in the standard surgical protocol and immediately tested. Likewise, a discarded sample of human pericardium (20x50mm) originally prepared for surgical implantation is tested with in the same day through approved IRB protocol.

Biaxial mechanical tests are conducted for each material using four linear motor configurations in the BOSE planar biaxial test system (BOSE, Framingham, Massachusetts) by sinusoidal stretching of square shaped samples (10x10mm) up to 20% in both axial directions (Figure B.1). Preconditioning cycle at 0.1 Hz started after removing the slack and zeroing the cell value in both axis then load cells were zeroed in the software. Preconditioning step covered the first 50 load cycles of the experimental protocol and this data set was not used in analysis. Each experimental load cycle includes 50 data points (25 for loading and 25 for unloading per sample) and a total 100 cycles were conducted for each material sample. Strains are measured in both directions through a camera tracking the tissue dye-marked fiducial points as well as linear motor positions.

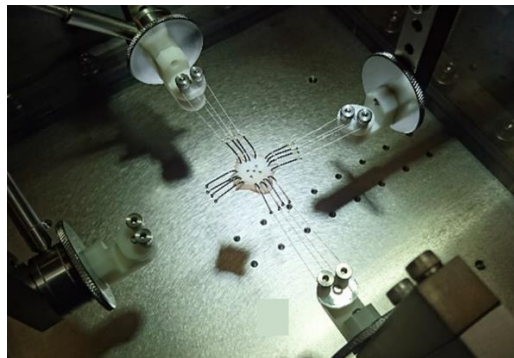


Figure B.1: Biaxial tensile test setup with the PTFE specimen oriented through fish-hook support system.

B.2 Poisson's ratio and Young's modulus

Appendix B

Average Young's modulus values corresponding to the load ranges encountered in patch reconstructions are computed from the planar biaxial tensile test data. For this purpose, the two-dimensional stress formulas that govern the planar biaxial tensile test configuration are used;

$$\sigma_x = \frac{E(\varepsilon_x + \nu\varepsilon_y)}{1-\nu^2}, \sigma_y = \frac{E(\varepsilon_y + \nu\varepsilon_x)}{1-\nu^2} \quad (\text{B.1})$$

Where σ_x , σ_y and ε_x , ε_y are the engineering stress and strain components in Cartesian coordinates, respectively. These stress and strain components are the arithmetic means of the measured force-displacement data via the following relations;

$$\sigma_x = \frac{F_x}{t l_y}, \sigma_y = \frac{F_y}{t l_x} \quad (\text{B.2})$$

Where t is the sample thickness that is obtained through an optical coherence tomography system (Thorlabs Inc, NJ, USA) at 0.5 μm resolution as discussed in the manuscript text. l_x and l_y are sample dimensions which both are $\sim 10\text{mm}$ in all tests.

The Young's modulus is computed through Equation (B.3) based on a linear regression fit to the sums of the average stress and strain values;

$$\sigma = \sigma'_x + \sigma'_y = \frac{E(w_1\varepsilon_x + w_2\varepsilon_y)}{1-\nu} = \frac{E\varepsilon}{1-\nu} \quad (\text{B.3})$$

Where w_1 and w_2 are weighting factors.

Finally, the Poisson's ratio values are estimated from the following approximation via linear regression.

$$\nu \approx \frac{\Delta L_y}{\Delta L_x} \quad (\text{B.4})$$

B.3 Stress-Strain data and computed linear elastic model material properties

Linear regression is implemented in biaxial tensile test measurements as described in Equation (B.3) and (B.4), in order to compute Poisson's ratio and Young's modulus, respectively. In Figure B.2, stress-strain data for all materials in both orthogonal directions are presented. Weighting factors for the stress function, Equation (B.3) are selected and kept the same for each material to minimize the residual error in the objective function. All specimens are stretched up to $\sim 10\%$ of their original length in order to investigate their linear response of hyperelastic materials. Computed Poisson's ratio and Young's modulus values in whole range for PTFE, Dacron and porcine pericardium are given in Table 2.2 of Chapter 2. The reported mechanical properties of materials used

aortic arch reconstruction, by Tremblay et al. agree well with the reported stiffness range (Tremblay et al.).

B.4 Discussion

Although the material model used in this study represents the physics faithfully well in the operating loading range, there are several limitations for further development. First of all, instead of using linear elastic material properties in the simulations, strain energy density function material models can be used for the patch and artery to better describe their nonlinear and time-dependent material properties. While more complex material models can easily be implemented, and the corresponding biaxial material property data is available in-house, for this manuscript the material model is kept simple so that it can provide us the physical insight on the relative material properties of patch and native tissue, providing comparative information on different patch strategies.

Biaxial tensile testing is an established technique to determine the mechanical properties of biomedical materials, which can provide both the linear and nonlinear elastic characteristics. Obviously, hyperplastic materials demonstrate linear response at small stresses and become nonlinear as the applied force increases. Therefore, average stiffness of hyperplastic materials can be computed by using linear model at small stresses. Besides, homogeneity and isotropy are other approximations to the realistic material in order simplify the case and provide rough estimations about the stiffness of the material where, in fact, the material itself may be nonhomogeneous and anisotropic up to an acceptable degree. A detailed nonlinear mechanical characteristics of these materials will be presented in a future publication (Donmazov 2016).

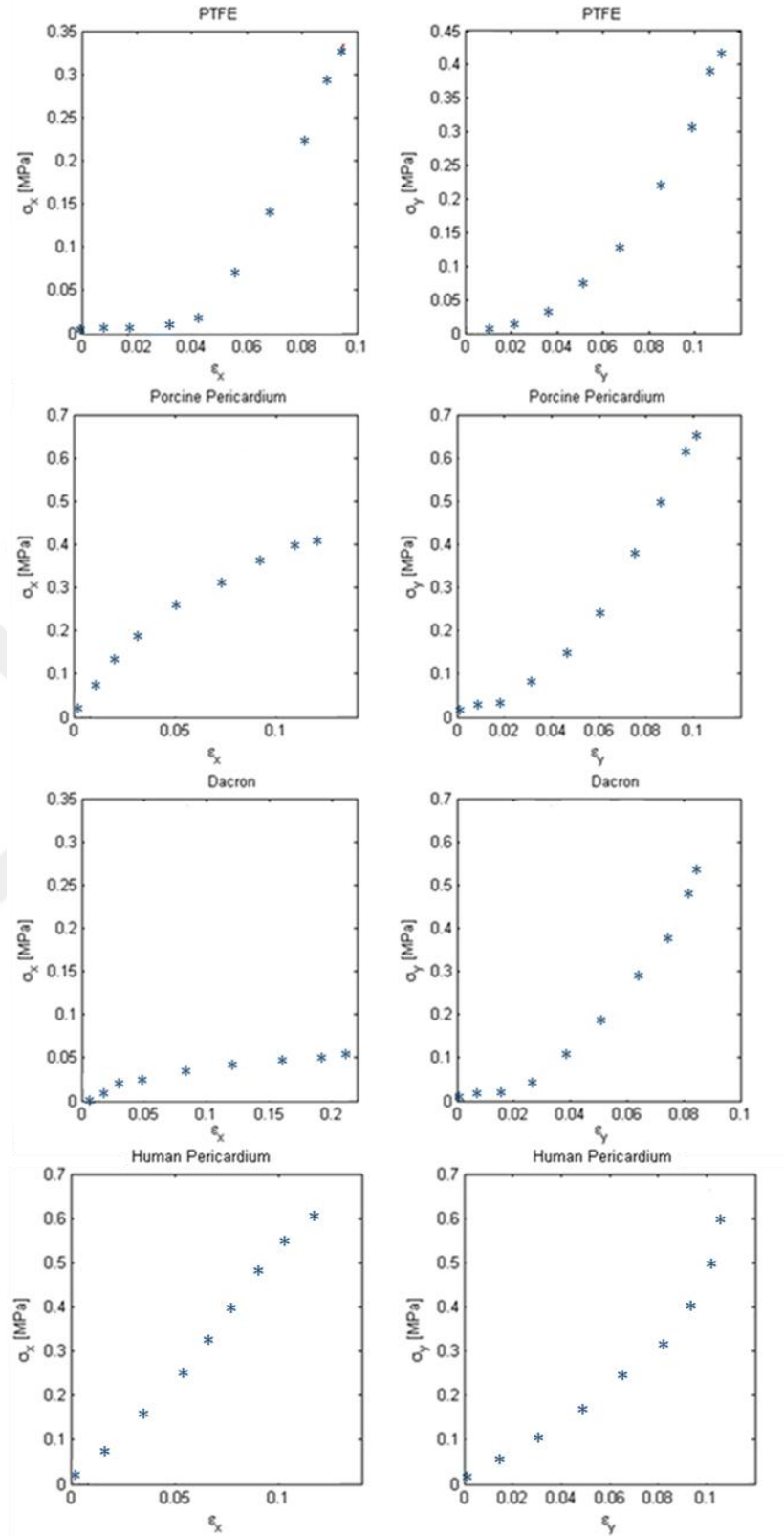


Figure B.2: Experimental stress-strain data for pediatric surgical materials; PTFE, Dacron, porcine and human pericardium represented by stars obtained from force-net displacement biaxial tensile test measurements.

Appendix C

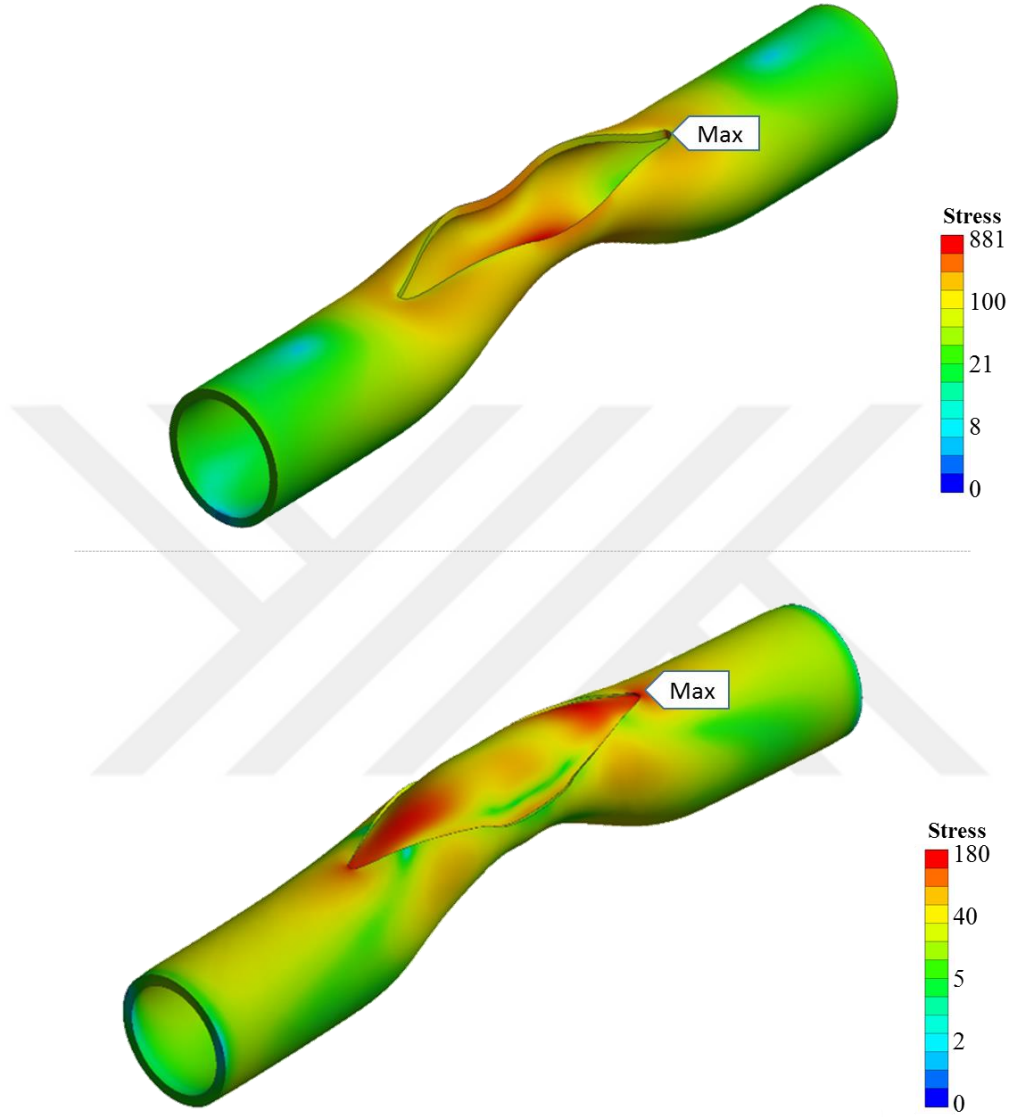


Figure C.1: (a) Equivalent stress distribution on the artery for the case Stenosis during the opening of slit in surgery. (b) Equivalent stress distribution on the patch and artery after pressurizing to post-operative blood pressure level on the case Stenosis. Stress gradient maps are shown in logarithmic scale to highlight the vessel and patch connection region's stress contours in various colors.

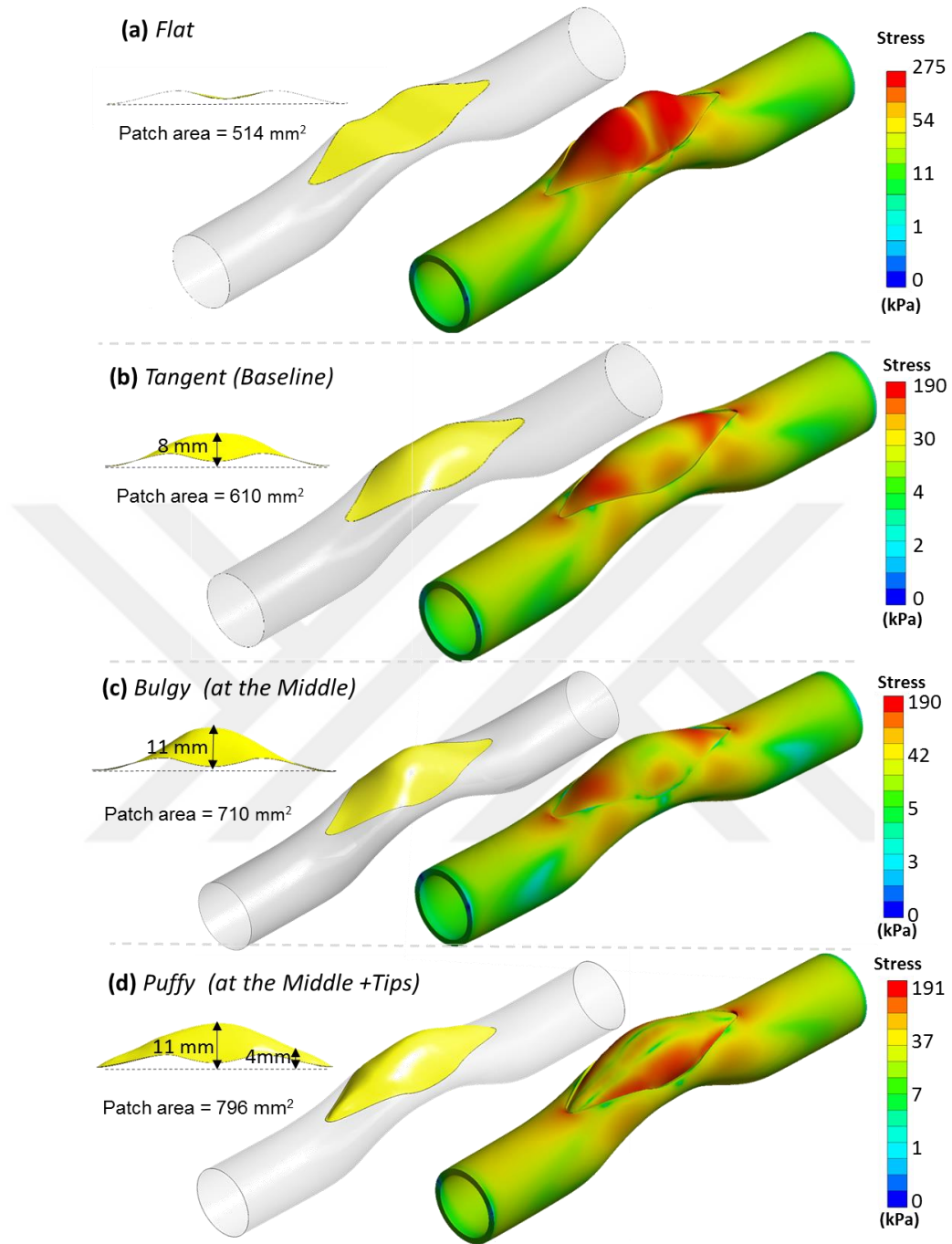


Figure C.2: The effect of initial patch shape on post-operative stress and deformations is studied on an idealized main pulmonary outflow tract. Simulations are performed for the initial patch configurations; (a) Flat patch with no lateral camber, (b) Tangent patch (baseline) with moderate camber (lateral height: 8 mm), (c) Bulgy patch with intense camber (lateral height: 11 mm), (d) a Puffy patch with excessive patch surface area causes bumped middle section and corners (lateral height: at the middle 11 mm, at the tips: 4 mm).

Appendix D

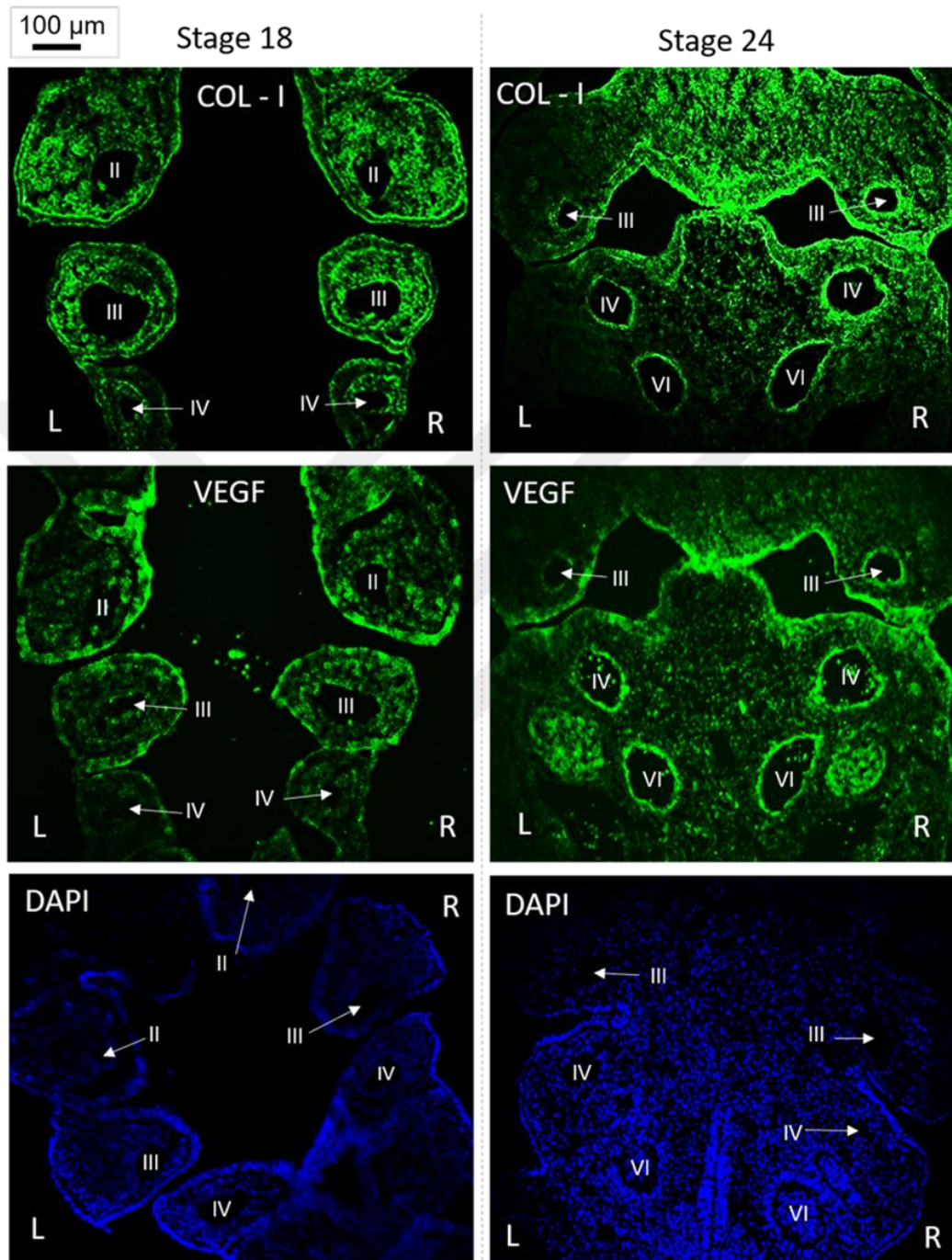


Figure D.1: Representative immunohistochemistry fluorescence (IF) images of CoL-I, VEGF and cell number (DAPI) for all aortic arches at two consecutive morphologically stable embryonic stages (Stage 18 and Stage 24) is acquired using a large field of view time-lapsed confocal scanning system (Nikon AZ100-C2Si). Localization of vascular matrix constituents at Stage 24 but not at Stage 18 is qualitatively evident.

Appendix E

SPACE-TIME REGISTRATION OF HISTOLOGY IMAGES OF THE GROWING DOMAIN

Our approach to prepare the initial arch geometries before the statistical analysis involves a short registration procedure based on boundary mapping with soft landmarks (Figure E.1). The only a-priori information about the geometric transformation is that the registration procedure should deform the underlying grid layout of the image in an elastic manner, since the original domain is known to come from an elastic family (Collagen).

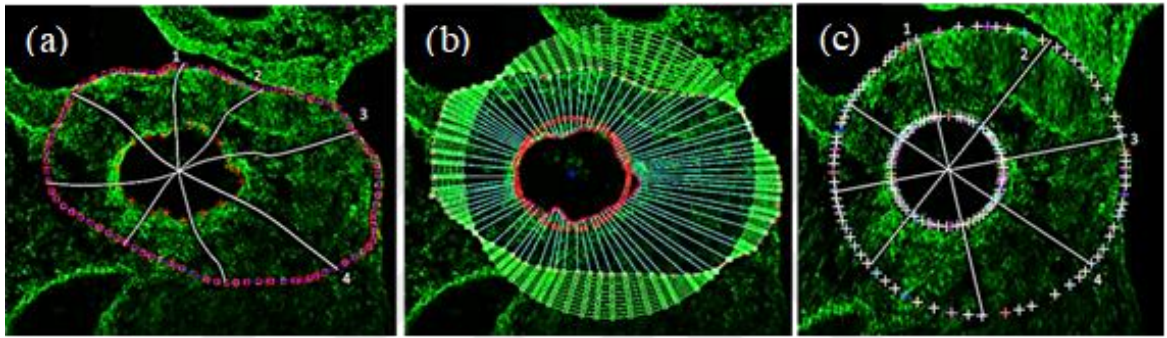


Figure E.1: The outcome of applying the image registration operator G is presented for the sample “Stage 24-Arch III-R” raw IF Col-I data. **(a)** The aortic arch boundaries are specified manually as the initial seed landmark set. **(b)** Circular goal landmarks have been identified using an area-preserving projective mapping approach. **(c)** The circular transformed domain of the aortic arch is obtained after elastic image registration through the minimization of the energy function.

To match the histology intensity images to a circular shape, we used a weighted free-from deformation (FFD) based “landmark-only elastic registration” function G . It converts gray level intensities (I_{HH18}) to $G(I_{HH18}, \mathbf{l}(I_{HH18}), \mathbf{w}_i)$. Vector $\mathbf{l}$ is defined as a landmark point set and $\mathbf{w}_i$ are the regularization weight sets used to guarantee the existence of an invertible smooth deformation field (Sorzano et al. 2005; Sotiras et al. 2013). Landmark point set ($\mathbf{l}$) includes the initial point set (arch boundaries) and goal point set (circular boundaries). Goal landmarks were identified by an in-house code. The algorithm used in this code is area preserving projective mapping to prevent stretching the deformation field to unrealistic excessive amounts. The projective mapping itself also behaves as an elastic procedure. Elastic image registration in the operator (G) is performed using ImageJ v3.91 software (Rueden et al. 2017) plugin through an energy function minimization based algorithm. The weights of the algorithm ($\mathbf{w}_i$) are set in a way

to devote more favor to the geometrical consistency of the image and landmark matching (Arganda-Carreras et al. 2006).

Subsequent statistical comparisons in next step of analysis were handled by transforming the Cartesian layout of the circular registered images to a polar form associated with a final manual landmark correction procedure. This correction procedure extracts the region of interest domain (arch boundaries) and maps it to rectangular a domain, which is a dimension free (equalized pixel size) version. The whole transformation procedure is called T operation (Figure E.2). We can express the image mapping procedure on the arch boundaries ($\partial\Omega$) as follows:

$$I_{(\partial\Omega)}(x, y) \xrightarrow{G} I_{(G(\partial\Omega))}(x, y) \xrightarrow{T} I_{(T(G(\partial\Omega)))}(r, \theta) \quad (E.1)$$

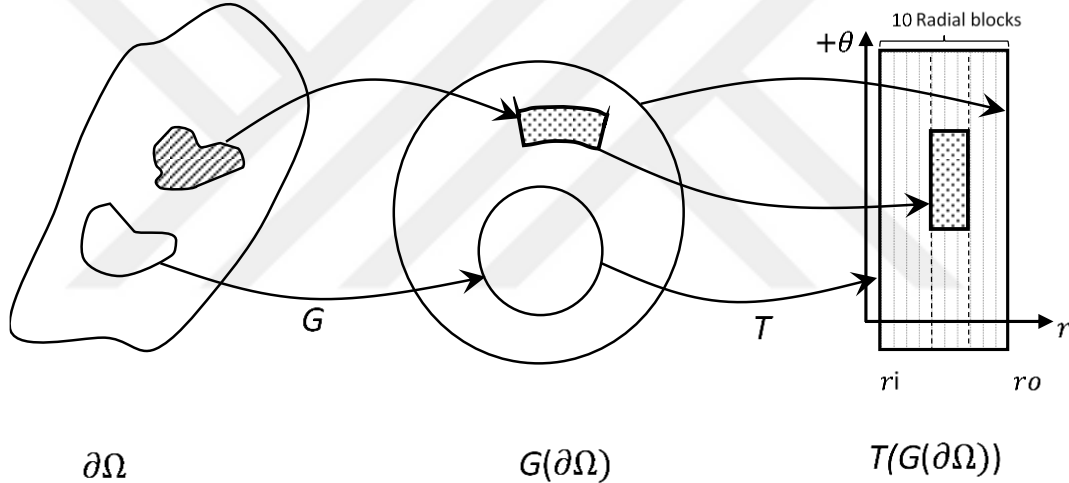


Figure E.2: The two main steps of the spatial image mapping is illustrated in this figure. Two separable transformation processes (G,T) are applied to the distorted arch structure leading the polar transformed-registered image. (G,T) are invertible. An elastic spatial mapping procedure (G) is applied on the aortic arch to obtain a circular registered version of intensity representations. The polar transformation (T) enables us to compare intensity levels non-dimensionally at the Cartesian domain.

The results of testing the mapping procedure on the distorted arch structures, with four various distribution patterns into a polar transformed-registered rectangular structure, are shown in Figure E.3.

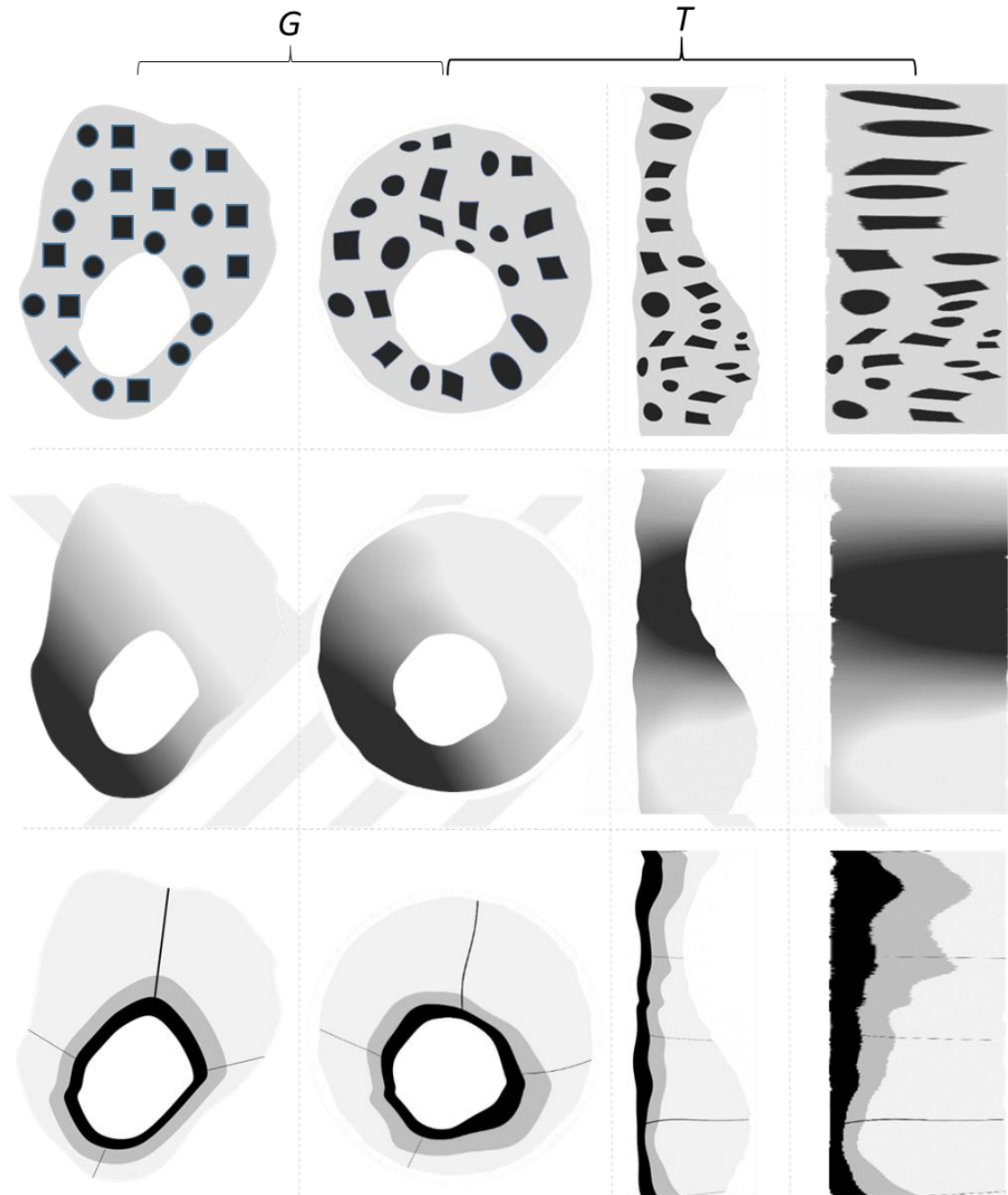


Figure E.3: Selected synthetic image sets used to verify the image registration procedure are displayed. The spatial mapping from the distorted arch structure into a polar transformed-registered structure is tested on three synthetically generated image sets. In the FIRST ROW, the synthetic image is tested to see the effect of the mapping procedure on the localized intensity hot spots. SECOND ROW illustrates the outcome of the mapping procedure on a hypothetical arch vessel having random microstructure localization. The THIRD ROW investigates the performance of the mapping procedure for an arch tissue having a layered vascular structure.

Appendix F

HYPOTHESIS TESTING AND STATISTICAL APPROACH

The statistical analysis of intensity levels of microstructural proteins measured at the aortic arch samples involves the testing of protein localization assumptions on the distribution clouds. Polar transformation of arch samples is illustrated briefly in Figure F.1a. The statistical fluctuations of collagen intensity value, $I(r, \theta)$ around the mean value, demonstrate a spatial pattern. However, there is no temporal pattern evident when we compare the statistical fluctuation in the circumferential direction around mean value between stages from a temporal perspective (Figure F.1b). Therefore, the θ variation is relatively suppressed without loss of generalization and the radial mean intensity values were used in statistical tests.

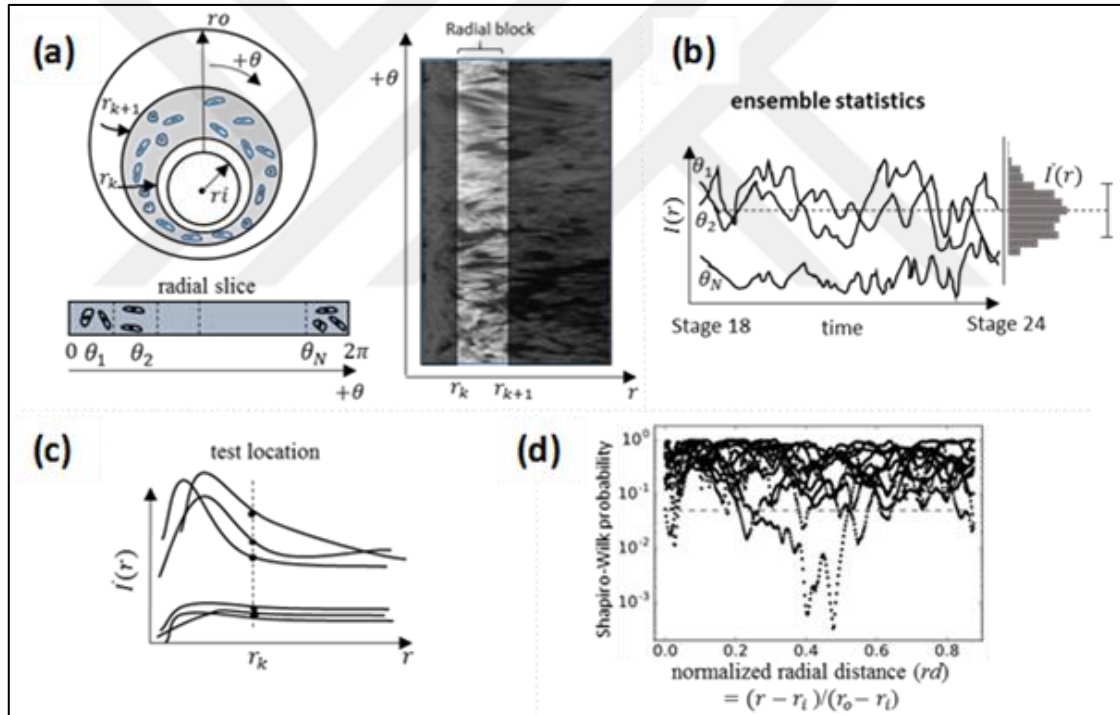


Figure F.1: (a) Polar representation of aortic arch sample image data are characterized by radial slices(r_k, r_{k+1}). These radial sections contain cellular compartments representing the production facilities of matrix constituents (e.g. Collagen). The intensity image of the resulting polar-transformed arch sample along r and θ directions are also shown. (b) The statistical fluctuation of $I(r, \theta)$ around the mean value has a spatial pattern and the statistics obtained from samples are equal for the ensemble. (c) The statistical test carried out for each radial slice by comparing the mean intensity levels for selected arch pairs. (d) The majority of sample groups conform to normal assumptions and the parametric tests report the local change in intensity levels.

Appendix F

The statistically significant differences in collagen intensity levels were tested using the acceptance probability of the null hypothesis H_0 , which states that “two arch blocks do not differ significantly (are similar) in terms of the protein intensity level”. The normality of collagen intensity was tested analytically by observing the W-statistics as supplied by the Shapiro-Wilk algorithm (python SciPy) (Shapiro and Wilk 1965). Tests were carried out on all sample groups (a total of 12 distinct aortic arch types at Stage 18 and Stage 24) with $n = 5$ observations for each group. The Shapiro-Wilk test results show that the majority of the collagen distribution patterns in the radial direction approximately follow the Gaussian normal distribution. According to the calculated probabilities, the normality is valid for the majority of the samples except for the Stage18-Arch III-L Arch, which is shown in Figure F.1d. For this typical arch, the normality test results show a deviation of $0.3 < r < 0.38$. Hence, the Kruskal-Wallis test is used to report on this sample as a nonparametric alternative, while the parametric t-test results are reported for the rest of the arches. This exception has no effect on the overall statistical conclusions, since the probability trends on the radial bands have not been affected. At a small region close to the outer vessel wall, which is smaller than 1 block (40 pixels) of the arch wall thickness, the calculated probabilities for the intensity levels have minor fluctuations around the 0.05 confidence limit. Therefore, only the persistent character observed for the first 9 radial blocks is tested and included in this analysis. Average probabilities above the 0.05 confidence limit for each radial block is reported as the accepted hypothesis H_0 and the lower values are rejected. For brevity in the main text above, only the comparison for Arch IV (future aorta) left and right sides at Stage 24 and the statistical comparisons for Arch III (future pulmonary arteries) at Stages 18 and 24 are provided (Figure F.4). In the radial blocks in Figure F.4, hypothesis rejection is presented in BLACK color while the GRAY coloring indicates hypothesis acceptance. The radial statistical comparisons for the rest of the arches (8 pairs) are provided in Figure F.2 to Figure F.5.

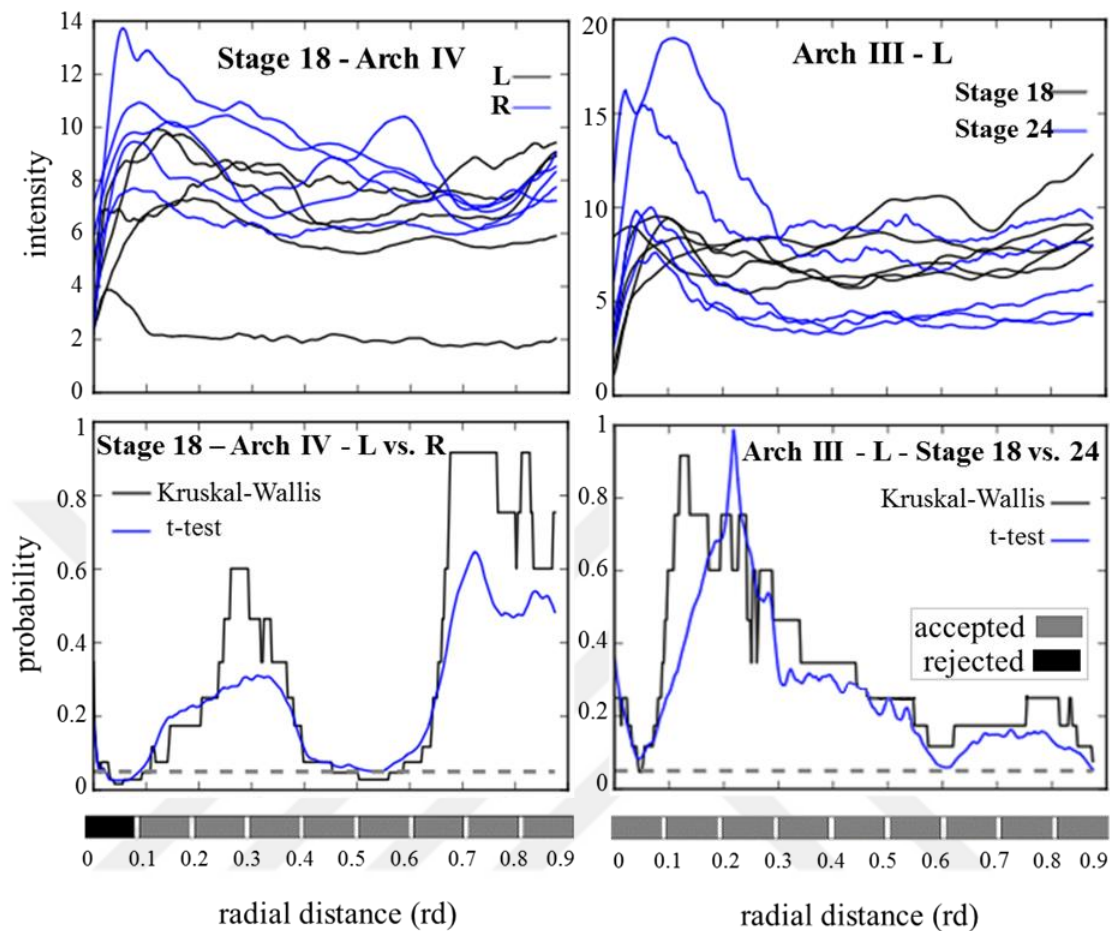


Figure F.2: FIRST ROW: representation of the statistical results for the Collagen intensity levels through radial direction is given for 2 pairs of arch vessels (Stage 18 - Arch IV - L vs. R) and (Arch III - L - Stage 18 vs. 24). SECOND ROW: the null hypothesis of “equal level of deposition” is tested against significant difference in Collagen deposition levels. The accepted (BLACK) and rejected (GRAY) regions of these parametric test results for the cross-comparison cases are summarized in the BOTTOM ROW. Please refer to Figure 3.4 in Chapter 3 for further details.

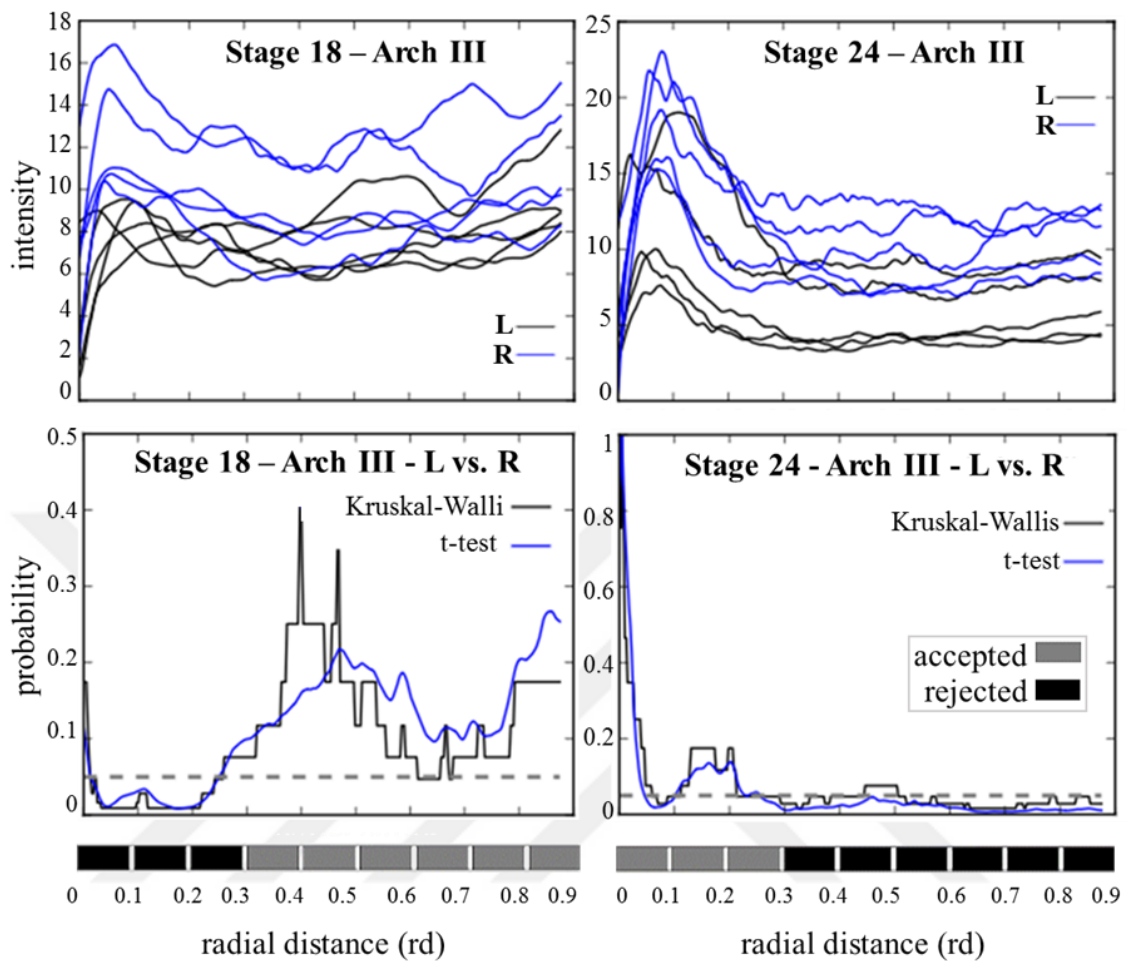


Figure F.3: FIRST ROW: representation of the statistical results for the collagen intensity levels through radial direction is given for 2 pairs of arches (Stage 18 -Arch III - L vs. R) and (Stage 24 -Arch III - L vs. R). SECOND ROW: the null hypothesis of “equal level of deposition” is tested against a significant difference in collagen deposition levels. BOTTOM ROW: the parametric test results are summarized by labeling the accepted and rejected regions for cross-comparison cases.

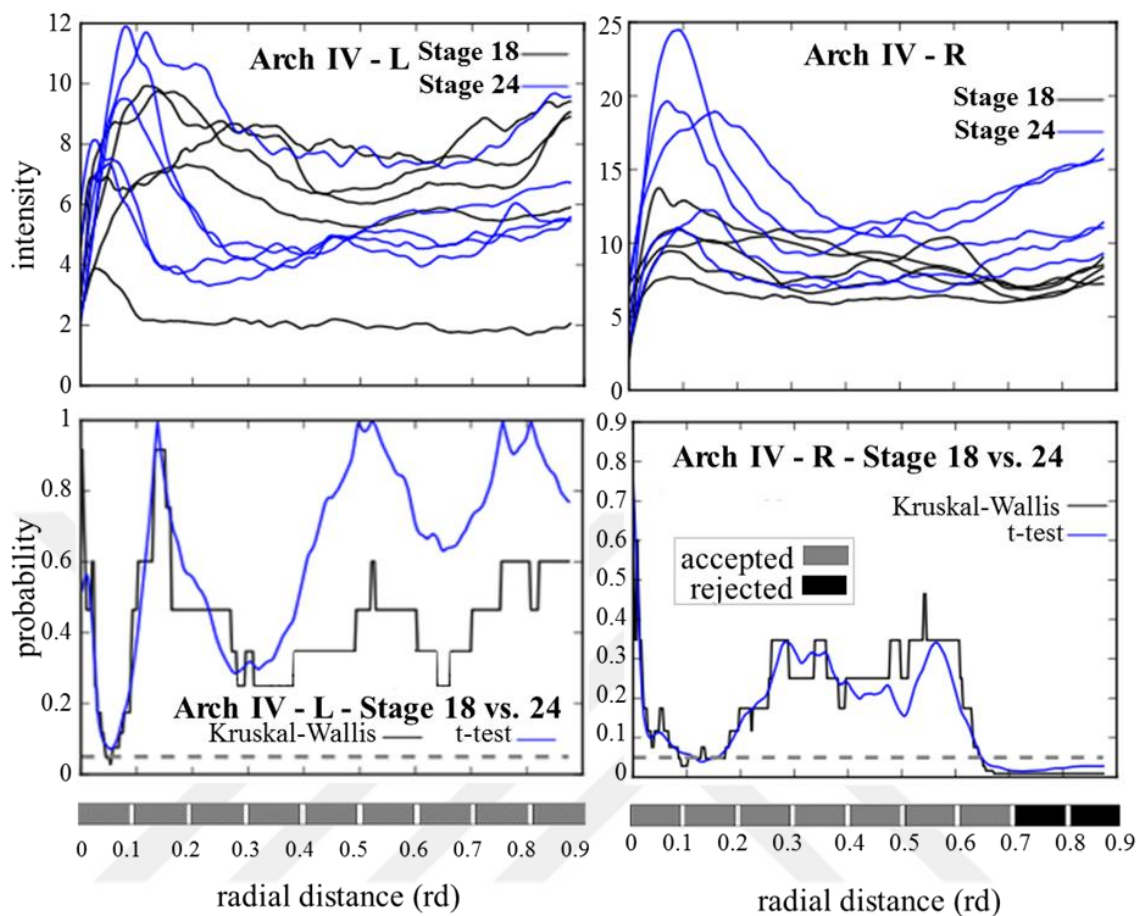


Figure F.4: FIRST ROW: representation of the statistical results for the collagen intensity levels through radial direction is given for 2 pairs of arches (Arch IV - L - Stage 18 vs. 24) and (Arch IV - R - Stage 18 vs. 24). SECOND ROW: the null hypothesis of “equal level of deposition” is tested against significant difference in collagen deposition levels. BOTTOM ROW: the parametric test results are summarized by labeling the accepted and rejected regions for cross-comparison cases.

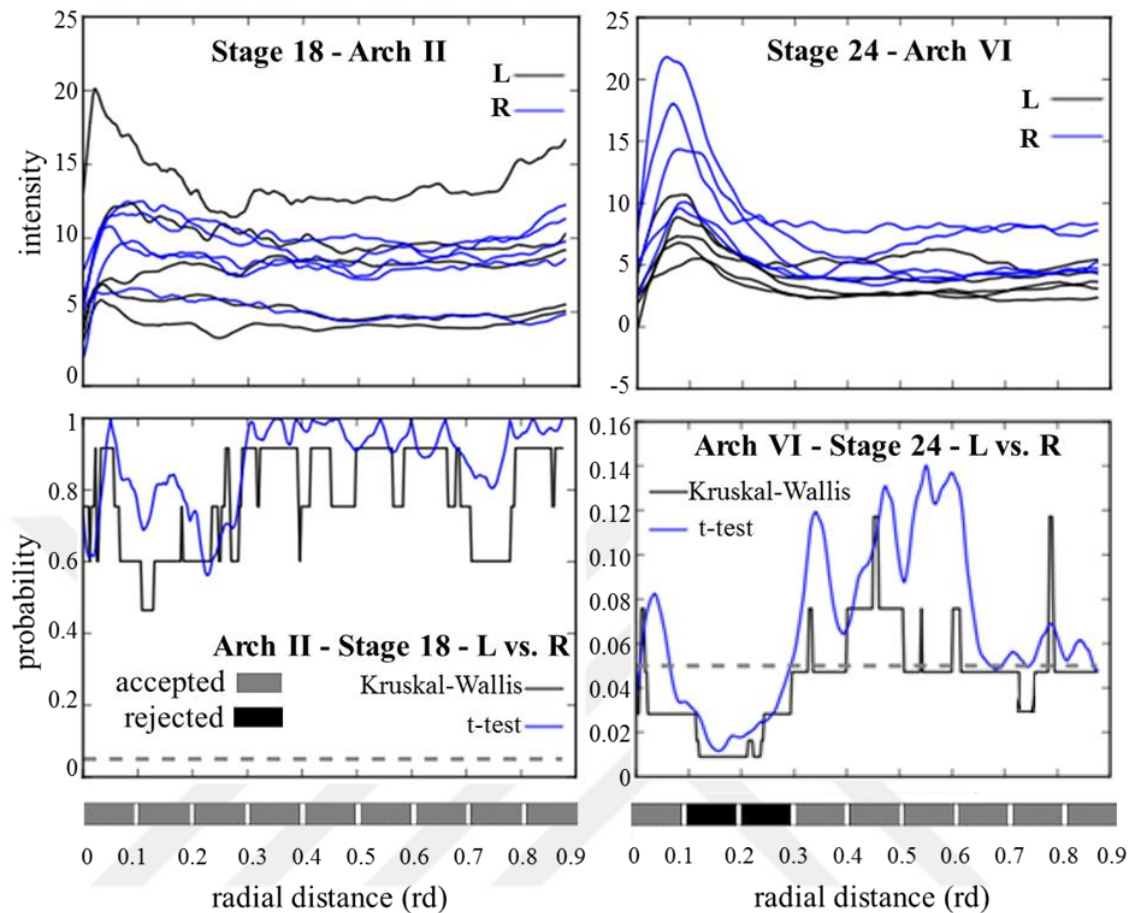


Figure F.5: FIRST ROW: representation of the statistical results for the collagen intensity levels through radial direction is given for 2 pairs of arches (Arch II – Stage 18 - L vs. R) and (Arch VI – Stage 24 - L vs. R). SECOND ROW: the null hypothesis of “equal level of deposition” is tested against significant difference in collagen deposition levels. BOTTOM ROW: the parametric test results are summarized by labeling the accepted and rejected regions for cross-comparison.

Appendix F

The functional layout of collagen distribution can be well characterized by a double-exponential decay function having a single peak point $\bar{I}_{\text{peak}}$ and a base point $\bar{I}_{\text{base}}$ (Figure F.6a). The normalized slope of the intensity level, which indicates microstructural localization is described by:

$$s = \frac{(\bar{I}_{\text{peak}} - \bar{I}_{\text{base}})}{\left(N_r^{-1} \sum_{r_{\text{peak}}}^{r_{\text{base}}} \bar{I}(r)\right) (r_{\text{peak}} - r_{\text{base}})} \quad (\text{F.1})$$

Where N_r is the number of pixels between r_{peak} and r_{base} . The positions of peak and base values are obtained by fitting a double exponential decay function and bisection method:

$$\bar{I}(r) = c + \sum_{j=1}^2 a_j \exp(b_j r) + \epsilon(r), \quad \epsilon(r) \xrightarrow{d} \text{iid}(0, \eta^2) \quad (\text{F.2})$$

This equation characterizes the layout of the intensity level through radial direction acceptably well. Since the experimental measurements are noisy at some levels, the nonlinear iterations are performed through the gradient-free Powell algorithm (Octave's powell algorithm), where the process gives plausible estimates for most of the data with the same initial set (John W. Eaton). The peak and base positions are defined with respect to the differential character of the decay. The peak position from the first derivative is:

$$r_{\text{peak}} = \frac{1}{b_2 - b_1} \ln \left(-\frac{a_1 b_1}{a_2 b_2} \right) \quad (\text{F.3})$$

The base level is defined as the point where the curvature of radius of $\bar{I}(r)$ is minimum on the interval $[r_{\text{peak}}, 0.375]$:

$$\min_{r_{\text{peak}} < r < 0.375} \frac{(1 + (a_1 b_1 \exp(b_1 r) + a_2 b_2 \exp(b_2 r))^2)^{3/2}}{|a_1 (b_1)^2 \exp(b_1 r) + a_2 (b_2)^2 \exp(b_2 r)|} \quad (\text{F.4})$$

The minimum level beyond r_{base} is set to 0.375 (150 pixels) cutoff value by trial. The normalization of the slope with the mean intensity level of the same interval provides a robust statistical quantity that can be compared pairwise. The Shapiro-Wilk algorithm confirmed normal distribution of slope values (Figures F.6b and F.6c). The statistical t-test was then carried out on each arch to compare the slope levels.

We also confirmed that the point clouds of all 6 arches at the same stage have common centroids for both Stage 18 and Stage 24 (please refer to Figure 3.6b in the Chapter 3. This means that the left and right laterals of an arch at a specific embryonic stage can be merged to obtain larger sample numbers for comparison, if needed. This merging of groups enables us to characterize symmetric arch pairs (regardless of left or right lateral) with a single statistic value (S), Equation 1.

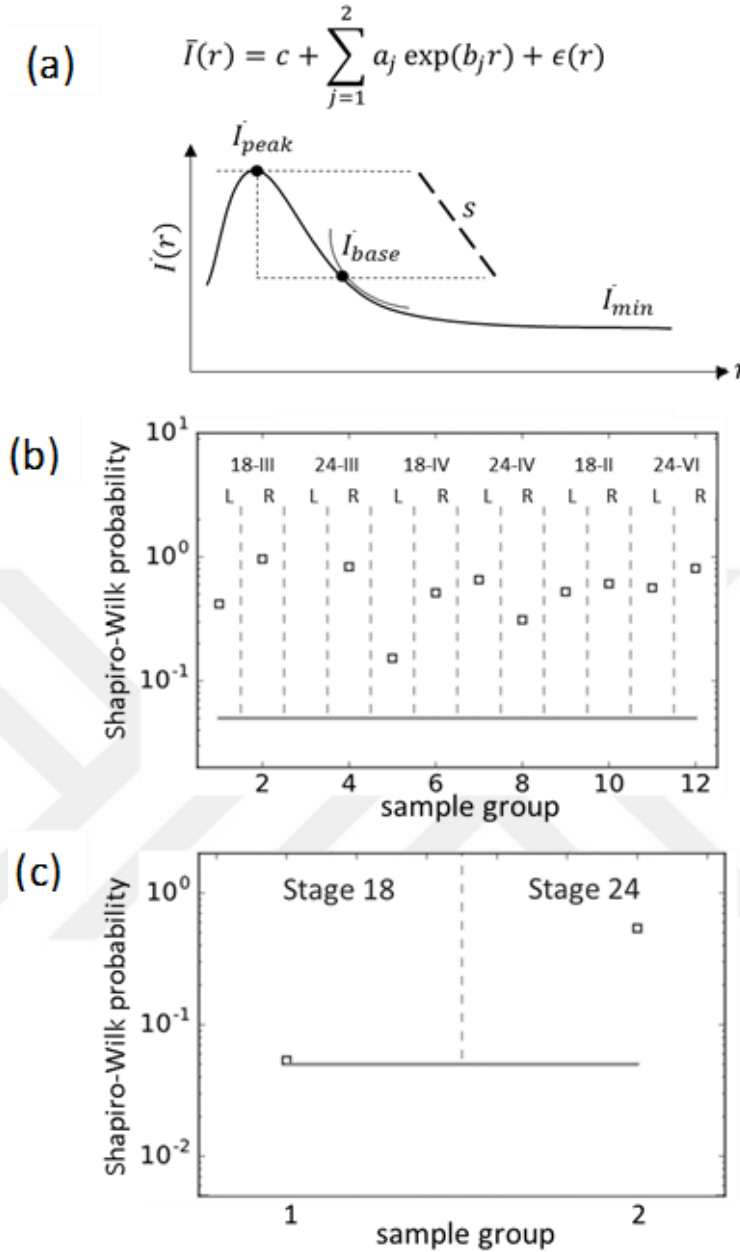


Figure F.6: In (a) the average amount of collagen deposited in the radial direction is described from the circumferentially averaged and normalized confocal measurements. The shape statistics of this trend and its localization is examined using the decay slope parameter (S) of the intensity level. In (b) the normal probabilities for all 12 sample groups (from 5 embryos) are considered for the radial decay slope (S) of the collagen level. All of the sample groups conform to normal assumptions and the parametric tests are reported for changes in s level. Since there are 6 individual arches available at each individual embryonic stage, the normal probabilities for “temporal-merged” sample groups ($N = 30$) are considered for the radial decay slope (S) of the collagen level (c). Both sample groups conform to normal assumptions and the parametric tests reported for changes in S level. Please refer to Figure 3.6 in Chapter 3 for further details.

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