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Tissue Engineering: Proposed Graft for Aortic Aneurysms

D-Dré Déani Wright

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By
D-Dré Déani Wright

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Dr. Arlene Courtney (Primary), Department of Chemistry and Dr. Michael LeMaster (Secondary), Department of Biology,
Thesis Advisors

Dr. Gavin Keulks,
Honors Program Director

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Abstract

The aorta is the main vessel exiting the heart, providing oxygenated blood to the systemic circulatory system. Because of its close proximity to the heart, the aorta must withstand and absorb high pressures. Not surprisingly, one of the most common problems associated with the aorta is due to this high-pressure environment, that being an aortic aneurysm. An aortic aneurysm is a rupture in a portion of the aortic wall that can potentially lead to death. To repair an aortic aneurysm, there are two surgeries, open chest surgery and endovascular aneurysm repair (EVAR), both of which insert stent grafts into the aorta to exclude the aneurysm. Complications can arise from either of these techniques or the stent graft used for repair. An autologous native vessel would be best in mimicking the native aorta, but given the current and near-future research, a biological stent graft could reduce the complications associated with the current procedures and stent grafts.

Introduction

The aorta is the largest artery in the human body. This vessel stems from the left ventricle of the heart and functions to deliver oxygen-rich blood to organs and tissues of the body. The entrance to the aorta is controlled by the aortic semilunar valve with the vessel then divided into four regions (Figure 1): the ascending (thoracic) aorta, aortic arch, descending (thoracic) aorta, and descending (abdominal) aorta. The wall of the aorta consists of three layers, the tunica adventitia, tunica media, and tunica intima[1].

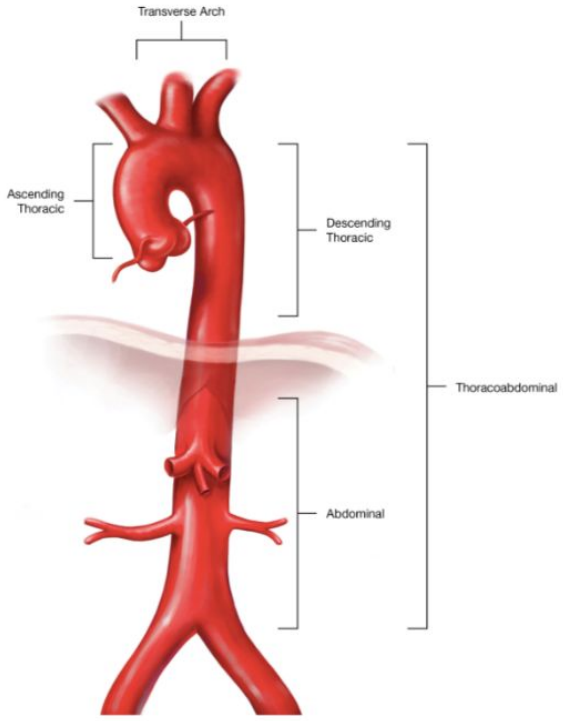

Figure 1: The aorta's regions[2].

The aorta must withstand high amounts of blood pressure with each heartbeat as it is the only artery stemming from the left ventricle of the heart. When the left ventricle of the heart contracts, blood is forced through the aorta causing it to expand. This expansion provides potential energy that helps the body maintain blood pressure during diastole, the

relaxation phase of the heart[28]. The aorta contains aortic baroreceptors, mechanical sensors that detect changes in blood pressure (Figure 2). An increase in blood pressure will trigger an increase in baroreceptor firing. This will cause an increase in cardiac inhibitor centers and a decrease in both cardiac accelerator centers and vasomotor centers thus leading to a decrease in cardiac output as well as an increase in vasodilation. Eventually, blood pressure will drop. Conversely, a decrease in blood pressure will trigger a decrease in baroreceptor firing. This will cause a decrease in cardiac inhibitor centers and an increase in both cardiac accelerator centers and vasomotor centers, thus leading to an increase in cardiac output and an increase in vasoconstriction. This will cause blood pressure to increase. As the blood pressure drops or increases, homeostasis is restored[63]. Because the aorta must withstand high amounts of blood pressure, any problems that occur could lead to a serious medical emergency.

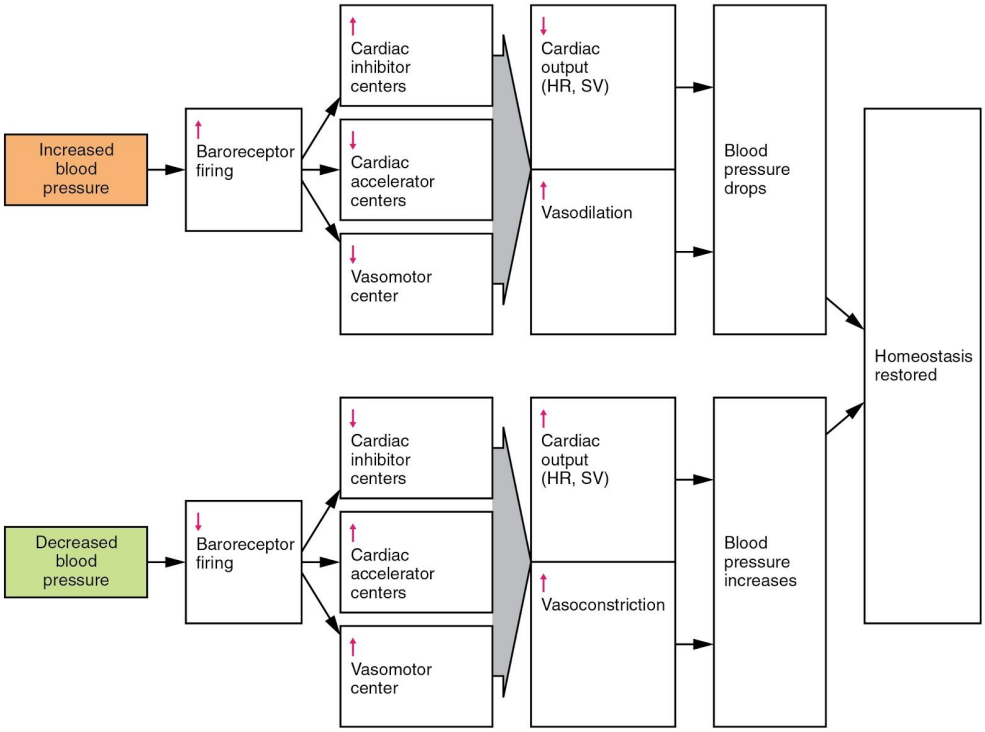

Figure 2: Flow chart of baroreceptors monitoring blood pressure[63].

An aortic aneurysm is one medical emergency that might arise. An aortic aneurysm starts as the weakening of the aortic wall leading to a bulging in a portion of the aorta. Once the aorta is 1.5 times its original size, an aneurysm is considered to have developed. Aortic aneurysms are dangerous because they can rupture and cause internal bleeding which could lead to death if not treated quickly. Aortic aneurysms most commonly occur in men as well as individuals who have a history of smoking. Additional factors linked with aortic aneurysms are high blood pressure, race, age, family history, or history of previous aneurysms[29]. About 200,000 people in the United States are diagnosed with an aortic aneurysm each year with about 15,000 fatalities annually from ruptured aneurysms. The incidence of aortic aneurysms in the United States has tripled over the past 30 years, with 95% of aneurysms treatable if they are detected early enough[39].

There are currently two procedures used to treat aortic aneurysms: open repair and endovascular aneurysm repair (EVAR). For both procedures, a stent graft, which is a woven polyester tube wrapped around a metal netting, is used (Figure 3). Open repair replaces the site of the aneurysm with a stent graft and has the aortic wall wrapped around it whereas EVAR places the stent graft in the aortic wall and is sewn in above and below the aneurysm site[14].

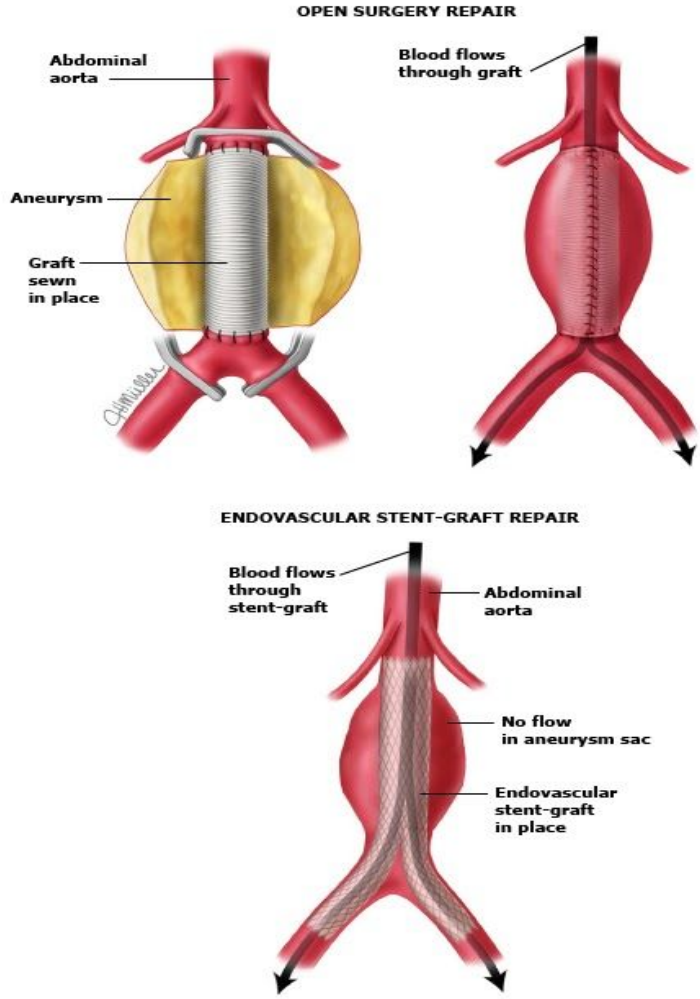

Figure 3: Stent graft placement in open surgery repair and EVAR[14].

While both procedures are able to repair the aneurysm, disadvantages do exist for each with one example being device migration, where the stent moves from the original implantation site.

The scope of my Honors' thesis is to research the aorta, aortic aneurysms, and the procedures used to repair them. Thereafter, I will attempt to utilize concepts in tissue engineering to suggest a biological or synthetic vascular graft that has a limited risk of complication and could be used in both open and EVAR surgeries. Such a graft could potentially save the lives of those who suffer from an aortic aneurysm. I do not expect to be able to solve such a complex medical issue given my limited biomedical research training, but my hope is to provide a starting point for future research.

Literature Review

Aorta

The aorta functions to deliver oxygenated blood which travels from the left ventricle of the heart to the aorta through the aortic semilunar valve. Not only does the aorta serve as a conduit for blood during ventricular systole, but it also acts as a reservoir for blood. Because of the aorta's elastic properties, half of the blood ejected from the heart per beat can be stored in the aorta followed by being pushed into peripheral circulation. This is known as the Windkessel function (Figure 4). This accounts for the aorta being able to convert the pulsatile flow of blood from the heart to smooth flow through other vessels downstream[28].

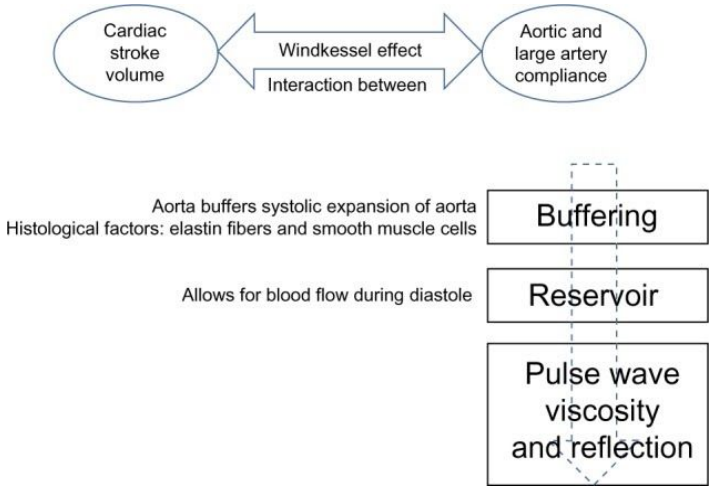

Figure 4: Diagram of the Windkessel effect[28].

The aorta can be divided into four regions: the ascending (thoracic) aorta, aortic arch, descending thoracic aorta, and abdominal aorta. The ascending aorta, stemming from the left ventricle, feeds the right and left coronary arteries which branch back to

supply the heart with oxygen and nutrients. The ascending aorta leads to the aortic arch where the vessel bends 180 degrees before turning into the descending aorta and descends to the descending thoracic aorta thus creating a loop or arch. The brachiocephalic trunk, left common carotid artery, and left subclavian artery branch from the aortic arch and serve as the pathway for blood to the upper body. The descending thoracic aorta travels behind the heart down to the diaphragm muscle between the ribs. It starts on the left side of the vertebrae, winds around the vertebrae, and ends in the front. The final portion of the aorta is the abdominal aorta which originates at the diaphragm and descends to the mid-abdomen where it splits into the two common iliac arteries supplying blood to the lower limbs and vital abdominal organs such as the liver, kidney, and intestines[4]. The dimensions of the aorta are important in determining a graft for it because it will need to be aligned and to allow for an adequate amount of blood flow. The ascending aorta is about 3 cm, the descending thoracic aorta is about 2.5 cm and the abdominal aorta ranges from about 1.8-2 cm. It should be noted that these diameter lengths vary based on age and sex[18].

The aortic wall consists of three layers, the tunica adventitia, tunica media, and tunica intima (Figure 5).

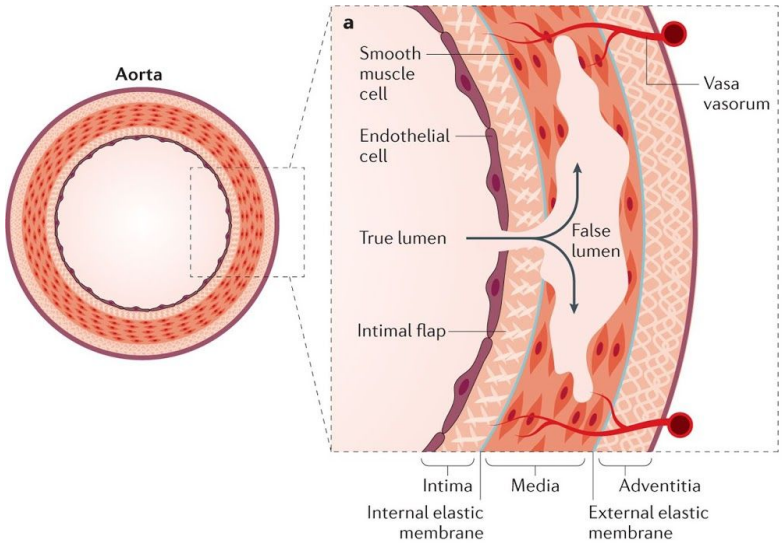

Figure 5: The aortic wall[32].

The tunica adventitia, the outermost layer, is composed of collagenous and elastic fibers which surround vessels (vasa vasorum) and nerves (nervi vascularis), and provides additional support and structure to the aorta so it does not over-expand. The tunica media is the middle layer composed of several layers of smooth muscle surrounded by elastic fibers which are enfolded by collagen fibers and proteoglycans. This bundle, known as the lamellar unit, forms the extracellular matrix. The lamellar unit itself is responsible for the tensile strength and elastic recoil properties of the aorta. This lets the aorta withstand high pressures with dilatation followed by returning to its initial diameter. This layer also allows for the expansion and contraction of the aorta with each heartbeat. It also regulates blood flow between arteries and capillaries which allow for efficient exchange of gases and nutrients when blood is within the capillaries. The tunica intima is the innermost layer which is thin and composed of endothelial cells, subendothelial tissue, and an internal elastic lamina. Elastin within the aortic wall is distensible and has a low tensile

strength. It functions as an elastic reservoir and distributes stress evenly to the wall and the collagen fibers. The extracellular matrix is designed to provide elastic recoil for the aortic wall as well as provide structural and mechanical properties needed for vessel functioning[57]. As previously noted, collagen, elastin, and smooth muscle cells all play a large role in the aorta's function.

The aorta undergoes various types of stress and strain (Figure 6) and must be able to withstand them all otherwise something requiring immediate medical attention may occur.

Stress	Force per area
Normal stress	Stress perpendicular to the area
Shear stress	Stress parallel to the area
Wall shear stress (WSS)	Stress induced by blood flowing over the valve or the luminal side of the vascular wall
Laminar shear stress	Shear stress caused by a streamlined flow
Oscillatory shear stress	Shear stress caused by oscillatory flow
Strain	Deformation measure
Normal strain	Relative changes in length of a line
Shear strain	Relative changes in angle of a square
Isochoric (isovolumetric)	Constant volume
Isotropic	Uniform in all directions
Vortical structures (VS)	Spatial region, within which the fluid is at rotational (vortical) motion
Finite element method (FEM)	Numerical concept to solve structural or fluid-mechanical problems
Computational flow dynamics (CFD)	Numerical method to compute fluid flow from given initial conditions
Fluid structure interaction (FSI)	Method to prescribe the mechanical interaction between fluid and solid domains

Figure 6: Biomechanics of the aortic wall and aortic valves[45].

The extracellular matrix in the aorta withstands a majority of the wall stress. There is arterial pressure associated with the aorta when blood is pumped out of it which can be translated into tension-dominated mechanical wall stress. As for the blood flow over the valvular and vascular endothelial layer, this induces a wall shear stress. The aorta inflates

causing the wall to deform isochorically essentially keeping the volume the same. Two different directions the aortic wall can inflate are circumferentially and axially (Figure 7) which both lead to thinning of the wall. They also act as the dominating stresses in the wall.

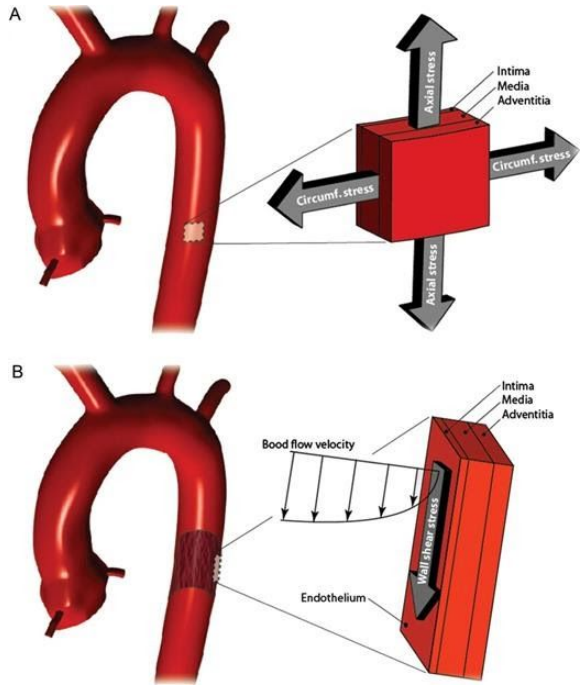

Figure 7: (*A*) Circumferential and axial stress directions on the aorta. (*B*) Consequential wall shear stress from blood flow over the endothelial layer[3].

Strain must also be maintained in the aorta. With the aorta being dynamically pressurized withstanding an average of 120 mmHg, the stress and strain on the wall will oscillate with the cardiac cycle. This stress and strain could lead to aortic stiffness. This exertion can induce a change sensed by structural cells like vascular smooth muscle cells as well as alter the extracellular matrix which could both lead to a structural change of the aorta. Aortic stiffness is described as an elastic resistance to deformation. It is affected by interactions between smooth muscle cells and the extracellular matrix which contains

elastin, collagen, and fibrillin fibers. If there is an increase in stiffness, there will be a decrease in aortic compliance because the aorta will lose its flexibility and extensibility needed to withstand high pressures. For example, aging can increase aortic stiffness which leads to a loss of collagen amount and affects an increment of collagen concentration and collagen subtypes. Three fundamental aspects of the dynamics of blood flow in the arterial wall are blood velocity, blood pressure, and rhythmic flow (pulsatility). The predominant regulators of convection would be endothelial permeability, elastic lamina integrity, and the physicochemical properties of the molecules such as mass, charge, an affinity for wall components, and hydrophilic properties[44].

The collagen and elastin network are primarily responsible for the passive mechanics of the aorta, and smooth muscle cells provide contractility and facilitate blood flow. Collagen is a structural protein with 5 types present in the aorta (Figure 8).

Collagen Type	Principle Tissue Distribution	Cells of Origin
I	Loose and dense ordinary connective tissue; collagen fibers	Fibroblasts and reticular cells; smooth muscle cells
	Fibrocartilage	
	Bone	Osteoblast
	Dentin	Odontoblasts
II	Hyaline and elastic cartilage	Chondrocytes
	Vitreous body of the eye	Retinal cells
III	Loose connective tissue; reticular fibers	Fibroblasts and reticular cells
	Papillary layer of dermis	
	Blood vessels	Smooth muscle cells; endothelial cells
IV	Basement membranes	Epithelial and endothelial cells

Figure 8: Table of different types of collagen with their tissue distribution and cells of origin[24].

Type I and III collagen also known as fibrillar collagens are the most prevalent types in the aorta. They can be considered the most important aspect of the aortic wall because they account for about 80-90% of the total collagen present in the aorta and can be affected by many different factors such as aging, sex hormones, and aneurysms. Types IV and V of collagen are also present, but only in the endothelial and smooth muscle cell basement membranes along with types I and III. Types I, III, IV are localized in the tunica intima and media in the ascending aorta. Types I and IV are present in the descending thoracic aorta in the tunica intima and media layers. Type III is also present in the descending thoracic aorta, but its localization is variable. As for the abdominal aorta, types I and IV are found in the intima and media layers and type III is localized heavily in the adventitia layer. The presence of type III collagen in the aortic wall increases the flexibility of the collagen fibrils. As for type I collagen, studies have shown it plays a role in the biomechanical and functional properties of the aorta. However, in the presence of homotrimeric type I collagen isotype, the aorta is significantly weakened. Most mature collagen molecules are cross-linked together by lysyl oxidase. These cross-links stabilize collagen fibrils and provide stiffness to vessels. The collagen within the lamellar units previously discussed has no definitive arrangement at low pressures, but at high pressures, they are recruited to support passive wall tension and restrict aortic distention[34].

The elastic fibers in the aorta allow it to expand and contract with each heartbeat. It is a multi-component structure with the main protein being elastin. Elastin itself is

composed of tropoelastin which is highly cross-linked and forms an insoluble complex. It contains mostly glycine and valine as well as modified alanine and proline structures[55].

The extracellular matrix, in general, achieves organism-specific mechanical properties. It withstands a majority of the stress on the aortic wall, provides elastic recoil, and provides structural and mechanical properties. It is primarily composed of two structural proteins, collagen, and elastin. The ratio between the two determines mechanical properties and smooth muscle cell phenotype and function. The extracellular matrix is critical for proper development. During development, smooth muscle cells start expressing extracellular matrix structural proteins causing an increase in wall thickness as elastin and collagen get added between the cell layers[6].

Smooth muscle cells are important in that they regulate contraction and dilation of the aorta to maintain vascular homeostasis, blood pressure, and flow. They are the most numerous cell type in arteries such as the aorta. Through different pathologies such as aneurysms, their contractile function may be compromised. With a loss of function, there could be a change in the mechanical environment in which the cells are exposed[45].

Aortic Aneurysms

Aortic aneurysms can occur anywhere in the aorta and can either cause a bulge or rupture in the aortic wall. It usually starts as a weakening of the aortic wall which may then lead to a rupture if left untreated. Once the aorta is 1.5 times its normal size, it is considered an aneurysm. Because the aorta is vitally important and needed for everyday functioning, an aortic aneurysm can lead to death in minutes because the pathway for the supply of oxygenated blood has been altered thus not enough blood going to the tissues

of the body. There are three types of aortic aneurysms, a thoracic aortic aneurysm (TAA), an abdominal aortic aneurysm (AAA) which is the most common, and a thoracoabdominal aortic aneurysm[29] (Figure 9).

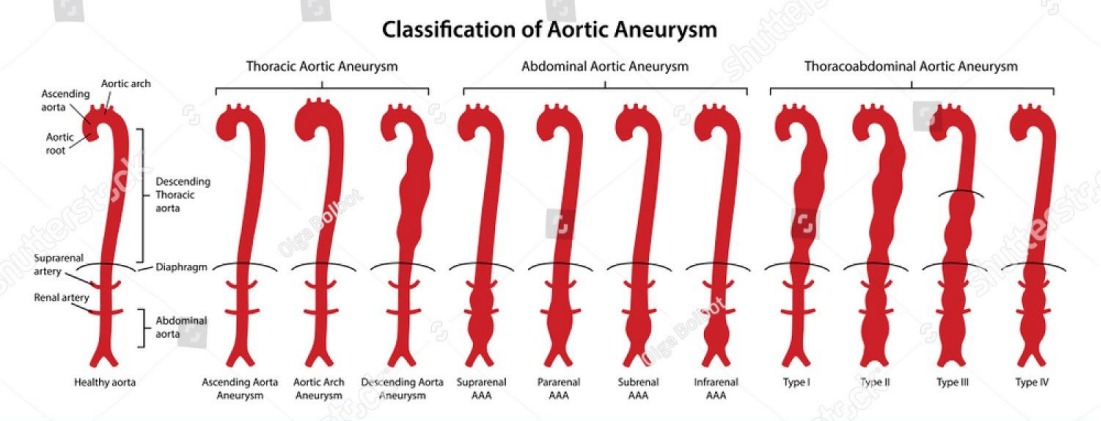

Figure 9: Classification of aortic aneurysms[11].

As each name entails, the thoracic aortic aneurysm (TAA) occurs in the chest region. This includes the ascending aorta, the aortic arch, and the descending thoracic aorta. Abdominal aortic aneurysms occur in the abdomen while thoracoabdominal aortic aneurysms can occur anywhere within both portions. Aortic aneurysms can also be classified by shape. It can either be fusiform, a uniform, tube-shaped, or it can be saccular which is small, round, and lopsided[56] (Figure 10).

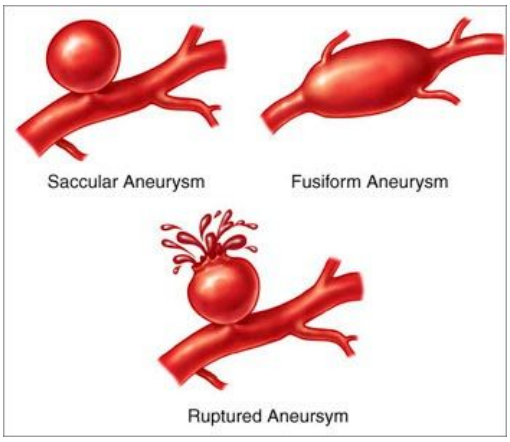

Figure 10: Type of shape for aneurysms[7].

The mechanisms of action for thoracic and abdominal aortic aneurysms (AAA) are very similar, however, there are a few differences between each type. Aortic aneurysms involve extensive structural remodeling and are characterized by the degradation of elastin, extracellular matrix proteins, loss of smooth muscle cells, and abnormal collagen. Apoptosis of smooth muscle cells and degradation of the tunica media have been strongly associated with AAA. Some things that cause apoptosis of smooth muscle cells are inflammation, production of reactive oxygen species, and stress from the endoplasmic reticulum. Structural integrity is lost with the apoptosis of smooth muscle cells thus causing the aorta to dilate and eventually rupture. In both thoracic and abdominal aortic aneurysms, the amount of elastin, collagen, and glycosaminoglycans are reduced compared to a normal aorta. Most of these changes are caused by matrix metalloproteinases and their inhibitors. Various types of metalloproteinases have been associated with AAAs. Inflammation, reactive oxygen species, and changes in the extracellular matrix all play a role in the formation of aortic aneurysms. The difference between a thoracic and aortic aneurysm is that the TAA can be broadly categorized as

syndromic, familial nonsyndromic, and sporadic with the latter category being diverse. The heterogeneity of a TAA makes it more complex particularly in the mechanistic studies of human samples and animal models. TAA is a multifactorial disease which allows it to have multiple mechanisms of action[22].

One mechanism for a TAA (Figure 11) is as follows: The mechanical forces push against the aortic wall inducing cellular and molecular responses. In the cellular response, the sensed mechanical force leads to a phenotypic switch from contractile vascular smooth muscle cells to secretory vascular smooth muscle cells. This switch will then lead to a change in matrix metalloproteinase, an increase in angiotensin II production, and a change in extracellular matrix compounds. Fibroblast's response to the mechanical force will lead to the activation of latent transforming growth factor beta in the matrix. These will all lead to a molecular response in the extracellular matrix. The imposed mechanical force will cause the elastic fibers to stretch leading to adaptive remodeling thus forming the bulge in the aorta[22].

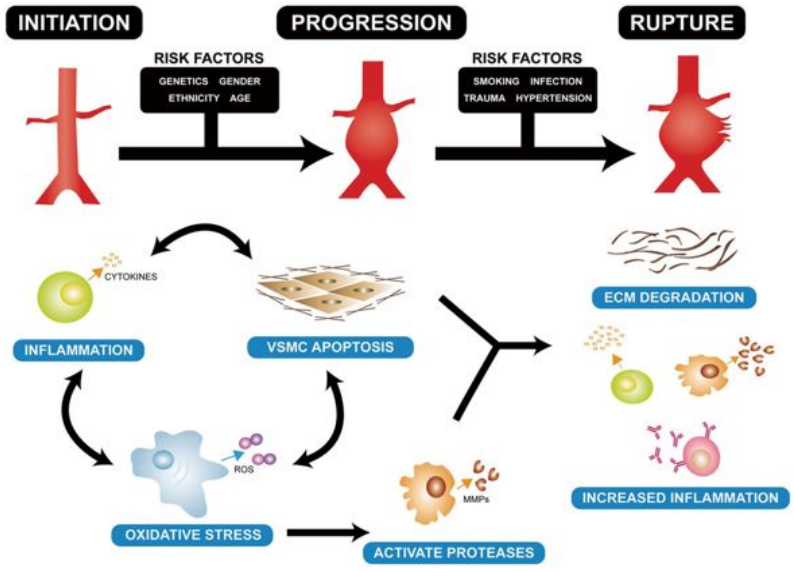

Figure 11: General aortic aneurysm mechanism[21].

A mechanism for AAA (Figure 12) based on genetic predisposition factors like age greater than 60, cigarette smoking, male gender, hemodynamic stress, and some others, starts with leukocyte recruitment into the tunica media. As lymphocytes and macrophages enter the aortic wall, there will be a production of pro-inflammatory molecules. The macrophages will produce proenzyme forms of metalloproteinases that become activated in the extracellular space. Sometimes tissue inhibitors of matrix metalloproteinase come in and neutralize them, but they are not able to prevent degradation of the structural matrix proteins like elastin and collagen. For years, metalloproteinase mediated elastin degradation, cyclic strain, and elevated wall tension will progressively cause aortic dilation. Collagen degradation will occur further weakening the wall. Smooth muscle cell death and senescence will lead to a depletion in smooth muscle cells causing disorganization in collagen. A cellular immune response is induced by the infiltration of T cells, B lymphocytes, plasma cells, and dendritic cells in the aneurysm tissues. Essentially, the promotion of micro-RNA 29 induces the degradation of the extracellular matrix followed by the formation of aneurysms. In general, when leading to an aortic aneurysm, there will be a decrease in collagen fiber, stenosis or stiffening of the vasa vasorum, and an increase in elastin fiber fragmentation. It will get enlarged, and there will be an increase in adipocytes followed by an increase in macrophage infiltration and metalloproteinases 2 and 9. This will all induce a bulge followed by a rupture of the aortic wall[26].

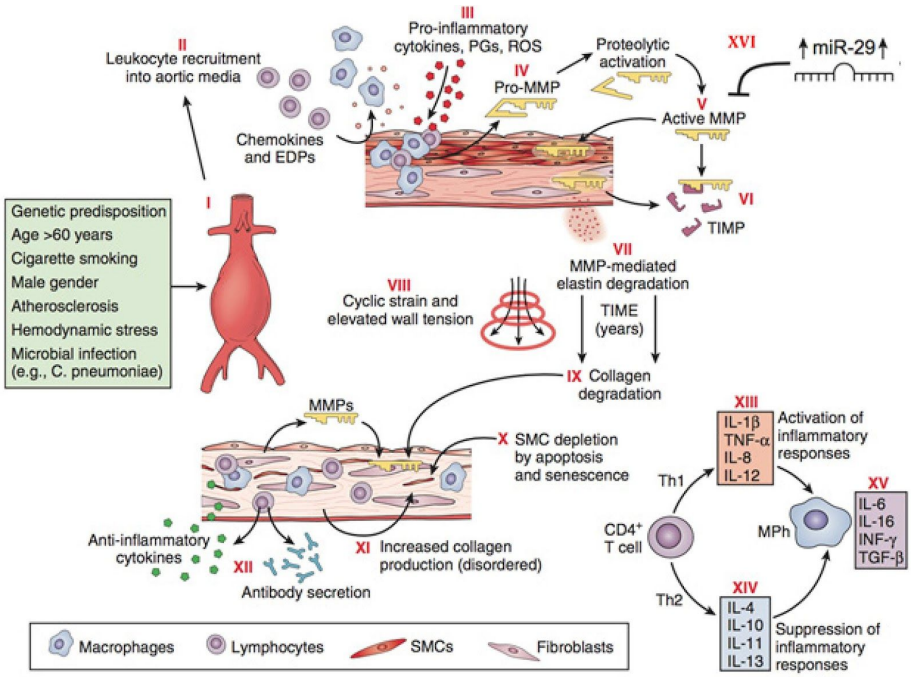

Figure 12: AAA mechanism[26].

Open Surgery vs Endovascular Aneurysm Repair

There are two procedure options for aneurysm repair, open chest/abdominal surgery or endovascular aneurysm repair (EVAR). In open surgery, the graft replaces the weakened portion of the aorta and the aortic wall is wrapped around it. To access the damaged artery, the surgeon must make a large incision in the chest or abdomen depending on where the aneurysm is located. For EVAR, a stent graft is placed in the aortic wall and secured to the aorta by being sewn in above and below the aneurysm. During the procedure, a surgeon will make two small punctures into the groin and insert a catheter equipped with the stent graft into the blood vessel. Through the use of X-ray technologies, the surgeon guides the catheter and stent graft up to the damaged area. Both have their advantages and disadvantages; it is still a matter of debate whether one procedure is “better” than the other.

Open surgery is the traditional dated procedure used to treat aortic aneurysms. Both open surgery and EVAR have a relatively high recovery rate of 93%-97% and 98%-99% respectively, however, their recovery time vastly differs. Because EVAR is minimally invasive, it is less painful and usually takes a patient about 2-4 weeks to recover. As for open surgery, there is a 3-6 month recovery period along with a higher surgical complication risk because of its invasiveness. Open surgery has a higher mortality rate of about 5% whereas when EVAR was introduced, it had a mortality rate of 2.4% in 2008. Though there is a notable difference in mortality rates between the two procedures, trials such as the DREAM, OVER, ACE, and EVAR I have shown that the early, high survival rates affiliated with EVAR only lasted around 3 years until the survival rates were the same for both procedures. EVAR is also associated with an increase in reinterventions thus recommending close follow up which leads to additional treatments[51]. EVAR is beneficial in that it allows for aneurysmal repair in patients not suitable for open surgery, but there are still critical complications associated with EVAR such as graft related complications. Multiple trials have shown increased rates of graft-related complications during long term follow-ups with the most crucial being graft migration and endoleaks[13,51].

The frequency of graft migration differs depending on the type of stent graft used and the aortic neck length. It is detrimental because the graft could migrate and allow blood to flow into the aneurysmal sac causing it to rupture. One study looked at AneuRx stent graft migration for 5 years (1996-2001). Migration occurred in 94/1119 patients with the mean amount of time after device implantation of 30±11 months. These results

were largely related to the low initial deployment of the device. The study found that the proximal fixation length and renal artery to stent graft distance were independently significant predictors of risk for stent graft migration. Every millimeter increase in the proximal fixation length decreased the risk of graft migration by 2.5%, and every millimeter decrease in the renal artery to stent graft distance increased the risk of migration by 5.8%. Because of the incidence of graft migration after the exclusion of an aneurysm, concern about the long term durability of EVAR has risen. Graft migration can also occur in open surgery, but it is more likely to occur in EVAR because of the way the graft is attached. The combination of the downward displacement forces and pulsatile nature of blood flow on aortic devices lead to device migration[60]. Another study from September 1997 to June 2004 compared the AneuRx and Zenith grafts. Similar to the previous study, it concluded that graft migration is affected by both device choice and aortic neck length. This study noted that if device migration goes untreated, it could take a malignant course and lead to a type I endoleak, aneurysm expansion, or rupture. Some risk factors found for migration included short proximal fixation length, aortic neck dilation, endograft oversizing, and structural failure. The comparison between the two grafts portrayed a significantly higher incidence of migration in the ANeuRx graft compared to the Zenith graft. This was done using Kaplan-Meier analysis which is used to estimate the survival function from a length of time. This study concluded that most patients with device migration required treatment for migration in the mid and long-term[54].

The most common complication after EVAR is an endoleak, specifically, type II endoleaks. An endoleak is continuous blood flow to the aneurysmal sac outside of the graft. There are 5 classifications of endoleaks (Figure 13). The reported occurrence of endoleaks is in 10%-30% of people at any point during follow up[40]. Type II endoleaks occur in 10%-44% of patients and comprise half of all endoleaks[42]. Type II endoleaks can further be classified by early if it occurs 30 days after EVAR, late if it occurs 1 year after EVAR, and persistent if it is present for more than 6 months after EVAR. The detection of type II endoleaks can be difficult because low-flow leaks may go unnoticed on scans. Classifying endoleaks can also be challenging to identify if multiple endoleaks overlap each other. To combat endoleaks, pressure sensors have been implanted to identify and monitor endoleaks. There is only one Food and Drug Administration (FDA) approved pressure sensor, a resonant circuit powered by an external radiofrequency antenna. The brand name for this device is EndoSure, CardioMEMS, Inc., Atlanta, Georgia. It has improved the detection of type II endoleaks. The current guidelines for a type II endoleak recommend intervention when the aneurysm sac diameter is more than 10 mm, but most type II endoleaks have a benign course and may spontaneously resolve[40].

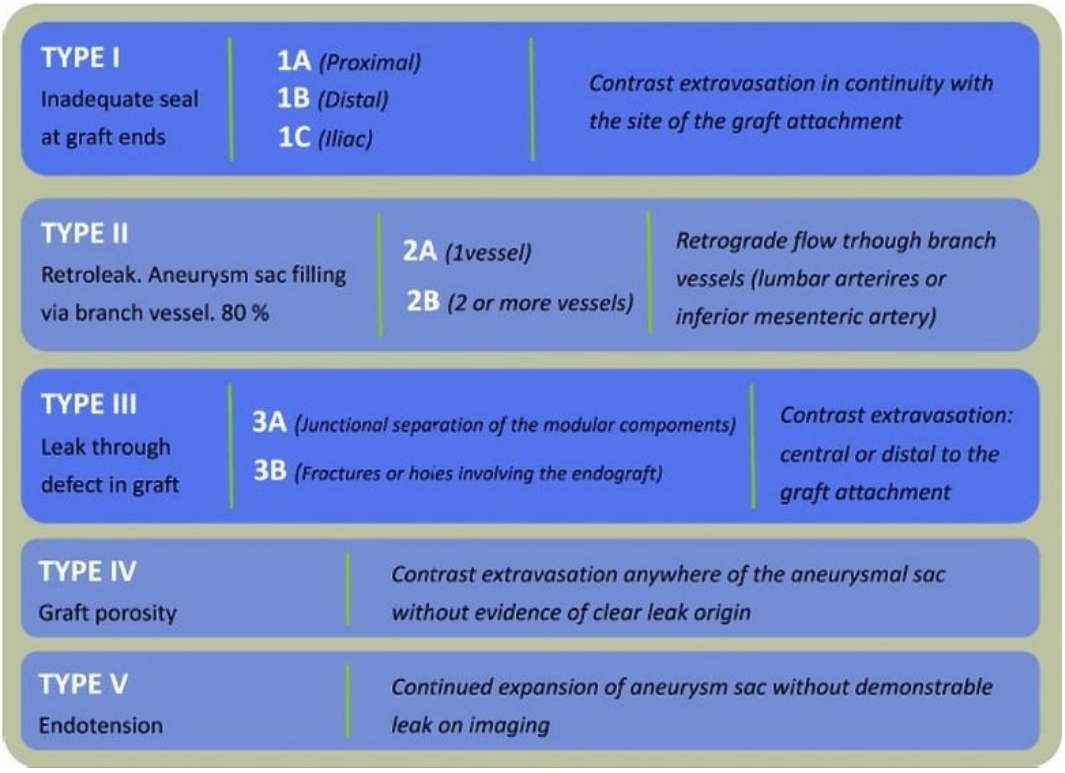

Figure 13: Types of endoleaks[19].

Open surgery is known to be more durable and suitable for younger patients with few medical comorbidities. If the patient is not suitable for open surgery, they may be a candidate for EVAR which is suitable for older patients with multiple medical comorbidities, prior aortic surgery, and/or prior abdominal surgery. Both procedures are relatively effective in controlling aortic aneurysms; it depends on the patient's fitness, anatomical suitability, life expectancy, and preference when choosing which procedure is best[51].

Tissue Engineering

Tissue engineering stems from the field of biomaterials and utilizes aspects of grafts, cells, and biologically active molecules to develop functional tissues. The ultimate

goal of tissue engineering is to generate a functional construct that can either restore, maintain, or improve damaged tissues and organs[33]. There has been a lot of work done on the tissue engineering of heart valves such as the aortic valve. There may be some similarities between the structure of the aortic valve and aortic wall allowing us to branch off of the ideas already present for tissue-engineered heart valves. Some similarities between the components of the aortic valve and the aortic wall include the presence of collagen, elastin, smooth muscle cells, and an extracellular matrix. There may be some ideas on a graft that is compatible with those components. Both the aortic valves and the aortic wall must be able to withstand high pressures and shear stress[43]. A difference between the two is the layers; the aortic valve has three thin layers, or laminas, whereas the aortic wall has three thick tissue layers, or tunicae. This may cause a difference in the material used because there may be different compatibility requirements. The mechanical environment must also be taken into consideration when making a graft. Some potential cell types that can be used in the graft could be smooth muscle cells, fibroblasts, and myofibroblasts. The first two are known to function in the native aorta. As for myofibroblasts, they are good for collagen formation which was previously stated as the most important component in the aortic wall. The cell types should be autologous to decrease the risk of immunologic complications after implantation, highly proliferative so it could last a long time and the regenerated organ or tissue, easy to harvest otherwise it would be virtually unattainable and unable to differentiate due to the adaptations that need to be made as other factors such as mechanical properties or surrounding structures change[53]. The graft should contain properties of the native aorta as well as some general

properties of biocompatibility, porosity, and mechanical properties. The type of graft can be a synthetic or biological vascular graft. Biological vascular grafts include autografts, allografts (homografts), and xenografts (heterografts) which use material from the patient, a cadaver, or another species respectively. Both have their advantages and disadvantages. A biological graft offers many mechanical, chemical, and biological advantages and processes important extracellular matrix proteins that can regulate cell adhesion and tissue degradation. As for a synthetic vascular graft, it has advantages of porosity, pore size, mechanical stability, and a controllable degradation rate. It could also have little to no immune response. Some disadvantages are the difficulty of creating a complex shape and the possibility of producing toxic degradation products[10]. Some other advantages and disadvantages for both types of grafts are shown in Figure 14 and 15.

	Biological vascular grafts				
	Autografts		**Allografts (homografts)**		**Xenografts (heterografts)**
	Arterial	**Venous**	**Arterial**	**Venous**	
Advantages	Closest approximation, less diameter mismatch, internal mammary artery anatomically nearby, excellent function	Durable and versatile, good results, infection resistance, relative availability	Off the shelf availability, better resistance to infection, transplant-recipient patients		
Disadvantages	Availability, vasospasm (radial artery), donor site morbidity	Availability, harvest injury, vein graft disease	Antigenicity, graft deterioration, early occlusions, chronic rejection, intake of drugs, infection risk		
Healing	Intimal thickening, myointimal hyperplasia (radial artery)	Endothelial desquamation, vein dilation, wall thickening, arterialization, re-endothelialization	Endothelial denudation, immune response, fibrotization		
First use	Jaboulay and Briau 1896	Goyannes 1906	Gross *et al*. 1948	Linton 1955	
Review e.g.	Nezic *et al.* 2006	Cooper *et al.* 1996	Fahner *et al*. 2006	Dardik *et al*. 2002	Schmidt and Baier 2000

	Synthetic vascular grafts					
	PET (Dacron, Terylen)		**ePTFE (Teflon, Gore-Tex)**		**Polyurethane**	
	Woven	**Knitted**	**Low-porosity (<30 µm IND)**	**High-porosity (>45 µm IND)**	**Fibrillar**	**Foamy**
Advantages	Better stability, lower permeability and less bleeding	Greater porosity, tissue ingrowth and radial distensibility	Biostability, no dilation over time	Biostability, better cell ingrowth	Compliance, good hemo- and biocompatibility, less thrombogenicity	
Disadvantages	Reduced compliance and tissue incorporation, low porosity, fraying at edges, infection risk	Dilation over time, infection risk	Stitch bleeding, limited incorporation, infection risk, perigraft seroma formation	Late neointimal desquamation in 90 µm IND, infection risk	Biodegradation in first generation, infection risk, carcinogenic?	
Healing	Inner fibrinous capsule, outer collagenous capsule, scarce endothelial islands	Fibrin luminal coverage, very sporadic endothelium, transanastomotic endothelialization in animals	Luminal fibrin and platelet carpet, connective tissue capsule with foreign body giant cells, no transmural tissue ingrowth	Macrophages and polymorphonuclear invasion, capillary sprouting, fibroblast migration, certain angiogenesis, thicker neointima, endothelialization in animals	Thin inner fibrin layer, outside foreign body cells, limited ingrowth	Better ingrowth with bigger pores
First use	Ku *et al.* 1957		Norton and Eiseman 1975		Boretos and Pierce 1967	
Review e.g.	Xue and Greisler 2003		Nishibe *et al.* 2004		Tiwari *et al.* 2002	

IND (internodal distance).

Figure 14 and 15: Type of biological and synthetic vascular grafts including their advantages, disadvantages, healing, first use, and review[10].

According to patent US20070293936A1[16], many stents and stent grafts are currently made by laser from a hollow thin-walled tube of nitinol (alloy of nickel and

titanium). A lattice-like pattern is etched into the tube to allow for the expansion of the tube. Stereolithography can be used to make such grafts. Stereolithography is a rapid prototyping technique that is used to fabricate solid, three-dimensional objects (Figure 16). It prints ultraviolet-curable (produces toughening or hardening of polymer) material layer by layer followed by post-curing the material with ultraviolet light. Stereolithography is advantageous because it largely reduces the amount of wastage compared to subtractive fabrication methods, has a high resolution, and provides uniformity in pores interconnectivity. It does, however, require large amounts of monomers and postpolymerization treatment to improve monomer conversion. An ultraviolet laser starts this process by depositing a layer of photosensitive liquid resin on the platform. Once this first layer solidifies, the platform lowers vertically and the second layer is formed on top of the first layer. This process is repeated until the wanted scaffold is obtained followed by being post-cured under ultraviolet light[17].

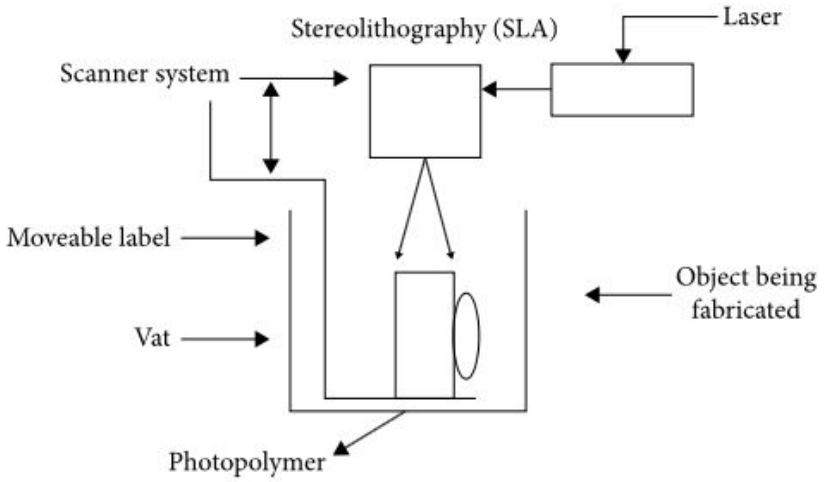

Figure 16: Schematic for stereolithography[17].

Another possible technique for making grafts is electrospinning, a conventional fabrication technique. Electrospinning makes fibers from a solution using electricity. This technique charges liquid under high voltage to promote the interaction between the surface tension and electrostatic repulsion (Figure 17). This interaction causes droplets on a spinneret to erupt and stretch. The homogenous mixtures made of such fibers provide high tensile strength.. A liquid jet is formed from the strength of the electric field exceeding the surface tension of the droplet. Electrostatic repulsion extends and whips the liquid jet until it hits the grounded collector. Within this process, the solvent evaporates and a nonwoven fibrous membrane is solidified and produced. Electrospinning can be problematic in obtaining three-dimensional structures because of the homogenous distribution of pores[17].

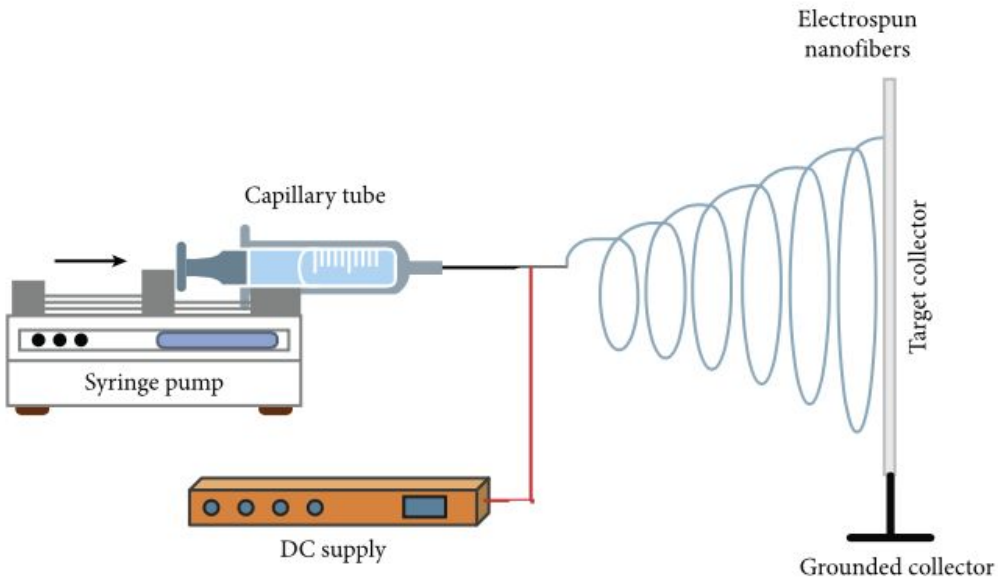

Figure 17: Diagram of electrospinning[17].

Synthetic Grafts vs Biological Grafts

The aorta must withstand large amounts of pressure, polymeric grafts that are stiffer and stronger are ideal. Biostability of such grafts is also important because biodegradation of the polymers could result in irreversible physical and chemical changes (i.e. swelling, crystallization, calcification) or the release of toxic byproducts[27]. Common synthetic stent grafts are made of polyethylene terephthalate (PET) or polytetrafluoroethylene (PTFE) which go by the names Dacron and Teflon, respectively. Both are efficient for use in arteries larger than 8mm in diameter because the materials activate thrombus formation on the lumen. Figure 18 highlights the important aspects of PTFE and PET.

TABLE 1. COMPARISON OF PTFE AND PET[5]

	PTFE	PET
Chemical name	Polytetrafluoroethylene	Polyethylene terephthalate (polyester/Dacron)
Biocompatibility	Excellent	Good
Chemical resistance	Excellent	Good
Friction	Exceptionally low	Low
Compliance	Very compliant	Very rigid plastic
Architecture	Can be formed into complex three-dimensional shapes	Must be woven/knitted to create flexible grafts
Porosity	Contains blood (if porosity is low enough)	Not liquid tight; must be preclotted or coated to contain blood
Ingrowth	Permeability can be controlled to enhance or inhibit ingrowth	Yes

Figure 18: Table comparing PET and PTFE[27].

Dacron is predominately used for aortas as it is strong with a tensile strength of 170 megapascals to 180 megapascals and a tensile modulus of 14000 megapascals. Its strength and high crystalline structure promote nonbiodegradability, but Dacron grafts tend to dilate over time. Knitted Dacron grafts also require preclotting with albumin,

gelatin, or blood to prevent seepage[27]. A study showed that PET/polyglycolic acid (PGA) stent grafts histologically and mechanically integrated with the native aorta. It achieved close to the same mechanical properties to the thin-walled woven polyester graft control graft used in the study. After 2 months, the PGA component of the PET/PGA stent graft degraded, but the host tissue replaced the degraded portions with a mixture of α-smooth muscle actin-positive cells and other host cells. Adhesion to the aortic wall was significantly enhanced with the PET/PGA stent graft[52].

As of now, there have not been any biological vascular grafts created or used for the aorta specifically in regards to aortic aneurysm repair. However, the "gold standard" for vascular replacement is the autologous native vessel[27]. A study on bio-stent grafts, self-expanding stents encased with connective tissue, inserted into the infrarenal abdominal aortas of three beagles showed no stenosis or aneurysmal changes after 1 month. The luminal surface of the graft was also covered in neointimal tissue which fused with the luminal surface of the native aorta. Endothelialization and lack of thrombus formation were also observed. The fusing of the cover tissue with the aorta is expected to prevent endoleaks and graft migration[59].

Stent Grafts

As previously stated, a stent graft, which is a woven polyester tube wrapped around a metal netting, is used in both procedures. As of 2008, there were five FDA-approved stent grafts for EVAR: AneuRx AAAdvantage, Excluder, Zenith Flex, Powerlink, and Talent. However, Powerlink was recalled by the FDA in 2014 due to continued reports of type IIIa and IIIb endoleaks[23]. Figure 19 provides the manufacturer,

initial FDA approval date, stent material, graft material, delivery system, and a distinctive feature for each. In 2013 and 2018, the GORE TAG Thoracic Endoprosthesis and Incraft AAA Stent graft system were approved respectively[49,50].

FDA-Approved Devices for EVAR

Device	Manufacturer	Date of Initial FDA Approval	Stent Material	Graft Material	Delivery System	Distinctive Feature
AneuRx AAAdvantage	Medtronic	1999	Nitinol	Woven polyester	Integrated sheath	No anatomic fixation nor pararenal stent
Excluder	Gore	2002	Nitinol	ePTFE	Separate sheath*	Infrarenal active (hooks) fixation
Zenith Flex	Cook	2003	Stainless steel	Woven polyester	Integrated sheath	Pararenal uncovered stent with suprarenal active (hooks) fixation
Powerlink	Endologix	2004	Cobalt chromium alloy	ePTFE	Integrated sheath	Unibody design
Talent	Medtronic	2008	Nitinol	Woven polyester	Integrated sheath	Pararenal uncovered stent

FDA, U.S. Food and Drug Administration; EVAR, endovascular aneurysm repair; ePTFE, expandable polytetrafluoroethylene.

*In contrast to the other stent grafts listed, the Gore Excluder is delivered through a separate sheath: there is no sheath integrated into the delivery system.

Figure 19: FDA-approved devices as of 2008[23].

The Medtronic AneuRx device (Figure 20) is composed of two parts, the main body with one leg attached and a contralateral leg segment. It is covered by a stent made of tubular metal webbing and sewn together at multiple points. The main body is positioned in the aorta and the contralateral segment is positioned in the iliac artery. The graft extends from the aorta past the renal (kidney) arteries into both iliac arteries. The graft's attachment above the renal arteries prevents it from migrating[61].

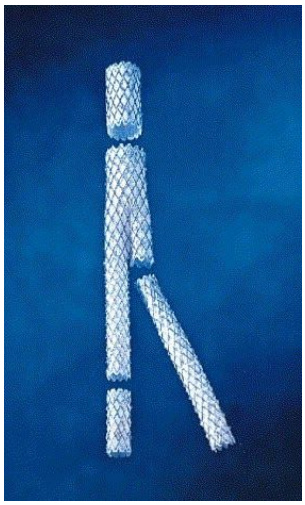

Figure 20: Medtronic AneuRx stent graft[61].

The Gore Excluder (Figure 21) is a 2-piece device. The bifurcated graft lines the aorta and extends past the renal arteries into both iliac arteries. The metal stent is covered by expanded PTFE (ePTFE). This graft has endo anchors, provides sealing and fixation between the graft and the native artery, which prevents certain types of endoleaks. Similar to the Medtronic AneuRx device, the main body is positioned in the aorta and the contralateral segment is positioned in the iliac artery thus extending from the aorta to below the renal arteries[46].

Figure 21: GORE Excluder stent graft[35].

The GORE TAG Thoracic Endoprosthesis device (Figure 22) can be used as a single device or a multiple device combination depending on the treatment needed. It is flexible and self-expanding constrained on the leading end of a delivery catheter. The endoprosthesis is composed of an ePTFE/fluoroethyl propylene graft supported and surrounded by a nitinol stent. The graft and stent are joined together by lamination of ePTFE/fluoroethyl propylene bonding tape. An ePTFE sealing cuff goes over the stent and is attached at each end[50].

Figure 22: GORE TAG Thoracic endoprosthesis[20].

The Cook Zenith Flex device (Figure 23) is a modular bifurcated system with a main bifurcated stent graft and two leg extensions. Its structure makes it the only endograft to provide a combination of both suprarenal and infrarenal fixation. The main body can vary between three different lengths, and the overlap between the main body and the leg extensions are adjustable. This allows for a broader application to different types of aortic aneurysms[46].

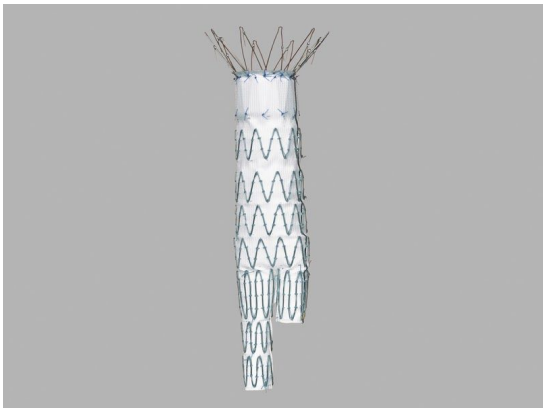

Figure 23: Cook Zenith Flex stent graft[62].

The Endologix Powerlink device (Figure 24) is a unibody bifurcated stent graft made of self-expanding cobalt-chromium alloy. The main body is from a single wire that is wrapped with thin-walled, low porosity ePTFE graft. The materials are attached to the stent at the proximal and distal ends to minimize graft holes. This stent graft also includes a proximal cuff and limb extension accessories to suit a variety of patient's anatomy[48].

Figure 24: Endologix Powerlink stent graft[58].

The Medtronic Talent device (Figure 25) is modular and consists of four stent graft components: bifurcated, contralateral iliac limb, iliac extension cuff, and aortic extension cuff. Each component has nitinol metal springs attached to woven polyester

graft material which are sewn together with sutures. The proximal and distal spring attachment points provide additional columnar strength. The bifurcated portion of the stent graft is positioned in the aorta followed by the contralateral iliac limb portion serving as a conduit for blood flow into the contralateral iliac artery. The aortic and iliac extension cuff components allow for an extension of the stent graft to accommodate the patient's anatomy[47].

Figure 25: Medtronic Talent stent graft[31].

The Cordis Incraft device (Figure 26) has three components, an aortic bifurcate prosthesis, and two iliac limb prostheses. It also has an iliac limb prosthesis used as an iliac extension prosthesis to extend the device. Each prosthesis has a series of short, electropolished, laser-cut, self-expanding nitinol stent rings covered by a seamless, low porosity, woven polyester PET graft. The nitinol stent-rings run throughout the entire length of the aneurysm and are sutured to the inner surface of the graft[49].

Figure 26: Cordis Incraft stent graft[12].

PROPOSED GRAFT

Materials

The base of the graft would be a mixture of PET and ePTFE as both have their share of advantages and disadvantages. PET's tensile strength and elastic modulus and ePTFE's low porosity, compliance, and biocompatibility are essential for the aorta. I would recommend a 4:5 ratio of PET:ePTFE because PET is primarily used for aortic aneurysm repair, and ePTFE is known to be soft and can change shape under pressure[38]. Considering how important collagen and elastin are in the native artery, the graft would be coated in collagen and elastin to mimic the native artery's function. The graft would also be coated with PGA as a study showed PGA promoted adherence to the native artery and degraded after 2 months.

Formation

Stereolithography has been the main method in fabricating grafts. This method is sufficient because it minimizes wasting material and can make curved grafts or grafts with branches needed for aneurysm repairs that go into the aortic arch or iliac arteries respectively. If the aneurysm does not require a branched graft, electrospinning should be used because of its ability to produce low porosity grafts.

Insertion

The method of implantation used in EVAR procedures will be used because it is minimally invasive, has a shorter recovery period, and has a high recovery rate. The

patient will be put under anesthesia followed by the surgeon making two small incisions into the groin (upper thigh). They will insert the catheter equipped with the biological stent graft into an artery and thread it up into the aorta to the aneurysm via x-ray guidance. The graft is then expanded inside the aorta and sutured into place thus forming a stable channel for blood flow[15].

Expectations

The goal is to fabricate a graft as similar to the native artery as possible. The materials chosen would get us close to achieving native artery properties because of each material's individual properties as discussed in the literature review. Although a stent is still present and there is the risk of migration and endoleaks, the materials chosen will greatly reduce these possibilities because they can adhere to the native artery and integrate with it. The thickness of the graft will also be increased with the collagen and elastin coatings providing extra strength and support. Electrospinning will be used to create a low porosity graft thus reducing the risk of endoleaks, and stereolithography will be used to create grafts that require branching for the iliac arteries. Overall, this hypothetical biological stent graft will be a safer, longer-lasting option for those who need aneurysm repair.

Conclusion

Although an autologous vessel is likely the approach and would most closely mimic the native aorta, a biological stent graft is a realistic option for the near future. I proposed a biological stent graft made of PET/ePTFE coated with collagen, elastin, and PGA that could be fabricated through electrospinning or stereolithography and inserted via a catheter and x-ray guidance in hopes to minimize the risk for endoleaks and migration along with imitating properties of the native aorta. While further research would be necessary to bring this proposed graft to realization, I hope this thesis serves as a starting point for future research.

References

(1) Aorta Anatomy https://ufhealth.org/uf-health-aortic-disease-center/aorta-anatomy (accessed May 2019).

(2) Aortic Aneurysm - UAB Medicine. https://www.uabmedicine.org/patient-care/conditions/aneurysm (accessed Feb 2020).

(3) Bäck, M.; Gasser, T.; Michel, J.; Caligiuri, G. Cardiovascular Research 2013, 99, 232-241.

(4) Bailey, R. What Is the Function of the Aorta? https://www.thoughtco.com/anatomy-of-the-heart-aorta-373199 (accessed May 2019).

(5) Becquemin, J.; Pillet, J.; Lescalie, F.; Sapoval, M.; Goueffic, Y.; Lermusiaux, P.; Steinmetz, E.; Marzelle, J. A Randomized Controlled Trial Of Endovascular Aneurysm Repair Versus Open Surgery For Abdominal Aortic Aneurysms In Low- To Moderate-Risk Patients. Journal of Vascular Surgery 2011, 53 (5), 1167-1173.e1.

(6) Beenakker, J.; Ashcroft, B.; Lindeman, J.; Oosterkamp, T. Biophysical Journal 2012, 102, 1731-1737.

(7) Brain Aneurysms | Memphis Vascular Doctors. https://memphisvascular.com/patient-education/brain-aneurysms/ (accessed Feb 2020).

(8) Bratby, M. Vascular Surgery and Interventional Radiology Endovascular Aneurysm

Repair (EVAR) Information for patients. https://www.ouh.nhs.uk/patient-guide/leaflets/files/100420evar.pdf (accessed Jan 2020).

(9) Brewster, D.; Jones, J.; Chung, T.; Lamuraglia, G.; Kwolek, C.; Watkins, M.; Hodgman, T.; Cambria, R. Long-Term Outcomes After Endovascular Abdominal Aortic Aneurysm Repair The First Decade. Annals of Surgery 2006, 244 (3), 426-438.

(10) CHLUPÁČ, J.; FILOVÁ, E.; BAČÁKOVÁ, L. Blood Vessel Replacement: 50 Years Of Development And Tissue Engineering Paradigms In Vascular Surgery. Physiol. Res. 2009, 58 (2), S119-S139.

(11) Classification Aortic Aneurysms Thoracic Abdominal Thoracoabdominal Stock Vector (Royalty Free) 1568172349. https://www.shutterstock.com/image-vector/classification-aortic-aneurysms-thoracic-abdominal-thoracoabdominal-1568172349 (accessed Feb 2020).

(12) Cordis Incraft™ AAA Stent Graft Promising 1 Year Clinicals. https://www.medlatest.com/companies/johnson-johnson/cordis-incraft-aaa-stent-graft-promising-1-year-clinicals/ (accessed Feb 2020)

(13) Dalainas, I.; Kakisis, J.; Mylonas, S.; Liapis, C.; Moulakakis, K. Endovascular Treatment Versus Open Repair For Abdominal Aortic Aneurysms: The Influence Of Fitness In Decision Making. International Journal of Angiology 2013, 22 (01), 009-012.

(14) Dalman, R.; Mell, M. UpToDate.

https://www.uptodate.com/contents/abdominal-aortic-aneurysm-beyond-the-basics/print (accessed Feb 2020).

(15) Department of Surgery - Endovascular Aneurysm Repair. https://surgery.ucsf.edu/conditions--procedures/endovascular-aneurysm-repair.aspx (accessed Feb 2020).

(16) Dobak, J. Systems and methods for creating customized endovascular stents and stent grafts. US20070293936A1, 2007.

(17) Eltom, A.; Zhong, G.; Muhammad, A. Scaffold Techniques And Designs In Tissue Engineering Functions And Purposes: A Review. Advances in Materials Science and Engineering 2018, 2019, 1-13.

(18) Erbel, R.; Eggebrecht, H. Heart 2006, 92, 137-142.

(19) Gaillard, F.; Cheng, J. Classification of endoleaks | Radiology Reference Article Radiopaedia.org. https://radiopaedia.org/articles/classification-of-endoleaks?lang=us (accessed Jan 2020).

(20) Gore® TAG® First Device FDA Cleared For Endovascular Repair Of Traumatic Aortic Transections. https://www.medlatest.com/companies/gore®-tag®-first-device-fda-cleared-for-endovascular-repair-of-traumatic-aortic-transections/ (accessed Feb 2020).

(21) Hu, C.; Zhu, K.; Li, J.; Wang, C.; Lai, L. Molecular Targets In Aortic Aneurysm For Establishing Novel Management Paradigms. Journal of Thoracic Disease 2017, 9 (11), 4708-4722.

(22) Isselbacher, E. Circulation 2005, 111, 816-828.

(23) Jackson, B.; Carpenter, J. Devices Used For Endovascular Aneurysm Repair: Past, Present, And Future. Seminars in Interventional Radiology 2009, 26 (01), 039-043.

(24) Jane, D. Reviews Archives - Best Collagen Products. https://www.bestcollagenproducts.com/tag/reviews/ (accessed Feb 2020).

(25) Jordan, W.; Alcocer, F.; Wirthlin, D.; Westfall, A.; Whitley, D. Abdominal Aortic Aneurysms In "High-Risk" Surgical Patients. Annals of Surgery 2003, 237 (5), 623-630.

(26) Joviliano, E.; Ribeiro, M.; Tenorio, E. Brazilian Journal of Cardiovascular Surgery 2017.

(27) Kannan, R.; Salacinski, H.; Butler, P.; Hamilton, G.; Seifalian, A. Current Status Of Prosthetic Bypass Grafts: A Review. Journal of Biomedical Materials Research Part B: Applied Biomaterials 2005, 74B (1), 570-581.

(28) Kassab, G. Biomechanics Of The Cardiovascular System: The Aorta As An Illustratory Example. Journal of The Royal Society Interface 2006, 3 (11), 719-740.

(29) Kotze, C.; Ahmed, I. Etiology and Pathogenesis of Aortic Aneurysm; INTECH Open Access Publisher, 2011.

(30) Laheij, R.; Buth, J.; Harris, P.; Moll, F.; Stelter, W.; Verhoeven, E. Need For Secondary Interventions After Endovascular Repair Of Abdominal Aortic Aneurysms. Intermediate-Term Follow-Up Results Of A European Collaborative

Registry (EUROSTAR). British Journal of Surgery 2002, 87 (12), 1666-1673.

(31) Medtronic | Talent Aortic Stent Graft System. https://www.whichmedicaldevice.com/by-manufacturer/49/386/talent-aortic-stent-graft-system (accessed Feb 2020).

(32) Nienaber, C.; Clough, R.; Sakalihasan, N.; Suzuki, T.; Gibbs, R.; Mussa, F.; Jenkins, M.; Thompson, M.; Evangelista, A.; Yeh, J.; Cheshire, N.; Rosendahl, U.; Pepper, J. Aortic Dissection. Nature Reviews Disease Primers 2016, 2 (16053).

(33) O'Brien, F. Materialstoday 2011, 14, 88-95.

(34) O'Donnell, P. Collagen - Basic Science - Orthobullets https://www.orthobullets.com/basic-science/9013/collagen (accessed May 2019).

(35) Over 250,000 patients treated with Gore Excluder abdominal aortic aneurysm endoprosthesis | Vascular News. https://vascularnews.com/over-250000-patients-treated-with-gore-excluder-abdominal-aortic-aneurysm-endoprosthesis/ (accessed Feb 2020).

(36) Powell, J.; Sweeting, M.; Ulug, P.; Blankensteijn, J.; Lederle, F.; Becquemin, J. Meta-Analysis Of Individual-Patient Data From EVAR-1, DREAM, OVER And ACE Trials Comparing Outcomes Of Endovascular Or Open Repair For Abdominal Aortic Aneurysm Over 5 Years. Journal of Vascular Surgery 2017, 65 (5), 1539-1540.

(37) Prinssen, M.; Buskens, E.; Blankensteijn, J. Quality Of Life After Endovascular And Open AAA Repair. Results Of A Randomised Trials. European Journal of Vascular and Endovascular Surgery 2004, 27 (2), 121-127.

(38) PTFE meaning. Pros and Cons of PTFE Coating explained by Holscot. https://holscot.com/pros-cons-ptfe-coating-meaning/ (accessed Feb 2020).

(39) Quintana, R.; Taylor, W. Circulation Research 2019, 124, 607-618.

(40) Saqib, N.; Charlton-Ouw, K.; Azizzadeh, A. Managing Type II Endoleaks - Endovascular Today. https://evtoday.com/articles/2013-feb/managing-type-ii-endoleaks (accessed Jan 2020).

(41) Shadwick, R. Mechanical Design In Arteries. Journal of Experimental Biology 1999, 202, 3305-3313.

(42) Sidloff, D.; Brown, A.; Saggu, G.; Bown, M.; Sayers, R. Type II Endoleaks: Challenges And Solutions. Vascular Health and Risk Management 2016, 12, 53-63.

(43) Stelt, B. Tissue engineering of aortic valves. Retrieved from http://www.mate.tue.nl/mate/pdfs/4335.pdf (accessed May 2019).

(44) Stent Grafting for treating Abdominal Aortic Aneurysms (EVAR). https://www.nbt.nhs.uk/sites/default/files/attachments/Stent%20Grafting%20for%20treating%20Abdominal%20Aortic%20Aneurysms%20%28EVAR%29_NBT003116.pdf (accessed Jan 2020).

(45) Steucke, K.; Tracy, P.; Hald, E.; Hall, J.; Alford, P. Journal of Biomechanics 2015, 48, 3044-3051.

(46) Strickman, N. Abdominal Aortic Aneurysm (AAA).

http://www.hgcardio.com/AAA%20web%20brochure%205.22.16.pdf (accessed Jan 2020).

(47) Summary of Safety and Effectiveness Data (SSED). https://www.accessdata.fda.gov/cdrh_docs/pdf7/P070027b.pdf (accessed Jan 2020).

(48) Summary of Safety and Effectiveness Data (SSED). https://www.accessdata.fda.gov/cdrh_docs/pdf4/P040002c.pdf (accessed Jan 2020).

(49) Summary of Safety and Effectiveness Data (SSED). https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150002C.pdf (accessed Jan 2020)

(50) Summary of Safety and Effectiveness Data (SSED). https://www.accessdata.fda.gov/cdrh_docs/pdf4/p040043s051b.pdf (accessed Feb 2020).

(51) Swerdlow, N.; Wu, W.; Schermerhorn, M. Open And Endovascular Management Of Aortic Aneurysms. Circulation Research 2019, 124 (4), 647-661.

(52) Takeuchi, M.; Kuratani, T.; Miyagawa, S.; Shirakawa, Y.; Shimamura, K.; Kin, K.; Yoshida, T.; Arai, Y.; Hoashi, T.; Teramoto, N.; Hirakawa, K.; Kawaguchi, N.; Sawa, Y. Tissue-Engineered Stent-Graft Integrates With Aortic Wall By Recruiting Host Tissue Into Graft Scaffold. The Journal of Thoracic and Cardiovascular Surgery 2014, 148 (4), 1719-1725.

(53) Tissue Engineering and Regenerative Medicine | National Institute of Biomedical

Imaging and Bioengineering https://www.nibib.nih.gov/science-education/science-topics/tissue-engineering-and-regenerative-medicine (accessed May 2019).

(54) Tonnessen, B.; Sternbergh, W.; Money, S. Mid- And Long-Term Device Migration After Endovascular Abdominal Aortic Aneurysm Repair: A Comparison Of Aneurx And Zenith Endografts. Journal of Vascular Surgery 2005, 42 (3), 392-401.

(55) Tsamis, A.; Krawiec, J.; Vorp, D. Journal of The Royal Society Interface 2013, 10, 20121004-20121004.

(56) Types of Aortic Aneurysms https://www.uwhealth.org/heart-cardiovascular/types-of-aortic-aneurysms/10973 (accessed May 2019).

(57) Wagenseil, J.; Mecham, R. Physiological Reviews 2009, 89, 957-989.

(58) Wu, Z.; Qu, L.; Raithel, D.; Xiromeritis, K. 12-Year Experience With The Endologix Powerlink® Device In Endovascular Repair Of Abdominal Aortic Aneurysms. Diagnosis, Screening and Treatment of Abdominal, Thoracoabdominal and Thoracic Aortic Aneurysms 2011.

(59) Yaku, H.; Mizuno, T.; Moriwaki, T.; Iwai, R.; Ishibashi-Ueda, H.; Yamanami, M.; Kanda, K.; Nakayama, Y.; Kawajiri, H. Implantation Study Of A Tissue-Engineered Self-Expanding Aortic Stent Graft (Bio Stent Graft) In A Beagle Model. *Journal of Artificial Organs* 2014, *18* (1), 48-54.

(60) Zarins, C.; Bloch, D.; Crabtree, T.; Matsumoto, A.; White, R.; Fogarty, T. Stent

Graft Migration After Endovascular Aneurysm Repair: Importance Of Proximal Fixation. Journal of Vascular Surgery 2003, 38 (6), 1264-1272.

(61) Zarins, C.; White, R.; Schwarten, D.; Kinney, E.; Diethrich, E.; Hodgson, K.; Fogarty, T. Aneurx Stent Graft Versus Open Surgical Repair Of Abdominal Aortic Aneurysms: Multicenter Prospective Clinical Trial. Journal of Vascular Surgery 1999, 29 (2), 292-308.

(62) Zenith Flex® AAA Endovascular Graft Bifurcated Main Body Graft | Cook Medical. https://www.cookmedical.com/products/ndo_aaamain_webds/ (accessed Feb 2020).

(63) 20.4 Homeostatic Regulation of the Vascular System. https://opentextbc.ca/anatomyandphysiology/chapter/20-4-homeostatic-regulation-of-the-vascular-system/ (accessed Feb 2020).