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Mechanical Effects of Surgical Adhesives on Ascending Thoracic Aortic Aneurysm Replacement

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Mechanical Effects of Surgical Adhesives on Ascending Thoracic Aortic Aneurysm Replacement

A Thesis

Presented to

the Faculty of the Daniel Felix Ritchie School of Engineering and Computer Science

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Master of Science

by

Dong Qiu

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ABSTRACT

Ascending thoracic aortic aneurysm (aTAA) is a potentially lethal disease which grows gradually over time and may lead to aortic dissection and rupture. Currently, aTAA surgical repair using Dacron graft is a well-established treatment. In addition, surgical adhesives are frequently used in the surgeries to seal the anastomotic site. This study aims to investigate mechanical effects of four commonly used surgical adhesives, namely BioGlue, CoSeal, Crosseal, and Tisseel, on the suture site using in-vitro digital image correlation (DIC) method and finite element (FE) simulations in an ovine model. In this study, first, mechanical properties of ovine ascending aorta were obtained by optimizing the FE simulation results with DIC data. Subsequently, Dacron graft was included to mimic the surgical repair. The simulation results showed Dacron graft reduces tissue stress and strain at the surgical site by approximately three times. Afterward, in the simulations, surgical glues were applied to the anastomotic site. CoSeal, Crosseal, and Tisseel exhibited small mechanical effects on the aortic wall. However, BioGlue significantly constrained the suture site movement and further reduced the stress value up to 85%. The results showed the mechanical properties of Dacron graft and surgical adhesives play an important role in the functional state of the tissue at the suture site. A compliance mismatch between graft, surgical adhesives, and tissue can restrict normal physiologic tissue dilation and may cause tissue remodeling. Further research is encouraged to develop new graft and adhesive materials with an elastic behavior in harmony with that of the soft tissue.
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CHAPTER 1: INTRODUCTION

Cardiovascular diseases remain the primary cause of death worldwide [1]. Aortic aneurysm and dissection are major health risk and associated with high morbidity and mortality rates. Currently, there is no medical treatment available to cure aortic aneurysm or dissection. For aortic aneurysms, the available medicines for aortic aneurysms are targeting on reducing dilation progression. Therefore, monitoring the size of the aneurysm and use surgical and interventional procedures to treat it before rupture is the most widely used solution in clinical practice.

1.1. Aneurysm

Aneurysms are balloon-like vessel structures caused by irreversible vessel dilations, which involve all three layers of the vessel. They can be divided into several primary categories based on locations. Cerebral aneurysms, aortic aneurysms, popliteal artery aneurysms, mesenteric artery aneurysms and splenic artery aneurysms are major aneurysm types. Aortic aneurysms are the most prevalent aneurysms.

Aortic aneurysms are life-threatening diseases and responsible for 4-5% of sudden death in the US [2]. Patients with aortic aneurysms are hard to be diagnosed because aortic aneurysms are usually asymptomatic until rupture. The rupture of aortic aneurysms is fetal; its mortality rate is up to 90%. Prompt surgical intervention need to be taken when aortic aneurysms are ruptured. However, the morbidity and mortality rates are still high even the patients received surgical treatment. Abdominal aortic aneurysm (AAA) and thoracic aortic
aneurysm (TAA) are two typical types of aortic aneurysms. AAAs and TAAs occur at the same vessel. However, the location and pathophysiology facts made different from each other [2].

1.1.1. Abdominal Aortic Aneurysms

AAA is more common than TAA. Aging, gender, and smoking are major factors for AAA. Based on the ultrasound scanning studies, there are about 5% males, whose age are over 65, are diagnosed with AAA [3]. However, this number is only about 1% for females [2]. Pathology studies have shown that AAAs have related to the extracellular matrix (ECM) degeneration, vascular smooth muscle cell (VSMC) apoptosis and inflammatory cell infiltration. Initially, leukocytes and macrophage are accumulated and stimulated at the aortic wall. Proinflammatory cytokines are produced. After several years of development, VSMCs are depleted at the infiltration site of lymphocytes, mast cells, and neutrophils. Meanwhile, the ECM proteins are degenerated by activated proenzyme, which is produced by macrophages and VSMCs. Although the adventitial fibroblasts are stimulated to repair the structure, the interstitial collagens are disorganized. As this progress continuous, AAA is formed and kept enlarging until rupture [2].

Based on the studies about the mechanism of AAA, the formation of inflammation plays a significant role in AAA. Therefore, studies are carried out to find a solution to treat AAA with pharmacological therapies by attenuate the inflammation. Doxycycline was found to be effective in preventing AAA formation but failed to slow the progression [2].
1.1.2. Thoracic Aortic Aneurysm

Conversely, TAAs do not have a significant gender difference and frequently occur at younger ages. Twenty percent of TAA patients have a positive family history in TAA. TAAs can be further classified into four categories. Sixty percent of them are ascending thoracic aortic aneurysms (aTAAs), forty percent of them are descending thoracic aortic aneurysms (dTAAAs), 10% of them involve aortic arch, and 10% include thoracoabdominal aorta, which may comprise multiple segments. The etiology and pathogenesis are different in each segment.

aTAAs majorly result from cystic medial degeneration, which behaves as dropout of VSMCs and degeneration of elastic fiber at media. Hypertension can significantly accelerate this process. In etiology, cystic medial degeneration has different causes. Since TAA shows a close relationship with the gene, the genetic cause of TAA has been extensively studied.

Marfan syndrome is usually found in younger aTAA patients. It is a heritable autosomal-dominant disorder, which is triggered by the fibrillin-1 genome mutations. Fibrillin-1 is one of the critical structural protein for microfibers of elastin. The expression of the mutated gene leads to the loss of elastin and the structure disorganization. Eventually, the stiffness and size of the aorta segment keep rising as the mutated protein increasingly expresses. Additionally, the familial thoracic aortic aneurysm syndrome is identified in the patients who do not exhibit overt connective-tissue disorder. This syndrome is proven to be an autosomal-dominant inheritance, which can also cause cystic medial degeneration. Several genome mutations have been mapped as the cause of the disorder. Since it can be
inherited and pass on without expression of the disease, it is hypnotized to be a polygenic condition. Moreover, bicuspid aortic valve patients have a higher chance to get aTAA [3]. It is hypothesized that patients with bicuspid aortic valve may have lower fibrillin-1 production during embryogenesis. Studies have manifested that the fibrillin-1 level in patients with bicuspid aortic valve is significantly lower than that in patients with tricuspid aortic valve [4]. The weakened aortic wall results in the dilation in ascending wall and aortic root. It is more likely to develop cystic medial degeneration at that regions.

Some diseases are also associated with aTAA. Syphilis used to be the most common cause of aTAA. A saccular or a fusiform aneurysm can be developed following the form of oblitative endarteritis at aortic medial vasa vasorum created by the spirochetes. However, this kind of cause is highly reduced by the use of antibiotics. Atherosclerosis is less common in ascending aorta than the other causes. It leads to the destruction of elastic fibers and VSMCs at media and the accumulation of ECM and lipids. Aortic arteritis, such as Takayasu’s arteritis and giant-cell arteritis, also can cause aortic aneurysms. Takayasu’s arteritis trigger oblirative luminal changes and happens more often on females than males [5]. A study has shown that 18% the giant cell arteritis patients suffer from aortic aneurysm [6].

1.2. Aortic Dissection

Aortic dissection is usually associated with aortic aneurysm. It can be either cause or consequence of aneurysm [7]. It has a prevalence of 0.5 – 2.95 cases in 100 000 people per year. All of the cases result in a weakened aortic wall, which progressively dilates and form aortic aneurysms. As the diameter of the aortic wall keeps increasing, aortic dissection and
rupture [8]. Studies have found that acute aortic dissection and its variants are responsible for 25% of TAAs from 1908 to 1994. aTAAs are accounts for 75% of the cases [7].

Aortic disease
- inherited
- degenerative
- atherosclerotic
- inflammatory
- traumatic
- toxic

Intramural haemorrhage/haematoma Class 2
Subtle, discrete dissection Class 3
Plaque rupture plaque ulceration Class 4
Trauma Class 5
Aortic dissection (AD) Class 1
Communicating AD
Non-communicating AD
Aortic rupture
Healing

Figure 1.2.1 Progression and regression of aortic disease aetiologies which can lead to aortic dissection and rupture [8]

Aortic dissection (AD) initiates from tear at the wall of the intima, from which blood can enter the layer between the intima and media. False lumen is created at the affected aortic wall. The outer layer of the false lumen is weak. The stress on the wall is higher than average value; therefore, it can keep longitudinal propagating and dilating over time.

ADs can be classified into two categories, type A (ascending and descending aorta) and type B (descending aorta), based on Stanford classification. The mortality rate is high in the acute stage for both types. 20% of the patients are dead before they reach to the hospital. It is reported that aortic rupture responsible for 80% of death before medical and
surgical treatment. Surgical treatment increases the survival rate to is 52% to 69% for type A and 70% for type B dissection within one year. The two-year survival rate is decreased to 40%-52% for type A and 60% for type B dissection [8]. Therefore, diagnosis and receive proper treatment for both aortic aneurysm and aortic dissection is important in increasing in survival rate.

1.3. Treatment for Aortic Aneurysm and Dissection

Aortic aneurysm and dissection are commonly related, the diagnosis and treatment protocol are roughly the same. Moreover, aTAAs is more lethal than the other types of aneurysms. Therefore, this study will focus on the treatment for aTAAs.

1.3.1. Diagnosis

Aneurysm size is highly associated with rupture risk. It is almost 0% for the 4-cm diameter aneurysm, 16% for the size between 4.0-5.9 cm. The rate is considerably increased to 31% when it reaches to 6 cm [9]. These values are slightly changed for each segment of the aorta since the physiological condition varies in different locations. Ascending thoracic aorta subject to a higher hemodynamic stress than the other portation of aorta. Therefore, mean aortic rupture diameter was reported at 6 cm for aTAAs and 7.2 cm for dTAAs. The simplest and the most important criteria for surgical intervention is aneurysm reaches to 5.5 cm in diameter [10]. Patients who are diagnosed with non-acute TAAs are recommended to have follow-up imaging studies to monitor the growth speed of aneurysm. The first follow-up imaging study is usually taken six months after the diagnosis. Surgical intervention is recommended when the aneurysm either shows a high growth speed or reaches to 5.5 cm in diameter [3].
Echocardiography, computed tomography (CT) and Magnetic Resonance Imaging (MRI), are widely used to diagnose aortic aneurysms and dissections. Echocardiography is a commonly available and relatively cheap technique, which generates 2D images by analyzing the reflected ultrasound. Transesophageal echocardiography (TEE) is regularly used to evaluate acute thoracic aortic disease. Transthoracic echocardiography (TTE) is suitable for accurately measuring the aortic dimensions near the aortic root. However, echocardiography is limited to the acoustic accessibility and patients’ cooperation. CT and CT angiography (CTA) can quickly generate accurate 3D image to detect dissection and branch vessel. Therefore, it is the first choice for urgent elevation. CT can assist the further evaluation by finding aortic rupture. CTA can obtain an aneurysm and dissection with complex geometry to provide information for the decision of surgical approach. However, it is inferior to MRI in determining inflammation changes. MRI is a safe, noninvasive method, which can provide a broad field of view of 3D complex geometry and relationships. It is superior to the other methods when the patient needs to take iodinated contrast [11].

1.3.2. Medical Management and Treatment

Currently, there isn’t any medicine to cure aortic aneurysms. The treatment is limited to monitor the size of aneurysms and performs open or endovascular surgeries to repair them until the aneurysms have a high chance to rupture.

According to the understanding of Marfan syndrome, β-blocker was found to be effective in reducing dilation rate in patients with this syndrome. Although it is not as effective as for Marfan syndrome than for the other etiology, its mechanism allows it to reduce dP/dt and blood pressure. Therefore, it is also prescribed for all patients with TAAs.
Since the aim of the medicine is bring the blood pressure down to 105 to 120 mmHg during systole, other antihypertensive agents might be prescribed when the β-blocker is unable to reach to an ideal result [3].

1.3.3. Surgical Treatment

As the technology of surgery, graft and postoperative care advances, the operative mortality risk is highly reduced compared with that for decades ago. There are some surgical approaches available to treat aneurysms and dissection [7].
Despite the Marfan syndrome, ascending aorta without aortic root is the only part to be operated in most cases [12]. A significant number of patients have aTAAAs below the innominate artery. In these cases, a supracoronary Dacron graft is applied to the sinotubular junction. A partial or full arch replacement is required when an aneurysm involves the aortic arch. It is necessary to reconstruct the brachiocephalic vessels when using full arch replacement [7].
In some cases, the aortic valve needs to be substituted. Valve and graft can be replaced separately [13]. However, there is a high risk of sinus aneurysmal dilation for patients with the Marfan syndrome. If an aneurysm involves aortic root, a graft which integrates with aortic valve prosthesis can be used to replace the abnormal tissues. As a consequence, the coronary artery needs to reimplant into the graft [7].

The replacement of aortic valve requires the patient to keep taking anticoagulation to reduce the risk of thromboembolism. Therefore, the best option to retain the native aortic valve, so that the function of left ventricle and aortic root can maintain with little risk of thromboembolism. Due to the limitation of the technology in graft and surgical technic, the aortic root replacement surgeries commonly included the replacement of aortic valve until the invention of a valve-sparing surgical method. The scalloped Dacron graft is used to replace the sinuses of Valsalva with a single proximal suture line. The essential part of the procedure is to reimplant the native aortic valve onto the tubular Dacron graft before the implant of Dacron graft. Like the valve integrated root replacement, the coronary arteries need to reimplant in the graft [14].

Endovascular stent-graft repair as a low-invasive method is widely used to treat AAAs, AADs, dTADs, and dTAAs. In this method, the catheter carries a stent enters from incisions at the groin. The stent is released from the catheter and placed at the location of aneurysms or dissection to support the weakened aortic wall and guide the flow back to normal condition. It has a shorter operation time and avoids the life-threatening procedures, such as thoracotomy and aortic cross-clamping [15]. As a result, it shows a lower short-term and mid-term risk of morbidity and mortality than open surgery [16].
Aortoplasty were frequently used to repair aTAAs by resecting a portion of ascending aorta and repair. However, due to its high aneurysm recurrence rate, it is no longer used for most of the cases. The surgical strategy depends on the extent of the aneurysm. For aTAAs, aortic valve, coronary artery, aortic root, ascending aorta and aortic arch are the major segments should be taken into consideration for the surgeries [7].

1.3.4. Post-procedural Complications

Although the patient received endovascular stent-graft repair have good short- and mid-term outcomes, it still needs time to observe and study the long-term consequences. Additionally, the complications remain higher than the open surgeries. Endovascular stent-graft repair has a higher chance to get endoleaks and reintervention comparing with the open surgery [17]. Since the incisions are at the groin, the chance of hematoma, infection, or lymphocele at groin is as high as 10%. If the catheter is large, it can introduce the artery dissection or perforation. Moreover, the whole surgical procedure needs high-quality fluoroscopy and digital subtraction angiography imaging to assisted the surgeon to operate precisely. The patients need to be injected with 50 to 100 mL iodinized contrast medium to get a reliable result in angiography imaging. This amount of iodinized contrast medium can increase the burden of kidneys and cause renal complications. Additionally, the application of stent graft will cause thrombosis. As a result, ischemic and occlusion can happen following the endovascular stent-graft repair. Although the occurrence rate is 1-3%, the one-month survival rate is only 50% when the ischemia occurs [18].

Various complications also challenge the outcomes of the open surgeries. Those complications are associated with the etiology, grafts and surgical options. Firstly, the
inflammation is one of the common complications in all open surgeries. Any contamination on graft or surgical instrument can cause infection. Moreover, the reoccurrence of aneurysm and dissection are potential postoperative complications. They are the primary causes of postsurgical mortality. Dissection commonly reoccurs if it is not entirely removed or there is a tear in the intimal wall. The reoccurrence rate of aneurysms and dissections is also higher in patients with genetic diseases, such as Marfan syndrome [19]. Additionally, aTAA s usually consort with aortic root and valve. Therefore, the long-term outcomes of some methods exhibit embolism and bleeding [20]. Perioperative bleeding is a high-risk complication. It can result in complications, such as false aneurysms, even raise the morbidity and mortality. Studies have shown that it is a predictor of early postsurgical mortality and responsible for myocardial infarction as well as renal failure.

1.4. Surgical Adhesives

Surgical adhesives, also known as tissue adhesives, are widely used in clinical practices for hemostasis. Following the application on the target tissue, they can polymerize and link the tissue together as a barrier to prevent leakage.

Based on the purpose, they are classified into three categories [21]. The primary type of them is hemostasis; they are developed to reduce the postsurgical bleeding at suture lines [22]. The mechanisms behind this type of adhesives are similar to the in vivo coagulation. The second type of surgical adhesives is used to seal leakage. The function of them is more than hemostasis. Based on the purpose, the sealant may need to close the leakage of air or lymphatic fluids. The third type of them can function as a delivery agent. The potential
substances can be delivered by them include but not limited to medicines, growth factors and cell lines [21].

Besides the classification based on purposes, the most frequently used categorization of the surgical adhesives is based on chemical components. Hydrogels, fibrin sealants, cyanoacrylates, collagen-based adhesives, gelatin based adhesives and albumin-based adhesives are the main available adhesives [21].

1.4.1. Hydrogels- based Surgical Adhesives

Hydrogels are also known as polyethylene glycol (PEG) polymers. They are one of the most promising surgical adhesives because their unique features allow them to carry and release substances at the applied location. They are potential drug delivery agent [23]. However, the current application of them is restricted to the sealant function. FocalSeal-L (Gynzyme Biosurgery, Inc., Cambridge, Massachusetts) is one of the earliest FDA-approved PEG polymers. It is not wise to use it for hemostasis because photoactivation is required to stimulate its adhesion. CoSeal (Cohesion Technologies, Inc., Palo Alto, California) is developed to reduce the photoactivation time. Hydrogen chloride solution and sodium phosphate/sodium carbonate solution are two primary PEGs. It can be stimulated within three minutes following the mixing of the two components [24].

1.4.2. Fibrin Sealants

Fibrin sealant is the most widely used type of surgical adhesive. Thrombin and fibrinogen, which are purified in vivo substances, are the two essential components for them. Therefore, they are biodegradable materials. The safety of them depends on the purification and additional substances. Pooled plasma and bovine source are two common
thrombin sources for fibrin sealants. Viral contamination and other hazards were the major safety issues in the early products. As the purification technique improves, the incident rate reduces. Some of the fibrin sealants contain calcium chloride and factor XIIIa or antifibrinolytics to improve the preferences [21]. However, the additional components may limit its usage. Crosseal (OMRIX Biopharmaceuticals, Ltd, Brussels, Belgium) and Tisseel (Baxter Healthcare Corp, Deerfield, Illinois) are contraindicated in neurosurgical application because they contain neurotoxic antifibrinolytic agent tranexamic acid [25] [26].

1.4.3. Cyanoacrylates

Cyanoacrylates are stronger than fibrin sealants. Nevertheless, due to its unbiodegradable and carcinogenic characters, this kind of tissue adhesives is limited to external or temporary usage [21].

1.4.4. Collagen-based Surgical Adhesives

Collagen-based surgical adhesives are primarily made of collagen and thrombin. Similar to the fibrin sealants, the materials are all purified from biological sources. It is a relatively safe biodegradable adhesive type. The basic concept behind it is to create a matrix to assist the clot formation at the target area. In addition to the basic materials, CoStasis (Cohesion Technologies, Inc.) introduced autologous human plasma into the recipes. It exhibits excellent result in hemostasis. Whereas, the long-term result needs to be further investigated.
1.4.5. Gelatin-based Surgical Adhesives

Gelatin-based adhesives are developed based on the biocompatible, bioabsorbable nature of gelatin. However, gelatin’s bond with the tissue is weak and unstable. Therefore, chemical modifications are made to improve the bioadhesive strength. Gelatin-resorcinol-formaldehyde-glutaraldehyde (GRFG) glues, and gelation-resorcinol-formaldehyde (GRF) glue are two chemical modified gelatin based adhesives [27]. Two separate condensation reactions happen after gelatin and resorcinol meet formaldehyde or glutaraldehyde. This reaction results in cross-linked gelatins and cross-linked resorcinol resin. The activated glue can form covalent linkages with functional groups on the tissue surface [28]. GRFG and GRF glues are widely used in Europe. GRFG glue has an excellent performance in sealing. It has been employed in thoracoscopic procedures to seal the air leakage. The postsurgical results of GRF glue reinforce ascending thoracic aortic aneurysm replacement surgery indicates a significantly lower reoperation rate and false lumen perfusion [29]. Nevertheless, both of GRFG and GRF are not approved by FDA due to the potential toxicity of formaldehyde [30].

1.4.6. Albumin-based Surgical Adhesives

Albumin-based surgical adhesives are conceptually derived from GRFG and GRF glues. The fundamental mechanism of this kind of surgical glue is based on the condensation reactions between albumin and glutaraldehyde. Albumins can cross-link together with the aid of glutaraldehyde [28]. The activated glue is not only able to chemically bond with cell surfaces and ECM but also mechanically link with the interstices of the graft matrix [27].
BioGlue (Cryolife, Kennesaw, GA), is one of albumin-based surgical adhesive [32]. It was firstly used in the US in 1997 under humanitarian device exemption for use in acute aortic dissections. In 2001, BioGlue was approved by FDA for the general use as cardiac and vascular surgery hemostatic adjunct. It has a broader use in Europe, in addition to cardiovascular surgeries, it has been accepted in pulmonary, genitourinary, dural, alimentary, and brow-plastic surgeries. However, the cytotoxicity of glutaraldehyde can affect lung, liver and aortic tissues. The polymerized glue still can release a certain amount of glutaraldehyde. Therefore, it may result in adverse long-term effects. Moreover, BioGlue is potentially responsible for redissection, false aneurysm, stricture and restricts the repair of aorta around aortic anastomotic site [28].
1.5. Effect of Stress on Aorta

The behavior of the cells on aorta is highly associated with mechanical homeostasis [33]. The in vivo mechanical environment is changed aTAA and aTAD replacement surgeries. Dacron does not have a consistent mechanical property with the aorta. Additionally, the surgical adhesive not only increases the thickness at the hemostatic adjunct but also introduced a layer of linear elastic material interacting with the anastomotic site [34]. Understanding on the mechanical effects of surgical glue after surgeries will reveal the causes of the adverse effects.

1.5.1. Aorta Structure

Figure 1.5.1 Structure of healthy human artery contains three layers, intima (I), media (M) and adventitia (A) [35]
Aorta is the largest artery in the body. It has three layers, adventitia, media and intima. Intima is the innermost layer, which contains a layer of endothelial cells, a thin basal membrane, and a subendothelial layer. The subendothelial layer consists of thinly dispersed smooth muscle cells (SMCs) and bundles of collagen fibrils. It is sensitive to the mechanical environment. It trends to non-atherosclerotic thickening to restore the baseline levels of stress. The non-uniform Type I and III collagen fibrils contribute to the primary mechanical function of the intima [36].

Media, which is composed of smooth muscle cells (SMCs), elastin, and bundles of collagen fibrils, is the layer in the middle. It is separated from intima by internal elastic lamina and adventitia by external elastic lamina. The collagen fibrils in media are 30% Type I and 70% Type III. They interconnect with SMCs and elastin and form circumferentially highly organized continuous fibrous helix [35]. Additionally, the elastic fibers are structurally linked obliquely with SMCs from elastic laminae. They are connected with intracellular contractile filaments, which has the same orientation with extracellular elastic fibers, by dense plaques or focal adhesions on the cell membrane. This structure is the intracellular tension-bearing or –sensor of the SMCs. As a result, it can distribute the circumferential load produced by hemodynamic motion evenly [33].

Adventitia is the outermost layer. Fibroblasts and fibrocytes are the principal cell types in it. It also contains thick bundled collagen fibres, which is mainly Type I, and histological ground substances. Since the adventitia is surrounded by connective tissues, the outer boundary is not clearly defined. The bundled collagens compose two major helically arranged fibres families. While the adventitia is less stiff than the media in stress-free
configuration, adventitia, particularly the collagen, is responsible for the mechanical stability and strength of the aortic wall. The straightened collagen fibres in adventitia can change the aortic wall into a stiff tube to protect the aortic wall from overstretch and rupture [35].

1.5.2. Mechanobiology

The medial SMCs and adventitial fibroblasts are essential to establish, maintain and restore the structural integrity. Since they are continuously subject to the cyclic pressure, there is no doubt that the mechanical environment is a major factor affects their phenotypes.

In tissue level, both of them can disassemble and resemble cytoskeletal proteins to adjust the stiffness to restore the stress to a safe level [37] [38]. The target stress level depends on the location and type of the cells.

They are also capable of regulating the ECM, including fibrillar collagen and glycosaminoglycan, according to the sensed mechanical environment. The regulation process of both intracellular structures and ECSs involve multiple mechanobiology reactions.

![Mechanism of Cell Responses](image)

Figure 1.5.2 Some of the key cell responses to stress (σ) or stretch (λ) [33]
Angiotensin II (Ang-II) and transforming growth factor-beta (TGF-β) are two major factors works in the regulation reactions. Ang-II is a vasoconstrictor, which regulates the production of intracellular contractile and ECMs. It is also associated with the ECM removal factors, such as monocyte chemoattractant protein-1 (MCP-1) and monocytes/macrophages (МΦ). For example, when SMCs are exposed to an increased load, the sensitivity of angiotensin-II type I receptor to the Ang-II is boosted. The production of TGF-β and connective tissue growth factor (CTGF) are subsequently increased. However, the interaction between ECM, integrins, and growth factor/cytokine signaling is complex. The activated Ang-II can also increase matrix metalloproteinases-2 (MMP-2), which a matrix-degrading factor. MMP-2 activates the latent TGF-β in ECMs [39].

The mechanism in fibroblasts is similar with that in SMCs. The latent TGF-β sequestered within the matrix can be activated by fibroblasts actomyosin contractility induced mechanical stresses. TGF-β can work with mechanical stress to transform the fibroblasts into myofibroblasts, which is a phenotype can differentiate into either fibroblast or SMC [40].

Following the aTAA or aTAD replacement, the resection adjunct will subject to a different physiological condition. The aorta can benefit from the regulation of the ECM and cell phenotypes to retain the adjust to the altered condition. However, the local change of the aorta may result in some drawbacks. Firstly, MMP can be triggered to degenerate the ECM, and active latent TGF-β. The degeneration of matrix is a potential cause of the change of the phenotype of resident cells and infiltration of inflammatory cells. Secondly, the thickness of local will increase or decrease in responding to the decreased or increased
stress, respectively. The cell phenotype and the ECM can be significantly altered by a certain amount of time. In the worst cases, aTAA may reoccur and finally result in aTAD and rupture, which usually leads to death.

In summary, the mechanical environment of the ascending aorta is critical to the postsurgical recovery. Dacron grafts have a lower stiffness than the ascending aorta. Therefore, the aortic wall of the adjunct is more vulnerable than the other aortic segments when the suture is the only method to keep the graft and aorta together. The primary goal of the application of surgical glue is to promote hemostasis. However, its thickness is not negligible when compared with the thickness. Additionally, the mechanical properties of them are significantly different from aorta and Dacron grafts. As a consequence, the surgical glue might have considerable effects on the adjunct. The study of its effects on aTAA replacement surgeries will be able to help us understand the causes of the reoperations and develop a way to improve the outcomes of surgeries.
2.1. Digital Image Correlation (DIC) Testing

GOM ARAMIS V8 Digital Image Correlation (DIC) system was used in this experiment. It provides a noninvasive displacement measurement. Therefore, this system is suitable for multiple situations, such as component testing and analysis, automotive industry, aerospace industry, biomechanics, research, and development.

It is a portable system which consisted of two high-speed cameras and sensor to capture the images simultaneously. They are mounted on an adjustable rod forming $25^\circ$ angle toward the center. The camera distance can be changed based on the template. Additionally, the stand allows the cameras rotatable in three different mutually perpendicular planes. It provides a high flexibility for the system. As a result, it can tilt to any angle to make the cameras at the perpendicular plane with the target object, and access to a wide range of objects, from vehicles to small tendons or ligaments.
Since the software can generate surfaces based on the pattern, the whole geometry of the aorta can be recorded if the entire geometry is captured at the same time. Mirror images can satisfy this situation by reflecting the hidden surface simultaneously without any effect on the sample. Two mirrors are enough to reflect most of the surfaces. Therefore, two mirrors were used in the test to regenerate the whole geometry of the ovine aortic root.

The input analogs allow other sources to input signals into the system so that it can record signals, such as pressure and force, at the same time. In this test, BDC system is connected with this system to record the corresponding pressure.

2.1.1. Presetting of DIC system

The cameras are required to be calibrated based on the sample size before the test because the focus and pattern quality is essential to the results because GOM Correlation 2017 analysis the images by tracking the pattern changes relative to the reference stage.
Therefore, both of the loaded and unloaded samples need to have a good pattern quality and lay within the field of view.

Since there were two mirrors and the sample size was about 100 mm in length and 50 mm in width, the calibration plate used in this test was the CP20 175x140. The focuses of the two cameras were adjusted under high exposures until the words on the plate were clear. Following the focusing, the position of the light sources was adjusted so that the camera can detect equal color distributions in the two images with the false color mode. Subsequently, one of the apertures was closed to 8-11. The other aperture was changed to match its image with the other image after the exposures time was adjusted until the red dot contrast shown in the first image. This procedure can balance the images between the two cameras to compensate for variations in light and hardware.

Following the adjustment of the light and hardware, the plate was placed on a vertical rotatable magnetic stand. According to the instruction in the software, a series of pictures were captured to calibrated the two cameras. The final calibration result was displaced in the calibration results window. If the calibration or scale deviation does not meet the criteria, recalibrated of the system necessary.

2.1.2. Material Preparation

The slaughter house’s protocol requires throat cut and heart stick during slaughtering. The ovine ascending aortas are likely to be damaged by the heart stick. Therefore, nine fresh ovine hearts with lungs are obtained from Superior Farm in the morning, to make sure some of the ovine hearts connected to the intact ascending aorta. The ovine hearts were processed by resecting the parts other than ascending aorta and heart. The connective
tissue was removed from the remaining ascending aorta and aortic root. Moreover, the left appendage was carefully resected with little damage to the coronary artery to ensure minimum leakage during the test. It is because the left appendage was preventing the aortic root from capturing by DIC cameras. The post-processed hearts were preserved in a refrigerator until the digital image correlation system was ready to use. The preservation of the samples was no longer than 96 hours.

The osmotic pressure has a significant effect on cells. Therefore, the material properties of soft tissue will change under different osmotic pressure due to the cellular deformation. In order to keep the material properties of soft tissues from changing, normal saline solution is usually used to maintain the osmotic pressure. 2 L of normal saline solution were prepared before the test by dissolving 20 PBS tablets into 2 L ultrapure water.
2.1.3. DIC Testing Protocol

Figure 2.1.2 DIC Testing

Before the test, the mirrors were fixed behind the aorta. Due to the limitation of the field of view, the mirrors were placed very close to the ascending aorta. Three markers were put on each mirror to determine the mirror surfaces in software. The distance and angle of the cameras were adjusted to find the most optimal spot to get relatively good patterns from the front image of the sample and both mirror images.

Excepting the DIC system, the testing system includes one pump, one compliance chamber, one stand for the heart and one container. One pump powerful enough to
pressurize the flow up to 120 mmHg, which was the desired maximum value. However, due to the pumping mechanism, the flow will introduce noise into the system. Therefore, a compliance chamber was applied to reduce the noise. A vent was added to the top part of the system to remove the air in the system.

Different from the normal physiological condition, the flow was conducted inversely to the heart during the test; therefore, it kept the aortic valve form opening, and the pressure applied to the aortic root was considered as static. Additionally, the damping caused by the valve was eliminated.

The prepared normal saline solution was poured into the clean container before the test set. Saline solution filled 2/3 of the compliance chamber so that the bottom of the large volume of fluid was at steady state. Both the anterior and posterior aorta had been applied with graphite pattern before the assembling of the aorta and the silicon tube. After the devices and heart were connected, the cap of the compliance chamber was holed with clamps on the iron stand to prevent the cap from coming out of the chamber. The vent was kept open until the air bubbles were removed from the whole system. Meanwhile, the clamps were applied to the coronary artery, which leaked due to the removal of the appendage. The position of DIC system and the location of the heart were adjusted so that they were at the optimal position with minimum glare on the soft tissue. The marker was defined on the heart. In this way, the global movement, which was majorly the noise caused by the pump, were removed from the raw data.
2.2. Geometry Reconstruction

![Figure 2.2.1](image)

Figure 2.2.1 The geometry reconstruction procedure. (a) are the geometries obtained in GOM correlation 2017; (b) and (c) are geometries combination and modification, respectively; (d) is geometry combined with aortic sinus.

The geometries were constructed in GOM correlation 2017 according to patterns applied on the aorta. The left and right initial geometries were flipped to the center based on the mirror plane locations with mirror function. The meshes of the three converted surfaces were exported as STL file and imported into RapidWorks (NextEngine, inc. Santa Monica, CA) for mesh refining.

The three surfaces were combined as one surface by filling the gaps between them with interpolated curves. Moreover, in order to make the boundary condition applied
correctly, the top part was extended to the location of zip tie, where the actual ovine aorta was fixed.

Since both top and bottom parts were moving according to the observation of the DIC images, an aortic sinus from human aortic root geometry was assembled to the combined surface. The surface of the aorta was built based on the mesh and transferred into Hypermesh to generate the desired mesh.

2.3. Mesh

Mesh element type and mesh density are critical to the simulation. They are directly related to the accuracy of the result. There are four types of shell element are commonly used in simulations, S3, S3R, S4, and S4R. S3 and S3R are triangular elements. They have a constant value throughout the element in bending and their approximation to the membrane strain. If they are going to be used in the simulation, the mesh density needs to be fine enough to counteract their defects.

Rectangular elements, such as S4 and S4R elements, are commonly used element for the problems that involve curved surfaces. Although S4R element can be used in most problems with a reduced computational time, it still has some defects. Firstly, the S4R element is a reduced integration shell element. There is only one integration point in this type of element. Moreover, it is sensitive to distortion and shear locking. It requires hourglassing control and distortion control during the simulation [41]. Despite the long computational time, the S4 element is a fully integrated element that can avoid the above problems with a highly accurate result. Therefore, S4 is the ideal element to be used in this study compared with the other shell elements.
The several mesh densities have been investigated to find the optimal mesh size which has high accuracy with minimum computational time. The meshes were created based on the initial geometry and compared with the displacement results.

2.4. Material Properties

The mechanical effects of BioGlue, CoSeal, Crosseal, and Tisseel were studied. According to a previous study, these four types of surgical glue exhibit linear elastic materials behaviors. BioGlue has highest mean Young’s modulus, $3.12204 \pm 1.639.68$ MPa. CoSeal and Tisseel have almost the same value, $0.10002 \pm 0.067.60$ MPa and $0.10259 \pm 0.041.13$ MPa. Crosseal shows the lowest mean Young’s modulus, $0.053.56 \pm 0.03259$ MPa [34]. This study used the mean values for the material properties in the simulation. The width of glue was assumed to be 4 mm. It was presumed that the thickness was uniformly distributed 2 mm.

The dimensions and material properties of Dacron graft were determined based on Bustos et al.’s study [42]. The data was extracted from the plot by Digitizer and transformed to engineering strain and stress. The calculated data was input in Abaqus (Simulia, Providence, RI) for hyperelastic material fourth order reduced polynomial model.

![Figure 2.4.1 Dimension of the Dacron geometry at longitudinal section](image)
Since the material properties of the aorta dependent on many factors, such as the weight, gender, age, and health condition of the ovine. The external factors such storage time and temperature also can affect the result. Therefore, the acquisition of material properties was critical to this study. The thickness of the specific sample used in this study was 2.64 mm. The initial mechanical properties of the ovine aorta were obtained from biaxial stretching. It was optimized by matching the DIC measurement to find the parameters for the simulation studies.

2.5. Constitutive Modeling

A linear function cannot describe the strain and stress relation of many materials. For example, soft tissues are a non-linear material. The strain-stress curve for it is not a straight line, and the loading curve has a different curvature compared with the unloading curve.

The hyperelastic material is a constitutive model developed from strain energy density function. Multiple models were developed for this type of materials. Fung has drawn up a strain energy function for the skin. It was further developed to be applied to other soft tissues [43]. Subsequently, Holzapfel model was developed based on the structure of arteries [44]. It is the ideal model for this study.
Holzapfel suggested the aortic wall is a thick wall problem and the primary mechanical properties were contributed by the collagen fibers in media and adventitia. They decomposed the isochoric strain-energy function $\Psi$ into $\Psi_{iso}$ and $\Psi_{aniso}$. The first term represents the low-pressure condition mechanical properties, under which the collagen fibers are not activated and non-collagen fibers exhibit isotropic material behavior. The second term represents anisotropic material properties under high pressure condition, in which the collagen fibers are activated and exhibit anisotropic behavior. The strain energy function is written as

$$\Psi = \Psi_{iso} + \Psi_{aniso} \quad (2.5.1)$$

The Cauchy stress tensor is associated with the right Cauchy-Green deformation tensor $C = F^T F$ and can be expressed as

$$\sigma = 2J^{-1} F \frac{\partial \Psi}{\partial C} F^T \quad (2.5.2)$$

where $F = \nabla x$ is the deformation gradient tensor. $J = |\det F|$ is the Jacobian of the transformation. The isotropic strain energy function $\Psi_{iso}$ depends on the following invariants,

$$I_1(C) = \text{tr} C, \quad I_2(C) = \frac{1}{2} [(\text{tr} C)^2 - \text{tr} C^2], \quad I_3(C) = \det C, \quad (2.5.3)$$

For incompressible materials, $I_3(C) = 1$. The anisotropic strain energy function $\Psi_{aniso}$ requires additional invariances, which are given by

$$I_4(C, M) = M \cdot (CM), \quad I_5(C, M) = M \cdot (C^2 M), \quad I_6(C, M') = M' \cdot (CM'), \quad I_7(C, M') = M' \cdot (C^2 M'), \quad I_8(C, M, M') = [M \cdot (C^2 M')] (M' \cdot M') \quad (2.5.4)$$

where $M$ and $M'$ are the unit direction vectors representing the two families of fibres in the reference configuration.
The strain energy function can be expressed by the invariances by using the following equation,
\[ \Psi(I_1, I_2, I_3, I_4, \cdots, I_8) = \Psi_{\text{iso}}(I_1, I_2) + \Psi_{\text{aniso}}(I_1, I_2, I_3, I_4, \cdots, I_8) \]  
(2.5.4)

After excluding the constant value and lower order invariants. The expression can be reduced to
\[ \Psi(I_1, I_4, I_6) = \Psi_{\text{iso}}(I_1) + \Psi_{\text{aniso}}(I_4, I_6) \]  
(2.5.5)

In order to particularize the two terms, the neo-Hookean model is used to match the isotropic part.
\[ \Psi_{\text{iso}}(I_1) = \frac{c}{2}(I_1 - 3) \]  
(2.5.6)
where c is a positive value coefficient which has the same unit with stress. The anisotropic part can be written as
\[ \Psi_{\text{aniso}}(I_4, I_6) = \frac{k_1}{2k_2} \sum_{i=4,6} \exp[k_2(I_i - 1)^2] - 1 \]  
(2.5.7)
where \( k_1 \) and \( k_2 \) are stress-like dimensionless parameters [44].

This model was firstly introduced by applying strain energy function for media and adventitia separately. In order to describe the transversely isotropic free-energy function structure tensor was stated by
\[ \mathbf{H} = \kappa \mathbf{I} + (1 - 3\kappa) \mathbf{M} \otimes \mathbf{M} \quad \kappa = \frac{1}{4} \int_0^\pi \rho(\theta) \sin^3 \theta \, d\theta \]  
(2.5.8)
where \( \kappa \) is used to describe the degree of anisotropy. \( \rho(\theta) \) is the density function associate with \( \theta \), which is the angle between local fiber direction vector \( \mathbf{M} \) and mean fiber direction vector \( \overline{\mathbf{M}} \).
κ is a parameter between 0 and 1/2. However, the parameter is inappropriate for soft tissue, when κ value is higher than 1/3 [35].

The transversely isotropic free-energy function can be defined as

\[ \Psi_{\text{aniso}}(l_1, l_4) = \frac{k_1}{k_2} \{ \exp[k_2 (l_4^* - 1)^2] - 1 \} \]  

and

\[ l_4^* = \text{tr}(\mathbf{C}) = \kappa l_1 + (1 - 3\kappa)l_4 \] (2.5.9)

The expression for non-collagen structure behavior is the same with the previously developed function. As a result, the final strain energy function for the aorta can be expressed as

\[ \Psi = \frac{c}{2} (l_1 - 3) + \frac{k_1}{k_2} \{ \exp[k_2 (l_4^* - 1)^2] - 1 \} \] (2.5.10)

Since water is the primary component of soft tissue, the aorta can be considered as an incompressible material [35]. The term associated with compressibility wasn’t considered in this study.

2.6. Biaxial Stretching

Biaxial stretching is a method to determine the material by stretching the material in two orthogonal directions with a known loading condition. The displacements and corresponding loads are recorded during the test. The material properties can be obtained by analyzing the data.
A planar biaxial stretching system (CellScale, Waterloo, Canada) was used to determine the material properties for the ovine aorta. Both the anterior and posterior aorta was cut into 1.5 cm by 1.5 cm squares. Similar to the DIC system, a pattern was required to apply to the specimens by graphite. After the pattern was applied to the sample, the specimens were mounted on the test apparatus using a set of four CellScale BioRakes which were magnetically mounted on the mutually perpendicular arms. There are two 1000g load cells were connected to the two orthogonal arms (Model 31, Honeywell Inc., Columbus, OH).

During the test, the posterior part of the specimen was placed in the saline solution bath, in which the temperature was controlled at 37 °C. There were ten pre-loadings and one testing in one test set. The preloading was designed to stretch sample 10% per second to recover the tissue to the normal physiological condition. The images were recorded and measured in pixels in the software. The pixel size was 0.0141 mm. The results were analyzed through a home-made MATLAB code to find out the initial guess of the
coefficients for Holzapfel model. The function used to interpolate the parameters was based on the equation of the strain and stress relation shown as

\[ \sigma - \sigma_{rr} = c(\lambda^2 - \lambda^{-2}\lambda_z^{-2}) + 2k_1[k_2(I_4^* - 1)\lambda \frac{\partial I_4}{\partial \lambda}] \quad \text{and} \]

\[ \lambda \frac{\partial I_4}{\partial \lambda} = 2[k(\lambda^2 - \lambda^{-2}\lambda_z^{-2}) + (1 - 3k)\lambda^2 \cos^2 \varphi] \quad (2.6.1) \]

where \( \sigma \) is either \( \sigma_{\theta \theta} \) or \( \sigma_{zz} \), \( \lambda \) is the corresponding stretch ratio, \( \lambda_{\theta \theta} \) and \( \lambda_{zz} \) [45]. In biaxial stretch testing, \( \sigma_{rr} \) is zero. Therefore, the Cauchy stress and Green strain data were used to fit in this equation to interpolate the unknown parameters.

2.7. Optimization

The initial material properties, which obtained from biaxial stretching, cannot represent the material properties of reality because biaxial stretching test only collected the two-dimensional data. The material properties can only be analyzed by assuming the material isotropic. However, aorta has three layers, adventitia, media and intima. Each layer consists of different types of cells and fibers which exhibit diverse material properties. An optimization procedure is required to get the optimal result of anisotropic properties.

The simulation results of four mesh density were analyzed to ensure the accuracy of the simulation. The total elements of the meshes were 1891, 4096, 8004 and 14615 respectively. The goal of this step was to determine the best optimization mesh density. Therefore, the loading used for this procedure was the pressure of two normal human cardiac cycles obtained from the previous study.
2.7.1. Simulation Settings in ABAQUS for Optimization

Since the optimization was based on data matching in both simulation result and DIC measurements, it was essential to set simulation conditions same with the conditions during DIC measurement.

Material orientation needs to be assigned on the geometry for the Holzapfelf model to represent the fiber orientation. According to the histology of aorta, the fiber direction is majorly aligned in the circumferential direction. The local cylindrical coordinate system at the top was picked to assign the material orientation, with the normal vector pointing toward positive radius direction.

Based on the observation of DIC measurement, although the top end was fixed with zip ties, the top end is still moving in the vertical direction. As a result, the boundary condition of the top end was defined as only movable vertically along the top local cylindrical coordinate system. Since the bottom end connected directly with aortic sinus which was considered to be fixed, a human aortic sinus was attached to the geometry, so that the boundary condition at the bottom can be applied as unmovable in all degree of freedom (DOF).

The pressure signal without the filter was recorded by connecting the pressure sensing analog of pulsatile pump systems (BDC Laboratories, Wheat Ridge, CO) with DIC system. The raw data was noisy due to the movement of the pump. Therefore, a fourth order Butterworth filter was used to filtrate the signal for a smooth pressure curve. The filleted pressure was applied on the internal face of the geometry pointing toward the surface. In
order to simplify the problem, the pressure was assumed to be uniformly distributed on the interior surface. The total step time was 45 s, corresponding to the DIC measurements.

Since the element size was relatively small to the overall geometry, Abaqus/Explicit was forced to use small time increments to integrate the entire model in a total time of 45 seconds. S4 elements further increase the computational time up to 40 mins for the simulation with 8004 elements.

Mass scaling method was used in the simulation to reduce the total time spent on optimization. However, the mass scaling is not a good option in explicit problems. It is only applicable when the mass scaling factor is small enough so that it doesn’t affect the kinetic energy significantly. Therefore, it was only an approach which can bring the result closer but not accurate [46]. Additional optimization without mass scaling was performed.

2.7.2. Optimization Setting in Isight

Isight (Simulia, Providence, RI) was used to optimize the material properties for simulation. The displacement of nine points at the center of the anterior surface was reported from the DIC measurement.
Figure 2.7.2 Optimization Workflow in Isight

The displacement of corresponding nodes in the mesh was selected to match with the reported data. Three parameters for Holzapfel model, C10, k1, k2, and kappa, were defined as the variables to be optimized because aorta is an incompressible material. After minimizing the squared difference between the DIC measurements and simulations results at each point, these parameters can represent the mechanical behavior of this ovine aorta sample.
2.8. Simulation of Mechanical Effects of Surgical Adhesives on Suture Site

After the acquisition of the optimized mechanical properties, six simulations were conducted to study the mechanical effects of surgical adhesives on the aortic wall after the aTAA replacements. Following the simulation of the intact aorta, Dacron replaced distal aorta geometry was constructed to mimic the geometry after aTAA replacement. The distal ovine ascending aorta was resected from 35 mm above the aortic sinus. Dacron model was built and assembled with the geometry in SolidWorks. The final geometry was transferred into Hypermesh to generate the mesh. Due to the complexity of Dacron geometry, the approximate individual mesh size was 0.75 mm.

![Figure 2.8.1](image)

Figure 2.8.1 (Left) Geometry of intact aorta; (Right) Remain aorta assembled with Dacron Graft

Subsequently, the simulations with surgical adhesives were conducted by create a layer of surgical adhesives on top of the anastomotic site. They are defined as a ring shape layer with a width of 4 mm, 2 mm on each component. Its thickness was 2 mm, which cannot be neglected compared with the thickness of the aortic wall. Therefore, the surgical glue was assigned as a layer overlapping the joint rather than applying a cohesive behavior between
the aortic wall and Dacron graft. The interaction between the surgical glue and the aorta-
Dacron geometry was general contact with rough interaction, which means it was a non-
slip condition. The internal surface of surgical glue was assigned as slave surface, and the 
external surface of the aorta-Dacron surface was assigned as the master surface.

2.8.1. Loading Condition

Since the initial geometry was considered to have 0 pressure, a ramp of pressure was 
increased to 77.5807 mmHg in 0.2 s. Ovine blood pressure measured by P. Segers et al. 
was approximately 95 mmHg for the maximum systolic pressure, and 75 mmHg for the 
minimum diastolic pressure [47]. However, the data was insufficient for ovine cardiac 
pressure curve. Therefore, the loading curve of two normal human cardiac cycles was 
acting on the internal surface. The total simulation step time was 2.2072 s.

![Figure 2.8.2 Pressure curve for comparative simulations](image)

The data at three time points, the peak of systole, the midway from systole to diastole, 
and the end of diastole, during the second cardiac cycle were selected to be analyzed. The 
peak of systole can reflect the worst case because it has the highest pressure. The point,
which has the mean value of the peak systolic pressure and end diastolic pressure, can represent the majority conditions during cardiac cycles. The end diastolic pressure is the lowest pressure. Investigation of the simulation at this point can provide information about the minimum mechanical impact on the aortic wall.

2.8.2. Boundary Condition

The boundary condition of the free edges had little effect on the simulation result because they were relative far from the suture site. In order to simplify the simulation process and decrease the computational time, both the top and bottom free edges were fully fixed in six DOFs.

2.9. Validation Study

The intact aorta geometry was simplified to a cylinder, so that the result can be validated by simplified simulation and analytical solutions. The thickness was defined as 2.64 mm and the length was set as 66 mm. Since the mechanical response at suture site was important to this study, the external diameter of the cylinder was 24 mm, which was close to the shape of the suture site.

According to Laplace’s Law, the circumferential stress can be calculated with the following equation,

$$\sigma_\theta = \frac{Pr}{t}$$

(2.9.1)

Where, $\sigma_\theta$ is the circumferential stress, P is pressure, r is the radius of the cylinder, t is the thickness of the wall.

Two ABAQUS/Explicit simulations were conducted to validate the result. In the first simulation, pressure was applied on the interior surface, and increase from 0 mmHg to
100 mmHg. There was no constrain set in this simulation. The circumferential stress at the center of the cylindrical surface was compared with the analytical result to ensure the simulation matches with the fact. In the second simulation, both the loading and boundary conditions were set as the same with section 2.8 to compare with the simulation of the intact aorta.
CHAPTER 3: RESULT

3.1. Optimization

The material properties of Dacron and surgical glues were obtained from previous studies [42]. The initial guess of the ovine ascending aorta was calculated from the biaxial stretching test. The result was $c=0.007472$ MPa, $k_1=0.0001219$, $k_2=2.777$, $\kappa=0.2416$. It took more than 1000 simulations to reach the final optimization result. The final result for the parameters were $c=0.02228$ MPa, $k_1=0.03857$, $k_2=0.6051$, $\kappa=0.2512$.

The nine points in DIC and nine nodes in the simulation were numbered differently in the software. They were reordered in the result to simplify the numbering.

Table 3.1.1 Nodes and points renumbering based on Figure 2.7.1

<table>
<thead>
<tr>
<th>Column in Image</th>
<th>Top</th>
<th>Middle</th>
<th>Bottom</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Center</td>
<td>Right</td>
</tr>
<tr>
<td>Software DIC</td>
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<td>48</td>
<td>50</td>
</tr>
<tr>
<td>Software Mesh</td>
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<td>14337</td>
<td>14255</td>
</tr>
<tr>
<td>Result DIC</td>
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<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Result Mesh</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Figure 3.1.1 The displacement plot of nine points with the best optimization result vs. DIC measurements

Compared with DIC measurement, the simulation showed the highest standard deviation 1.7920 mm at point 7, and the lowest standard deviation 0.9121 mm at point 3.

Table 3.1.2 Summary of the comparison between DIC and simulation

<table>
<thead>
<tr>
<th>Point and Node number</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Deviation (mm)</td>
<td>1.209967</td>
<td>1.177141</td>
<td>0.912118</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Point and Node number</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Deviation (mm)</td>
<td>1.433431</td>
<td>1.338675</td>
<td>1.088829</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Point and Node number</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Deviation (mm)</td>
<td>1.792047</td>
<td>1.633311</td>
<td>1.432252</td>
</tr>
</tbody>
</table>
3.2. Convergence Study

Four mesh densities were studied and listed as follow,

Table 3.2.1 Mesh density setting

<table>
<thead>
<tr>
<th>Mesh</th>
<th>Coarse</th>
<th>Middle</th>
<th>Fine</th>
<th>Finest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average individual element edge size (mm)</td>
<td>1.5</td>
<td>1</td>
<td>0.75</td>
<td>0.55</td>
</tr>
<tr>
<td>Number of element</td>
<td>1891</td>
<td>4096</td>
<td>8004</td>
<td>14615</td>
</tr>
</tbody>
</table>

From coarse to the finest mesh, the number of elements was double at each increment. The results of the maximum displacement four simulations with respect to time were plot as follow,

![Plot of maximum displacements of four mesh densities with respect to time](image)

Figure 3.2.1 Plot of maximum displacements of four mesh densities with respect to time

The finest mesh density was studied to ensure the convergence of the subsequent simulation studies. The four mesh densities had similar maximum displacements. The
curves for coarse, middle and fine mesh are almost overlapping with each other. The finest mesh had slightly lower maximum displacements.

There was no significant difference observed among coarse, middle and fine mesh. The maximum displacement difference between coarse and middle mesh had the lowest derivation. Both middle-coarse and fine-coarse difference did not exceed 3%. Most of the differences between fine and finest mesh were lower than 8%. The maximum difference was 10.2015 %. Moreover, the peak difference appeared around 0.15 s. Following a significant increase, the difference was reduced to approximately 3% and then start to rise again.

3.3. Comparative Simulations

Six simulations were conducted to investigate the mechanical effect on the aortic wall after aTAA replacement. The surgical glues were removed from the viewport to obtain a direct view of the region covered by them. Additionally, the exterior edges were set as invisible to have a distinguished color distribution of that area.

3.3.1. Stress Results

Maximum In-plane principal stress under three conditions, second systole peak, second diastole and the midway from the second systole to diastole, were plotted in the propose of comparison.
Figure 3.3.1 Maximum in-plane principal stress of the anterior surfaces at the peak of systole

Figure 3.3.2 Maximum in-plane principal stress of the anterior surfaces between systole and diastole
Figure 3.3.3 Maximum in-plane principal stress of the anterior surfaces at the end of diastole

Figure 3.3.4 Maximum in-plane principal stress of the posterior surfaces at the peak of systole
Figure 3.3.5 Maximum in-plane principal stress of the posterior surfaces between systole and diastole

Figure 3.3.6 Maximum in-plane principal stress of the posterior surfaces at the end of diastole
The first geometry in each image represents the intact ascending ovine aorta. The second is the remaining aorta sutured with Dacron graft. The following four illustrations are simulations for four types of surgical glues, BioGlue, CoSeal, Crosseal, and Tisseel.

The radial stress and shear stress on the aortic wall of the anastomotic site were negligible compared with those stresses on the other sections. The axial stress was zero in every potion of the geometries throughout the simulations. Additionally, circumferential stress was the dominate stress in the simulation. It had approximately the same value with maximum in-plane principal stress.

According to the simulation results, the intact ovine aorta had the highest maximum in-plane principal stress value. The value at the point, which remained on the surgical glue covered anterior aortic wall after the replacement, was 0.205216 MPa at the peak pressure systole and 0.092631 MPa at the end of diastole. The replacement of Dacron graft considerably reduced the values on the aortic wall near the joint. The reduction was approximately three times during systole and two times under the lowest cardiac pressure. Moreover, the application of BioGlue further reduced the stress value on the aortic wall. Compared with the second image, the decrease of stress value caused by BioGlue was significant under cardiac pressure. However, there was no significant stress change observed on Tisseel, Crosseal and CoSeal applied suture site. The anterior surface exhibits higher stress values than the posterior surface.

3.3.2. Strain Results

Maximum in-plane principal strains on anterior and posterior surfaces are plotted as follow,
Figure 3.3.7 Maximum in-plane principal strain of the anterior surfaces at the peak of systole

Figure 3.3.8 Maximum in-plane principal strain of the anterior surfaces at the peak of systole
Figure 3.3.9 Maximum in-plane principal strain of the anterior surfaces at the end of diastole

Figure 3.3.10 Maximum in-plane principal strain of the posterior surfaces at the peak of systole
Figure 3.3.11 Maximum in-plane principal strain of the posterior surfaces at the peak of systole

Figure 3.3.12 Maximum in-plane principal strain of the posterior surfaces at the end of diastole
According to the observation of the difference in the geometry under the same pressure, ovine aorta showed significant dilatation compared with the Dacron graft. Additionally, the plots indicated the enlargement was significantly reduced on the aortic wall of the anastomotic site.

Both aTAA replacement with and without surgical glue was able to change the local strain values at the joint considerably. The strain value on Dacron was significantly lower than that on aortic wall. The aortic wall strain at the suture was reduced up to 136% compared with the value on the intact aortic wall. BioGlue can further restrict local derivation. It can reduce the anastomotic site aortic wall strain value by 67% on the anterior surface, and 25% on the posterior surface. Similarly, the other glues were able to reduce the strain value. However, they only have a small contribution to the reduction. Crosseal had the minimum impact at the joint. Similar to the stress results, CoSeal and Tisseel had almost the same effect. Moreover, the result on posterior surfaces was lower than the anterior surfaces.

3.4. Validation Study

The average element edge size was 1.5 mm, which was the same with the mesh of the mesh of the ovine ascending aorta. There were 2200 elements in the mesh of the cylinder. The result of cylinder simulation without constrain and the analytical result was plotted as follow,
Figure 3.4.1 Comparison of circumferential stress in cylinder simulation without constrain and in analytical result

The maximum difference between the simulation result and the analytical result was 5.33%. Most of the differences were below 5%.

The comparison of the cylinder and the aorta is shown as below,

Figure 3.4.2 Comparison of circumferential stress at the center in cylinder simulation and in the simulation study of intact aorta

The circumferential stress at the center of the external intact aortic wall had the same trend but a smaller value compared with the that in the cylinder simulation.
CHAPTER 4: DISCUSSION

The simulations showed the Dacron graft significantly constrained the movement of the anastomotic site. Consequently, the stress and strain were increased on Dacron and decreased on aortic wall. It led to a significant compliance mismatch at the suture site. Additionally, the application of surgical adhesives can aggravate the compliance mismatch. CoSeal, Crosseal, and Tisseel have a small constraint effect on the suture site. The maximum stress reduction caused by them was 11.7689%. The BioGlue has considerably higher Young’s modulus than them. It brought down the stress value up to 85% at the anterior surface. This observation showed the strain and stress on the aortic wall were sensitive to the mechanical properties of the implant and surgical adhesives.

The convergence and validation studies showed that the simulation results were reliable. The small difference between validation simulation and the simulation for intact aorta was because the selected point was on a curve with a radius smaller than 12 mm. Since the aortic wall experienced large deformations, the thickness of the aortic wall decreased significantly when the geometry was stretched by the applied pressure. Eventually, the analytical result with constant thickness, 2.64 mm, was lower than the simulation result.

The result of the mechanical effects of surgical adhesives was contradicted to the initial assumption, in which the glues with same thickness was expected to have same mechanical effects on the suture site. In this study, the stress and strain values in the local
coordinate system, which was used to define the material orientation of the aortic wall, showed the stress and strain values along axial and radial direction were significantly small compared with the circumferential stress. According to the Laplace’s Law for a homogenous material cylinder, the increase of thickness cause circumferential stress reduction. The application of the surgical glues was assumed to be able to significantly reduce the strain and stress value regardless of the mechanical properties of the adhesives. However, the application of surgical glues not only increased the thickness but also introduced a layer of the component with different material properties. Subsequently, the condition was no longer suitable for the hypothesis.

Studies have shown that the aneurysmal aortic wall has a larger physiological dilation and increased stress than the normal aorta [48]. They mutually promote each other and finally result in either dissection or rupture. On the other hand, the aTAA replacement surgery with and without surgical adhesives can decrease the stress value to a ‘safe’ level. The short-term result is proven to be considerably improved. However, the aorta is not a simple mechanical structure whose components and mechanical response to the external load would not change over time. In fact, SMCs and fibroblasts can respond to the change of the mechanical environment, and adjust the cellular structures and ECMs to recover the stress back to the ‘safe’ range. Therefore, the mechanical environment is essential to the long-term result of the surgery.

Following the surgeries, the mechanical environment is substantially changed, and the damaged soft tissue also initiates its recovering process. According to the result of the simulations, Dacron graft alone can reduce the stress at the anastomotic site by
approximately 300%. CoSeal, Crosseal, and Tisseel have a small mechanical effect on the anastomotic site. If the suture is done by a skilled hand, the long-term results of the surgeries with and without these surgical adhesives might have a little difference with each other. Nevertheless, BioGlue is stiffer than the other glues and can constrain the strain of the suture site at a lower level. Under the decreased strain and stress environment, the SMCs and fibroblasts are stimulated to restore the normal physiological condition, in which the cells experience a higher strain and stress value.

This procedure is the net effect of mechanobiology respond. Both SMCs and fibroblasts can paradoxically produce synthetic and degradative ECM molecules [39] [49]. The cells become less sensitive to the mechanical signaling. The stimulation of both TGF-β and MMP are inhibited. However, the activity of MMP is higher than TGF-β until the strain reduces to the natural level. During this procedure, ECMs are remolded with higher turnover/formation ratio [39].

Initially, on the cell membrane, the binding sites, which are primarily the Ang-II receptors and TGF-β receptors, and channels for the large molecules on the cellular membrane are closed due to the low stress on the VSMCs [50] [51]. In the ECMs, the TGF-β1, which is one of the major types of functioning TGF-β, remains inactive and attached to the latent TGF-β1 binding protein (LTBP) because the proteases show lower activity under reduced stress [52]. As a result, there is only a small amount of TGF-β bond with latency associated peptide, and large latent complex (LLC) have a lower chance to bind to integrin on the cell surface. [53] Additionally, in VSMCs, the pathways, such as Smad pathway, are suppressed, so that the gene expression and activation of TGF-β are decreased. These
changes in ECMs and VSMCs eventually lead to the reduced ECMs generation, which exhibits reduced production of fibrillin-1. The fibroblast response to this stimulation by differentiating into myofibroblasts, reducing the protein and cytokine expression including the production of collagens, matrix metalloproteases (MMPs), and tissue inhibitors of MMPs. The collagen remodeling ensured an optimized method to reconstruct the ECMs for the mechanical environment [49].

Since the body can recognize the aortic wall at the suture site as a wounded tissue, the inflammation is unavoidable process to repair the damaged tissue. Inflammatory cells such as macrophages can be recruited and infiltrate into the suture site. After the inflammatory cells contacted with the active inflammatory factors, which secreted by the wounded tissues, such as tumor necrosis factor alpha (TNF-α) and interleukins (ILs), they can trigger the inflammatory cells to generate MMPs [54]. The overexpressed MMPs can degenerate the ECMs and finally result in a thinned aortic wall.

In addition to the atrophic remodeling, the aortic wall, especially the SMCs in media, may exhibit apoptosis [55]. Over time, the aortic wall at the suture site is getting thinner. Additionally, most of the currently available surgical adhesives are biodegradable. The thinned aortic wall will be exposed to elevated pressure and flow velocity caused by the mismatched compliance at the anastomotic site after the degradation of surgical glue. As a result, the application of stiff surgical adhesives, such as BioGlue, has higher chance to get inflammation, impaired vascular growth, and stenosis of the lumen [56].

As the surgical adhesives absorbed by the body, the empty spots are replaced by connective tissues. If the blood leaks into the layer between the connective tissues and the
aortic wall, pseudoaneurysm can occur. Pseudoaneurysm is one of the most common
complications after the application of BioGlue. Postsurgical pseudoaneurysm is the
predominant indicator for reoperation. It is a lesion contains blood, which comes from the
disrupted arterial wall, locates at periarterial connective tissue [57]. Destruction of
inflammatory tissue is frequently detected during the formation of pseudoaneurysm [58].
Additionally, pseudoaneurysm can be formed following the tear of the aortic wall, which
is caused by the mismatch of stiffness between surgical glue and the soft tissue [59]. Other
complications, such as reoccur of dissection and aneurysm, may also occur following the
surgical repair [60]. Although the surgical adhesives can be consumed by the body, it still
requires months or years to degrade them completely. For example, the BioGlue can stay
in the body for two years after application. The mechanical constrains of the surgical
adhesives may last until they are totally consumed. Consequently, the stiff surgical
adhesives have a higher risk of complications, which caused by adverse tissue remodeling.
Therefore, the surgical adhesive should be evaluated by comparing the benefits and the
long-term outcomes.

Since this study was based on the in-vitro test result and FE simulation, there are
limitations in this study. Ovine aorta was used in this study. Its mechanical properties and
normal aortic pressure are different from that of human aorta. Moreover, the normal
physiological parameters of the sheep, such as weight, gender, age, and medical history,
are unknown. They are critical factors which can considerably affect mechanical properties
of the specimen.
The received ovine aortas were attached to lung and connective tissues. As a result, the lungs were removed, and the connective tissues were cleaned by using a blunt-blunt scissors. This procedure took about 3 hours due to the quantity of specimen. Additionally, the specimens were preserved in the refrigerator for 48 hours until the DIC system became available. These procedures can cause the change in mechanical properties.

The DIC test result was highly correlated with the quality of the mesh patterns and the software. Though, keeping the pattern unimpaired on a soft tissue was difficult. For example, the wet surface was reflecting the light, some of the surfaces could not be captured due to the glare. Furthermore, the soft tissue in this study was pressurized with normal saline solution. A small amount of solution could leak from the fixation and wash the patterns away under high pressure. Consequently, some of the surfaces could not be generated in the software. During the test, the top end of the ovine ascending aorta was not entirely fixed. It led to prolonged computational time in the simulation for the optimization.

The optimization result would be more accurate if the data on every surface, including the two mirrored surfaces, were used. Nevertheless, the result was not optimized for the mirrored surfaces because there were no reference points found in the mirror images. Additionally, the optimization simulation had multiple limitations. Firstly, the geometry used for the optimization may not represent the reality. In the optimization, ovine ascending aorta geometry was assembled with aortic sinus to simplify the boundary condition. It would lead to an unrealistic loading condition at the bottom portion. Secondly, the pressure used in the optimization was idealized. Although hydrostatic pressure was applied during DIC test, the pressure was assumed to be constant throughout the ascending aorta.
Moreover, the geometry constructed from the DIC measurement was not under zero pressure because the recorded initial pressure was 20 mmHg. The geometry at zero pressure can be obtained by using backward incremental method [61]. However, this method was not implemented due to the limitation of time. Instead, 20 mmHg pressure was subtracted from the pressure result and applied on the initial geometry. Lastly, due to the limitation of the optimization time, the final result has high standard derivations. The result could be more reliable if the result has lower standard derivation.

In the comparative simulation study, in which six simulations were conducted to investigate the mechanical effect of surgical adhesives on suture site, some of the conditions were idealized. Firstly, the Dacron and aorta were assumed to be smoothly linked by suture without any overlapping. They were defined as one surface separated into top and bottom part, which defined as Dacron and ovine ascending aorta, respectively. Moreover, the interaction between the aorta-Dacron geometry and the glue was idealized as rough contact, which indicates there is no relative movement happens between the two surfaces. In result, it would be more precise if the cohesive behavior was assigned to the interface. Finally, the pressure was defined as uniformly distributed and perpendicular to the aortic wall. However, blood is pumping from the left atrium to the aorta in normal physiological condition. The movement of the flow can exert the force along the axial direction on the interior aortic wall. Therefore, the axial stress and shear stress on the aortic wall could not be investigated in this study. Shear stress has been studied and shown a close relation with SMCs differentiation and proliferation [62].
CHAPTER 5: CONCLUSION AND FUTURE WORKS

5.1. Conclusion

The enlargement of aTAAs can lead to fatal results, such as dissection and rupture. Dacron graft is commonly used to replace the pathologically changed aorta. In order to improve the hemostasis and strength of the suture site, surgical adhesives are frequently used in the surgeries. In this study, the mechanical properties were optimized based on DIC measurement, and the mechanical effects of the aTAA replacement with and without surgical glue were studied via FE simulations.

DIC is an image related noninvasive method, which records the mechanical response and corresponding geometry simultaneously. These features can significantly improve the accuracy of the result compared with the traditionally invasive mechanical properties research method, such as uniaxial and biaxial stretching.

According to the result, the mechanical properties of the implant and surgical adhesives play an essential role in the mechanical response. Soft glues, such as CoSeal, Crosseal, and Tisseel, have little effect on the mechanical reactions compared with surgical repairs only with Dacron graft. Despite the chemical effect of the surgical glue, they would have the similar long-term result to the aortic wall. On the other hand, stiff glue, such as BioGlue, can further decrease the stress and strain near the joint. It would aggravate the compliance mismatch and lead to adverse tissue remodeling.
In summary, the stiff surgical glues can increase the mismatch compliance and the risk of complications, such as aortic stenosis, adventitial inflammation, and reoccurrence of an aneurysm. Therefore, the surgical glue should be evaluated by comparing advantages and drawbacks before usage. The goal of the future design of graft and surgical adhesives is suggested to minimize the compliance mismatch between the graft, adhesives, and tissue to decrease the risk of adverse tissue remodeling.

5.2. Future Work

In the future work, fresh human hearts, with detailed physiological condition report, would be used as the model to obtain a reliable result for a human. During DIC test the fixation method would be improved so that the boundary condition can be simplified to both ends fixed in six DOFs. Additionally, the zero-pressure geometry would be recorded to avoid the deviation of the aortic mechanical property result. In this way, the accuracy can be increased and the computational time can be considerably reduced.

This study is limited to the in-vitro condition. The in-vivo environment is more complicated than the assumptions. The cellular reaction not only relates to the mechanical environment but also involve many biochemical stimulations. Moreover, the components of the glue are usually stored separately, and mixed upon use. Accordingly, the mechanical properties of the surgical glue can vary significantly based on the application method, component ratio, and chemical bonding. Therefore, subsequent in-vivo studies should be conducted to verify the result in this study. The tagged-MRI is one of the potential method for in-vivo study. It can be used replace the DIC measurement to analysis the in-vivo postsurgical displacement result.
REFERENCES


APPENDIX

The results of the simulations at one point of the surgical glue covered aortic wall is listed as follow. The relative differences are calculated by comparing with the results from the simulation for remain aorta and Dacron graft.

Table A.1 The stress and strain comparison at the peak of second systole

<table>
<thead>
<tr>
<th>Maximum In-Plane Principal Stress</th>
<th>Aorta</th>
<th>Aorta-Dacron</th>
<th>BioGlue</th>
<th>CoSeal</th>
<th>Crosseal</th>
<th>Tisseel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior (MPa)</td>
<td>0.2052</td>
<td>0.052504</td>
<td>0.01210</td>
<td>0.04632</td>
<td>0.04966</td>
<td>0.0483</td>
</tr>
<tr>
<td>Relative Difference (%)</td>
<td>290.86</td>
<td>0.0000</td>
<td>76.9384</td>
<td>11.7698</td>
<td>5.4187</td>
<td>8.0031</td>
</tr>
<tr>
<td>Posterior (MPa)</td>
<td>0.1825</td>
<td>0.041207</td>
<td>0.02546</td>
<td>0.04237</td>
<td>0.04364</td>
<td>0.0421</td>
</tr>
<tr>
<td>Relative Difference (%)</td>
<td>342.89</td>
<td>0.0000</td>
<td>38.2106</td>
<td>2.8238</td>
<td>5.9255</td>
<td>2.2033</td>
</tr>
<tr>
<td>Max In-Plane Principal Logarithmic Strain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>0.5069</td>
<td>0.263563</td>
<td>0.08633</td>
<td>0.24936</td>
<td>0.25016</td>
<td>0.2508</td>
</tr>
<tr>
<td>Relative Difference (%)</td>
<td>92.35</td>
<td>0.0000</td>
<td>67.2450</td>
<td>5.3862</td>
<td>5.0846</td>
<td>4.8303</td>
</tr>
<tr>
<td>Posterior</td>
<td>0.4857</td>
<td>0.205611</td>
<td>0.14235</td>
<td>0.20785</td>
<td>0.21953</td>
<td>0.2089</td>
</tr>
<tr>
<td>Relative Difference (%)</td>
<td>136.26</td>
<td>0.0000</td>
<td>30.7644</td>
<td>1.0919</td>
<td>6.7706</td>
<td>1.6473</td>
</tr>
</tbody>
</table>
Table A.2 The stress and strain comparison at the mid-point between second systole and diastole

<table>
<thead>
<tr>
<th>Maximum In-Plane Principal Stress</th>
<th>Aorta</th>
<th>Aorta-Dacron</th>
<th>BioGlue</th>
<th>CoSeal</th>
<th>Crosseal</th>
<th>Tisseel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior (MPa)</td>
<td>0.146934</td>
<td>0.037312</td>
<td>0.007946</td>
<td>0.037593</td>
<td>0.040776</td>
<td>0.038278</td>
</tr>
<tr>
<td>Relative Difference (%)</td>
<td>293.7961</td>
<td>0.0000</td>
<td>78.7039</td>
<td>0.7512</td>
<td>9.2828</td>
<td>2.5890</td>
</tr>
<tr>
<td>Posterior (MPa)</td>
<td>0.124832</td>
<td>0.030666</td>
<td>0.021054</td>
<td>0.032868</td>
<td>0.03522</td>
<td>0.032523</td>
</tr>
<tr>
<td>Relative Difference (%)</td>
<td>307.0724</td>
<td>0.0000</td>
<td>31.3434</td>
<td>7.1826</td>
<td>14.8511</td>
<td>6.0550</td>
</tr>
<tr>
<td>Max In-Plane Principal Logarithmic Strain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>0.442899</td>
<td>0.204573</td>
<td>0.069611</td>
<td>0.207568</td>
<td>0.210545</td>
<td>0.210095</td>
</tr>
<tr>
<td>Relative Difference (%)</td>
<td>116.4992</td>
<td>0.0000</td>
<td>65.9727</td>
<td>1.4640</td>
<td>2.9193</td>
<td>2.6993</td>
</tr>
<tr>
<td>Posterior</td>
<td>0.407482</td>
<td>0.162302</td>
<td>0.121202</td>
<td>0.172792</td>
<td>0.188192</td>
<td>0.172136</td>
</tr>
<tr>
<td>Relative Difference (%)</td>
<td>151.0641</td>
<td>0.0000</td>
<td>25.3232</td>
<td>6.4633</td>
<td>15.9517</td>
<td>6.0591</td>
</tr>
</tbody>
</table>
Table A.3 The stress and strain comparison at the end of second diastole

<table>
<thead>
<tr>
<th>Maximum In-Plane Principal Stress</th>
<th>Aorta</th>
<th>Aorta-Dacron</th>
<th>BioGlue</th>
<th>CoSeal</th>
<th>Crosseal</th>
<th>Tisseel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior (MPa)</td>
<td>0.092631</td>
<td>0.0288796</td>
<td>0.00423</td>
<td>0.02432</td>
<td>0.028727</td>
<td>0.028399</td>
</tr>
<tr>
<td>Relative Difference (%)</td>
<td>220.7492</td>
<td>0.0000</td>
<td>85.3525</td>
<td>15.7880</td>
<td>0.5294</td>
<td>1.6659</td>
</tr>
<tr>
<td>Posterior (MPa)</td>
<td>0.077451</td>
<td>0.0230342</td>
<td>0.015223</td>
<td>0.022475</td>
<td>0.02747</td>
<td>0.022967</td>
</tr>
<tr>
<td>Relative Difference (%)</td>
<td>236.2448</td>
<td>0.0000</td>
<td>33.9104</td>
<td>2.4294</td>
<td>19.2592</td>
<td>0.2900</td>
</tr>
<tr>
<td>Max In-Plane Principal Logarithmic Strain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>0.347464</td>
<td>0.169516</td>
<td>0.05305</td>
<td>0.149955</td>
<td>0.15695</td>
<td>0.163246</td>
</tr>
<tr>
<td>Relative Difference (%)</td>
<td>104.9742</td>
<td>0.0000</td>
<td>68.7050</td>
<td>11.5393</td>
<td>7.4129</td>
<td>3.6988</td>
</tr>
<tr>
<td>Posterior</td>
<td>0.308066</td>
<td>0.124368</td>
<td>0.099479</td>
<td>0.128433</td>
<td>0.148156</td>
<td>0.128531</td>
</tr>
<tr>
<td>Relative Difference (%)</td>
<td>147.7052</td>
<td>0.0000</td>
<td>20.0125</td>
<td>3.2685</td>
<td>19.1271</td>
<td>3.3473</td>
</tr>
</tbody>
</table>
Table A.4 (left) The circumferential stress comparison between simulation and analytical results; (right) analytical result of thickness and radius at the corresponding time

<table>
<thead>
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