Remodelling and Pathology Development Associated with Aneurysmal Ascending Aortic Tissues

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The human ascending aorta (AA) is exposed to very high shear and pressure stresses exerted by the blood flow ejected from the left ventricle outflow tract. This vessel has a unique structural behaviour which adequately redistributes the energy captured from the blood flow ejection to sustain a more continuous blood flow through the entire vascular system. Unfortunately, this vessel is prone to a pathological dilation process involving significant structural changes that can lead to fundamental modification of its mechanical behaviour and functions. Genetic and/or environmental factors have been implicated in the disease process. It is believed that in particular the forces created by blood flow (hemodynamics) can be a stimulus for vessel remodelling. For patients suffering from this deadly condition, surgical replacement or repair is the best solution to increase life expectancy. However, the replacement materials available as a treatment have a significant impact on the blood flow, the biomechanics of the aortic arch, and the entire vascular system. In this review we summarise the current understanding of the pathogenesis mechanisms involved in the dilation of the AA from a mechanical and biochemical point of view. We will also underline the needs for better replacement materials in surgical repair to improve graft patency.

L'aorte ascendante humaine est exposée à de fortes contraintes de cisaillement et de pression exercées par l'écoulement sanguin, lui-même éjecté par le ventricule gauche du coeur. Ce vaisseau sanguin montre un comportement structurel unique qui redistribue adéquatement l'énergie capturée par la paroi artérielle de façon à produire un écoulement sanguin davantage continu dans tout le système vasculaire. Malheureusement, ce vaisseau est trop souvent associé à un processus de dilatation pathologique durant lequel on observe des changements structurels significatifs en plus de causer de profondes modifications dans son comportement mécanique. On croit que des facteurs génétiques et/ou environnementaux sont impliqués dans la progression de la maladie. En particulier, les forces générées par l'écoulement sanguin pourraient stimuler le remodelage de la paroi. Pour les patients qui souffrent de cette pathologie mortelle, la chirurgie demeure la seule solution pour augmenter de façon significative l'espérance de vie. Par contre, les matériaux de remplacement utilisés pour traiter la maladie ont un impact significatif sur l'écoulement sanguin, sur la biomécanique de la crosse aortique et sur le reste du système artétriel. Dans cette revue de littérature, nous résumons la compréhension actuelle des mécanismes de la pathogénèse de la dilatation de l'aorte ascendante humaine d'un point de vue biomécanique et biochimique. Nous allons également souligner le besoin immédiat de développer de nouveau matériaux de remplacement utilisés lors de la reconstruction aortique afin d'améliorer le succès de la chirurgie à long terme.

Keywords: aneurysms, hemodynamic remodelling, mechanical properties, biochemical composition

INTRODUCTION

Our understanding of how aneurysms form has improved greatly in the past 50 years. We now know that the biomechanics of the ascending aorta (AA) greatly influence the initiation and progress of AA diseases. Treatment of dilated AA tissue requires surgical intervention and replacement materials, which can in turn alter the AA biomechanics. In this review we summarise our current understanding of the pathogenesis of AA

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aneurysms and its relation with AA biomechanics and biochemical composition. We also highlight the mechanical differences in commonly used surgical replacement materials with native and dilated tissues. Overall this work make clinicians and researchers appreciate the importance of biomechanics in the pathogenesis of AA diseases along with highlighting the promising research directions that need to be taken to offer better treatments to patients.

BACKGROUND

Human AA dilation (commonly called aneurysms) is the most common condition requiring surgical treatment (Kouchoukos and Dougenis, 1997). The overall incidence of AA aneurysms has been estimated at 10 cases per 100 000 people (Bickerstaff et al., 1982; Olsson et al., 2006; Clouse et al., 1998). If an AA aneurysm is left untreated, it can rupture or dissect and be a fatal event with a mortality rate close to 95% (Bickerstaff et al., 1982; Johansson et al., 1995). This is why surgical replacement is routinely performed after an AA dilation is detected, despite the considerable risks of thoracic surgery, in particular for the elderly.

Unfortunately, aortic aneurysms are a medical condition under which many mechanistic pathways are believed to be involved in the dilation process. There is still an active debate between two schools of thoughts (genetic predisposition or environmental factors) regarding the underlying mechanisms which initiate and maintain aneurysm formation. Indeed, genetic predisposition and environmental factors have been linked to imbalance in the synthesis and degradation of AA tissues. This abnormal remodelling of the medial layer weakens the wall of the AA and leads to aneurysm formation or dissection and rupture of the AA. It has been established that dilation of the AA is associated with aortic valve insufficiency (Mueller et al., 1997) suggesting that abnormal hemodynamic forces may be involved in this abnormal tissue remodelling. In this case, pathological dilation of the AA would be the result of abnormally increased mechanical stresses generated from the disturbed hemodynamics. The term hemodynamics refers to the dynamics of the blood flow. As the blood flows in the AA, it exerts pressure and shear stresses on the inside wall of the vessel which are transmitted deep in the aortic wall as tissue stresses. Although hemodynamic forces act only on the surface of the inner wall, they are the main contributors to the stresses experienced by the vascular walls.

Patients with severe dilation of the AA will undergo surgery to replace the diseased part of the tissue with a relatively inelastic Dacron graft and various patching materials from synthetic and/or biological sources. This treatment shows good durability and actual grafts are easy to handle for the surgeon. Unfortunately, these grafts are unable to restore any physiological properties of the native AA. The non-compliant nature of Dacron grafts is believed to cause secondary complications like increased thrombosis (formation of a blood clot inside a blood vessel) and alteration of peripheral vascular blood flow (Miyawaki et al., 1990; Stewart and Lyman, 1992; Kim et al., 1995). Moreover, the mismatch between the mechanical properties of the native vessel with the replacement materials is believed to cause local tissue remodelling such as aneurysms and limit graft function (Ballyk et al., 1998; Surovtsova, 2005).

By identifying mechanisms involved in the pathogenesis of such vascular diseases, cardiologist and surgeon will have the tools to perform early diagnostics and improve prevention treatments for patient with existing family history as well as offering better treatment options for patients with dilated tissues. Indeed, structural data on the mechanics of the healthy and diseased tissue will help in designing new replacement materials that would closely match the mechanical properties of aortic tissues and greatly improve the performance of the actual replacement materials.

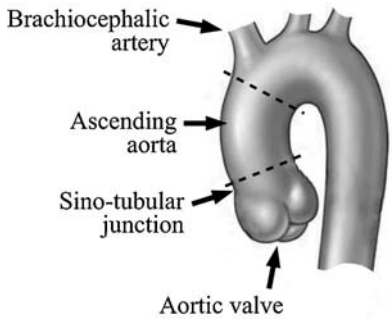

Figure 1. Ascending aorta location. Image adapted from the Cleveland Clinic foundation website.

THE FUNCTIONS AND STRUCTURE OF THE ASCENDING AORTA

The AA is the largest vessel of the vascular system with a mean diameter of 33 mm for adult human (Wolak et al., 2008). This vessel is located just above the sinus of the aortic valve (see Figure 1). It starts at the sino-tubular junction and ends at the brachiocephalic artery.

The AA is uniquely constructed to withstand large stresses from the hemodynamics of the left ventricle outflow tract. Most of the blood pumped travels through the AA and then into the entire arterial system of the body. Because of its intrinsic elastic properties, the blood flow and pressure stresses cause the AA to distend during systole. The energy from the left ventricle ejection is captured in part by the expansion of the vessel walls and redistributed by elastic recoil of the vessel during diastole (Wagenseil et al., 2009). These unique mechanical properties minimise pressure losses through the entire vascular system and regulate blood flow.

The wall of the AA is composed of three distinct layers, the intimal, the medial, and the adventitial layers (Figure 2). The intimal layer consists of a monolayer of endothelial cells (ECs). The medial and the adventitial layers are the main load-bearing structure of the arterial wall (Halloran et al., 1995). The medium is a composite structure of concentrically arranged and equidistantly spaced elastic laminae between which exists a network of collagen fibres and vascular smooth muscle cells (VSMCs) (Silver et al., 1989). The adventitial layer is primarily a network of collagen fibres, which give strength and serves as a protective sheath to the artery under high blow pressure. Because of its relatively high content in collagen and elastin in respect to its relatively low content in VSMCs, the AA is categorised as an elastic artery.

Structural Components

Amorphous elastin is a protein, which arranges in elastic concentric sheets and allows the aorta to passively expand and recoil. It has an uncommon amino acid composition of hydrophobic residues such as glycine (Gly), valine (Val), and alanine (Ala). Amorphous elastin assembly occurs on microfibrils, which are filaments of 8–16 nm in diameter (Vrhovski and Weiss, 1998). Microfibrils are glycoproteins known as fibrillins and are the non-elastic component of the elastin fibres (Robb et al., 1999). These microfibrils are established before the elastin assembles and provides a scaffold for the deposition and the crosslinking of

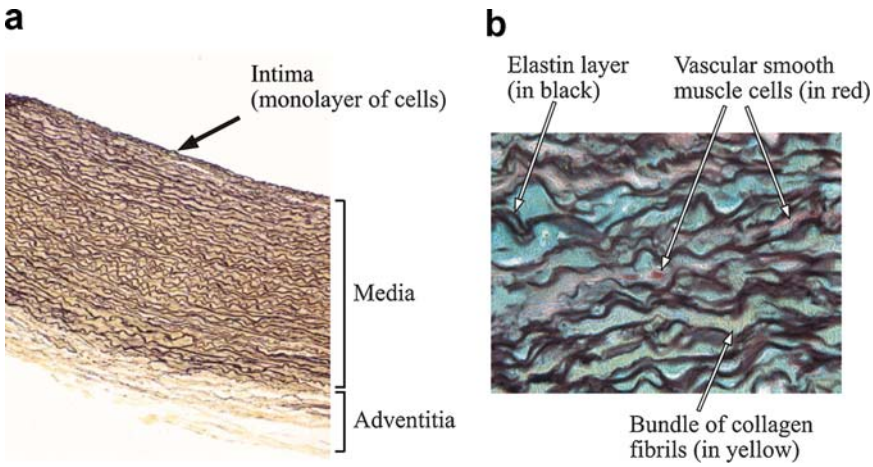

Figure 2. a) Ascending aorta wall description showing the intimal, the medial, and the adventitial layers. b) Microscope images from histology slides of the aortic tissues with a movat pentachrome stain.

amorphous elastin (Vrhovski and Weiss, 1998; Trask et al., 2000). After elastin deposition, a final enzymatic crosslinking process occurs with elastin-specific crosslinks desmosine and isodesmosine (Vrhovski and Weiss, 1998; Debelle and Tamburro, 1999). Mature elastin is highly insoluble.

Collagen is the other major extracellular protein present in the vasculature. More than 29 types of collagen have been identified and described in the literature. Type I and III are the most common in the mature aorta (Arteaga-Solis et al., 2000). Fibres of collagen are found in the medial but mainly in the adventitial layer. Collagen fibres in the medial layer help to bind the VSMCs with the elastic laminae. In the adventitia, the interwoven and thick collagen fibre network form a sleeve around the medial layer providing mobility but stability and strength by limiting the degree of distention of the vessel under high blood pressure.

VSMCs can also be considered has a structural component. It has been shown that VSMCs contribute to the aortic wall stiffness when contracted (Sparks and Bohr, 1962; Attinger, 1968; Dobrin and Doyle, 1970; Cox, 1976) but have a negligible contribution when they are in a relaxed state. We refer to the passive mechanical properties, when VSMCs are not contracted, in opposition to the active mechanical properties with the VSMCs contracted.

Remodelling Components

ECs, VSMCs, and fibroblasts are the main cell types involved in the remodelling process of aortic wall. ECs cover the inside wall of all blood vessels thus they are in direct contact with blood flow. It has been extensively shown that ECs are sensitive to shear and pressure stresses and can respond to these stimuli with the production of structural proteins such as collagen and elastin (Divya et al., 2007). Moreover, they are also capable of producing matrix metalloproteinases (MMPs), which contribute to the degradation of collagen and elastin, a double role that allows them to perform vascular remodelling (Haas, 2005).

VSMCs produce collagen, elastin, and MMPs (Mecham et al., 1991; Newby, 2006). They are also involved in the production and degradation of the extracellular matrix proteins and contribute to the remodelling of the aortic wall in term of reinforcement and reorganisation of the existing structure. VSMCs are, by far, the biggest cell populations in the healthy aortic wall and therefore they play a primary role in the remodelling process. Moreover, it has been shown that VSMCs migration and proliferation can be up- or downregulated from cell stretching (Jiang et al., 2009).

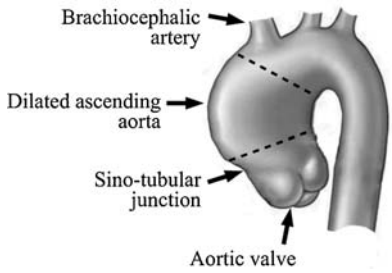

Figure 3. Illustrating an aneurysm at the ascending aorta. Image adapted from the Cleveland Clinic foundation website.

Fibroblasts are mainly located in the adventitia and responsible for the production of collagen fibres (Prockop and Kivirikko, 1995). They are also capable of producing MMPs to degrade collagen for further structural reorganisation or reinforcement in the adventitial and medial layer (Helary et al., 2005).

PATHOGENESIS OF THE DILATION

An aneurysm is a local and irreversible dilation of the aortic wall, which can lead to rupture (Figure 3). A part of a vessel is termed aneurysmal if the maximum diameter of this vessel is 50% greater than its original size (Rosamond et al., 2007). For the human AA, it corresponds to a diameter greater than 50 mm.

Aneurysm formation implies that the vessel wall could not maintain its normal configuration or integrity under the hemodynamic load. The vascular wall repairs and reconstructs itself under what seems like permanent deformation, which evolves to an irreversible dilation. This deformation can be explained by an abnormal increase of mechanical stresses, a reduced resistance from the arterial wall or a combination of both. Structural changes in the media are also believed to be responsible for this dilation; however, the link between hemodynamics and changes in cell phenotype is still unknown.

Aneurysms are characterized by medial changes with degeneration of the extracellular matrix and loss of VSMCs (Kazi et al., 2003; Isselbacher, 2005). Wassef et al. (2001) suggest that these structural changes are accelerated by the action of MMPs, which are responsible for elastin and collagen degradation (MMP-2 and MMP-9). LeMaire et al. (2005) have shown that AA aneurysms

exhibited an increased MMP-9 expression supporting the hypothesis of an increased collagen fibres degradation and thus leading to the weakening of the arterial wall. In addition, it is known that the expression of these enzymes is affected by the hemodynamic stresses, which support the hypothesis that the disturbed hemodynamics plays a role in the progression of aneurysmal tissue.

Along with abnormal level of the MMP content, aneurysms at the AA are also associated with valve diseases where the disturbed hemodynamics is believed to play a role in the progression of the disease. It has been reported that patients with a bicuspid aortic valve (BAV) have thinner elastic lamellae and greater distance between elastic lamellae than patients with a normal aortic valve (Olearchyk, 2004). In addition, Nistri et al. (2002) have clearly shown that young male subjects with BAV display large aortic size and abnormal elastic properties of the AA. Although, a genetic predisposition has been hypothesised (Nataatmadja et al., 2003), other investigations strongly indicate that this dilation is a consequence of perturbed hemodynamic forces due to the presence of the bicuspid valve (Wilton and Jahangiri, 2006; Guntheroth, 2008).

Patients with a tricuspid aortic valve (TAV; normal configuration for the aortic valve) have also shown abnormal medial degeneration where an imbalanced connective tissue turn over with aging (Robert and Labat-Robert, 2000) due, in part, to hemodynamic forces, particularly with patients with valve diseases, is hypothesised. LeMaire et al. (2005) sought to determine whether AA aneurysms in TAV are associated with increased MMP expression and whether MMP expression differs between BAV patients and TAV patients. They found that aneurysms in the TAV patients exhibited diminished elastin content, increased MMP-9 expression and normal MMP-2 levels. In contrast, BAV aneurysms were characterised by a preservation of elastin content, normal MMP-9 levels, and elevated MMP-2 expression. Although both valve types have a distinct MMP level profile, this finding suggests that medial degeneration does also exist in patients with TAV but it is still hard to distinguish if the medial degradation is the results of abnormal hemodynamic forces or natural turn over the vessel structure.

Bicuspid Valve Phenotype

There are mainly two types of aortic valves which are associated with dilated AA: BAV and TAV. It is believed that different remodelling patterns exist where hemodynamic forces on the wall of the AA are dependent on the type of aortic valve present. However, BAV is commonly used to describe different phenotypes of BAV, which leads to confusion in the literature. The first distinction that must be made is regarding the true BAV (type 0) which are aortic valves with only two leaflets of the same size with no raphe present (Sievers and Schmidtke, 2007). Type 1 BAV (T1-BAV) is an aortic valve with one raphe which fuses two leaflets while the third one is free to move. This type is the most common one (Sievers and Schmidtke, 2007). There are three different raphe positions: L-R, right and left coronary leaflet are fused, N-R, non- and right coronary leaflet are fused and N-L, non- and left-coronary leaflet are fused. The most common raphe position is L-R (Sievers and Schmidtke, 2007). Care must be taken when analysing the findings reported in the literature as multiple bicuspid morphologies and phenotypes exist (Schaefer et al., 2007; Sievers and Schmidtke, 2007).

Schaefer et al. (2007) have found that L-R BAV is associated with a larger and stiffer sinus of Valsalva and smaller arch diameter than N-R BAV. In a more recent study, Schaefer et al. (2008) also found that L-R BAV is associated with male gender and normal aortic shape but a larger sinus diameter. Moreover, N-R BAV is associated with AA dilation and larger arch dimensions. It seems clear from these studies that some morphological properties of the AA are BAV phenotype dependent. We think that performing phenotype grouping is essential when investigating the pathogenesis mechanisms involved in AA aneurysms especially when hemodynamic forces are believed to be involved in the disease process. These two studies are the only ones to date, which have made the distinction between BAV phenotype associated with dilated AA.

PASSIVE AND ACTIVE MECHANICAL PROPERTIES OF THE ASCENDING AORTA

Ultimately, dilation occurs due to a change in the AA mechanical properties. The mechanical analyses of aneurysms have been most widely studied in abdominal aortic tissue under passive mechanical testing. Early works from He and Roach (1994) have shown that dilated tissues were significantly stiffer than healthy tissue under uniaxial testing. The directional dependency in stiffness has been investigated by Raghavan et al. (1996) using uniaxial tensile testing from dilated tissue samples cut in the axial and circumferential direction. They found no difference in stiffness in both directions for dilated tissue concluding that dilated abdominal tissues were isotropic. Thubrikar et al. (2001) also performed uniaxial tensile testing on abdominal aneurysms but on sample taken at specific locations on the aneurysm. They concluded that significant regional variations in thickness and stiffness exist and this must be taken into account to understand where rupture might occur. Later Raghavan et al. (2006) also came to the same conclusion that regional variations exist in dilated abdominal tissue in thickness, stiffness, and failure properties when comparing samples from the anterior and posterior side of the aneurysm.

Mechanical analysis of abdominal aortic tissue from both aneurysmal and healthy tissue have served as a basis to extend acquired knowledge to the AA and attempt to better understand the pathogenesis of dilated AA. Early work of Okamoto et al. (2002, 2003) showed the nonlinear behaviour of aneurysmal tissues under biaxial testing and a decrease in extensibility with age. They also found that the mean circumferential stress increased with blood pressure and diameter, which support the clinical importance of blood pressure control and serial evaluation of aortic diameter. However, no directional dependency in stiffness was found. Since aneurysms of the AA are associated with Marfan syndrome, BAV and diseased TAV patients, Okamoto et al. carefully split the patient population and found significant difference in distensibility between patient groups. Using uniaxial testing, Vorp et al. (2003) investigated the maximum stiffness of tissue strips that were cut in the longitudinal and circumferential direction of dilated tissues. They found a directional dependency in ultimate stiffness where the axial direction was the stiffest and on average dilated tissues were significantly stiffer than healthy tissues. Until very recently, Okamoto and Vorp's studies were the only ones regarding the characterisation of dilated AA tissue from a human source.

In a recent study, Iliopoulos et al. (2009) investigated local variations in the mechanical and biochemical properties in dilated and healthy human AA. They were able to show that some heterogeneity exists in stiffness in healthy and aneurysmal AA around the circumference of the vessel but very few and weak statistical differences were found. Unfortunately, no information on the valve type was provided. This distinction between valve types is essential in aneurysmal AA tissues since the remodelling of the

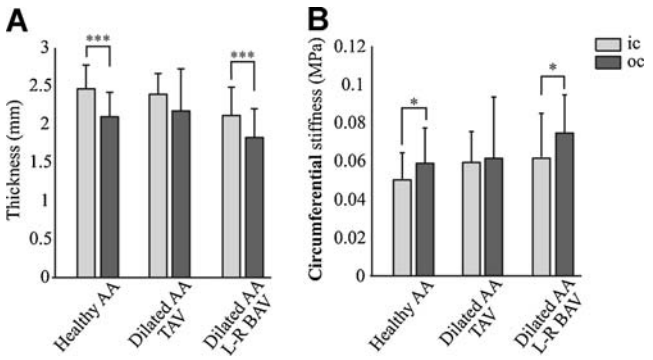

Figure 4. Local variations in thickness (a) and circumferential stiffness (b) between the inner (ic) and outer curvature (oc) for healthy and dilated AA with a TAV and L-R BAV. ***P-value <0.001, t-test; *P-value <0.05, t-test.

vessel involved in the dilation is believed to be dependent on valve type (Isselbacher, 2005). The works from Okamoto et al. (2002, 2003) are the only existing studies on the mechanical properties of dilated AA tissue that distinguished TAV from BAV and showed differences in the overall stiffness between these two types of valves. In addition to valve type, we believed that grouping BAV phenotypes is required to better understand the contribution of hemodynamic forces in the dilation process. Two recent studies from our research group (Choudhury et al., 2009 and Figure 5) have investigated the local mechanical and biochemical properties of healthy and dilated AA. In these studies, we have carefully grouped the sample by valve type and BAV phenotype (the latter study) in addition to precisely take samples from specific locations around the AA. We showed for the first time that a significant heterogeneity in stiffness and thickness exists around the circumference of healthy AA with a normal TAV and dilated AA with a L-R BAV (see Figure 4). We also found on average that L-R BAV tissues were significantly thinner and stiffer than healthy and dilated TAV tissues. Locally, the inner curvature in healthy and L-R BAV tissues was the least stiff and the thickest. This shows that local remodelling of the ascending aortic tissue exist in dilated tissues but is also present in healthy sample which supports the hemodynamic remodelling hypothesis. We think that natural reinforcement occurs at the outer curvature to compensate for the increase in stresses from the directed blood flow that exerts high forces at this location. As the blood flows through the aortic arch, it makes almost an 180° turn to reach the descending aorta. This change in direction is made possible only if the ascending exerts a force on the flow. From a mechanical point of view, the outer curvature exerts a greater force on the blood flow than the inner curvature. Inversely, this directed blood flow exerts higher shear and pressure stresses on the inner wall surface of the outer curvature, which are transmitted deep in the aortic wall of the outer curvature as tissue stresses. Over a long time this local distribution of fluid stresses could trigger and maintain dilation. On the other hand, the inner curvature, less stiff, is not exposed to the directed blood flow ejected from the left ventricle. Moreover, we showed that remodelling was valve dependent. Unfortunately, at this time we have not collected a significant number of other BAV phenotypes (N-R or N-L) to compare the effect of valve morphology on the mechanical behaviour of the tissues. Further investigation is needed and such study will provide valuable data.

VSMCs are the largest cell population in the vascular tissue. They are mainly responsible for the remodelling of the aortic wall and therefore are believed to play an important role in the local remodelling, which occurs during aneurysms formation and progression. It has been well documented that VSMCs can switch from a contractile to a synthetic phenotype (Shanahan and Weissberg, 1998; Ailawadi et al., 2009). In a recent study from our research group (Tremblay et al., 2010), we studied the variation in contractile phenotype around the circumference of the AA. Early works on the effects of VSMC contraction on vessel mechanical properties have been mainly conducted by Cox (1975, 1976, 1977); Dobrin and Doyle (1970); and Dobrin and Rovick (1969). In brief, they found an increase in stiffness under active mechanical testing in particular at low strain values in canine carotid and iliac arteries. Along with stiffness, the anisotropic properties of aortic tissue have been investigated under passive and active testing. Using uniaxial testing on strips cut in the circumferential and axial direction, Attinger (1968) found the anisotropy of dog arteries to increase under active testing where the circumferential direction was the stiffest, which correspond the principal orientation of the VSMCs. However, no studies have looked at the local contribution of VSMCs to the mechanical properties of aortic tissues. In our study (Tremblay et al., 2010), we found on average that contracted VSMCs increased tissue stiffness but no difference where found around the pig AA. However, we found that the magnitude of contraction was significantly different around the circumference of the pig AA. The outer curvature showed a weaker contraction than the inner curvature although the latter had the lowest VSMC density. These results strongly support the hypothesis of a phenotype variation around the circumference of the vessel and could explain why tissue remodelling occurs non-uniformly. This could explain local predisposition in tissue degradation or remodelling capabilities that would occur in the outer curvature where dissection and dilation are most likely to occur (Gomez et al., 2009).

COLLAGEN AND ELASTIN CONTENT

Structural changes in the composition of the AA are hypothesised to cause dilation. While reinforcing the hypothesis that collagen strongly contribute to increase stiffness and that elastin contributes to increase distensibility, Sokolis et al. (2006) have also reported that elastin becomes load-bearing at low strain, and collagen at physiologic but mostly at higher strain values. This suggests that aortic stiffness must be characterised at both low and high strain values in order to correlate the elastin and collagen content with the mechanics in aneurysmal human tissue. Regardless of the technique used to quantify the collagen and the elastin content, very few studies have been able to demonstrate that a change in the composition of the arterial wall results in a change in the mechanical properties of the arterial wall. In dilated human AA tissues, Iliopoulos et al. (2009) found that elastin, but not collagen content, decreased in aneurysmal specimens and displayed a lower wall thickness with a higher stiffness than healthy tissues. Contradictory results were found by de Figueiredo Borges et al. (2008) showing a decrease in collagen content in aneurysmal tissues compared to healthy tissues. However, these two studies provided no information on valve type present making it difficult to test the hypothesis that the pathogenesis mechanisms involved in the dilation are dependent on the AA valve type. Indeed, aneurysms associated with TAV have shown severe elastin degradation and lost of VSMCs (Collins et al., 2008) where BAV are associated with a reduction in elastin when compared to TAV and to healthy tissues (Cotrufo et al., 2005). However, contradictory results have been reported where elastin was preserved in BAV and but decreased in TAV (LeMaire et al., 2005) or

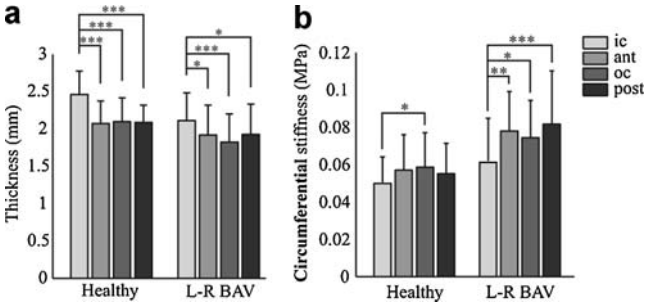

Figure 5. a) Local variations in collagen content between the inner (ic) and b) outer curvature (oc) for healthy and dilated AA with a TAV and L-R BAV. *P-value <0.05, t-test.

significant differences in elastin and collagen content were found between the two valve types (Fedak et al., 2003). We know that MMPs have the capabilities to degrade elastin and collagen during aortic remodelling. In the literature, all existing studies regarding the MMPs expression in dilated AA tissue have found an increase in MMP-2 in BAV in comparison to TAV in which an increase in MMP-9 was found. They all conclude that unique MMP level profiles are observed in TAV and BAV, which suggests different mechanisms of extracellular matrix remodelling involved in the pathogenesis of dilated AA tissue (Fedak et al., 2003; Boyum et al., 2004; LeMaire et al., 2005; Ikonomidis et al., 2007; Schmoker et al., 2007). These studies clearly show that distinct MMP profiles exist between valve types but no one has compared the MMP profiles between BAV phenotype which, again, could give support to the hemodynamic remodelling hypothesis.

A hallmark of hemodynamic remodelling is focal changes in tissue content and structure. Regionally, very few studies have investigated the variation in collagen and elastin. Corte et al. (2006) have found that collagen was reduced in the outer curvature in comparison to the inner curvature in BAV tissues. Complementing this study, Cotrufo et al. (2005) observed more severe elastic fibre fragmentations in the outer curvature versus the inner curvature in BAV tissues. However, Collins et al. (2008); and Iliopoulos et al. (2009) found no particular region on the aortic circumference that was more severely affected regarding collagen and elastin content and/or fragmentation. A recent study from our research group (see Figure 5) showed that significant heterogeneity in collagen content exists around the circumference of healthy and dilated AA, L-R BAV. Moreover we found that L-R BAV tissues were significantly thinner and stiffer than healthy and TAV tissues but this finding was not correlated with an increased collagen content where high strain stiffness (tissue stiffness under high strain) and collagen content was hypothesised to be correlated (Lesauskaite et al., 2001). In addition to collagen content itself, the structural organisation and the crosslinking network of the tissue need further analysis to better correlate the mechanics with the structure and understand the impact on vessel stiffness.

AORTIC REPLACEMENT MATERIALS

Today, the only available treatment for ascending aortic aneurysms is surgery: removing the diseased part of the aorta and reconstructing the vessel with a synthetic graft and patching materials from synthetic or biological sources. Michael E. DeBakey was the first to perform the resection and replacement of an AA aneurysm with a homograft in 1954 (DeBakey et al., 1954). This achievement is considered as the most dramatic progress made in aortic aneurysm surgery to date and marks the initiation of modern aortic surgery. Although Goyanes (1906) used the saphenous vein to treat peripheral arterial disease to reestablish the native arterial continuity of small arteries, DeBakey's technique was now applicable to any size of artery. Later, the initial enthusiasm towards this new technique was tempered by difficulties in harvesting, preparation, and durability of homografts. As a result, Arthur Voorhees proposed a synthetic substitute made of Vinyon-N to overcome the shortcomings (Voorhees et al., 1952). Since then, many type of synthetic grafts have been developed for the treatment of vascular diseases. Nowadays, surgeons use grafts and patches made of manufactured synthetic material and from biological sources. Since the ideal vascular prosthetic does not exist, the proper material choice is highly dependent on the type of treatment required. The ideal graft would have characteristics to minimise the thrombosis reaction state over time (Moore, 2002). More specifically, it should be impermeable, thromboresistant, compliant, biocompatible, durable, resistant to infection, easy to sterilise, easy to implant, readily available, and cost-effective (Scales, 1953).

For AA aneurysms resection, a cylindrical shape synthetic graft is mainly used. In addition, surgeons may use grafts from biological sources like pericardium (sac that contains the heart) for fitting or patching if needed. Many types of pericardium can be used: porcine, bovine, or human. The variety of materials used in AA surgery begs the question: are all these materials mechanically compatible with the native surrounding tissue?

Mechanical compatibility of graft materials used for the treatment of aneurysms of the AA and their ability to behave mechanically similar to the native aortic tissue are essential. It has been shown that compliance mismatch is an important contributor to thrombosis and graft patency (Abbott et al., 1987). Indeed, this mismatch is believed to contribute to local intimal hyperplasia (thickening of the intimal layer) due to stress concentration (Ballyk et al., 1998; Surovtsova, 2005) or abnormal wall shear stress (Weston et al., 1996) at the junction between native tissues and vascular prosthetics or graft materials. Moreover, Stewart and Lyman (2004) found an abnormal protein distribution at the junction thus depriving the wall from proteins in the mainstream blood flow, which could potentially lead to intimal hyperplasia. Compliance of vascular prosthetic for the AA affects the pressure into the whole arterial system (Dobson et al., 2006) and distal prosthetic hemodynamics (Miyawaki et al., 1990; Stewart and Lyman, 1992; Kim et al., 1995). It has been shown that reduced arterial compliance has been implicated as a risk factor for future cardiovascular events in hypertensive patients (Schiffrin, 2004; Sollers et al., 2006). In brief, replacing sections of the arterial system with non-compliant tubular material may affect the hemodynamic of the whole arterial system over a long period of time, in which case a better material would be essential for the treatment of young patients. Thus comparing the mechanical response of all tissues (including the native tissues) involved in aortic reconstructions will help to better understand the outcome of AA surgery and predict prosthetics and/or grafts patency rate.

Most of the mechanical analyses performed on pericardial tissues compared the effect of glutaraldehyde (a fixative) on the mechanical response of these tissues. Both bovine (Lee et al., 1989) and human pericardium (Vincentelli et al., 1998, 2000) have been tested uniaxially to propose better tissue fixation treatment to improve its durability and stiffness for better handling during surgery. However, none of these studies have compared their findings with the mechanical properties of native tissue. Lee and Wilson (1986) compared the mechanical behaviour of woven and knitted Dacron grafts and expanded polytetrafluoroethylene

(PTFE) grafts with the canine iliac artery and iliac vein using uniaxial testing. They showed significant differences in stiffness between the synthetic materials and the native tissues. Recently, Tai et al. (2000) have also compared graft materials with the human saphenous vein and muscular artery using pressure-diameter testing. They also found significant differences between the graft materials and human tissues, which supports the need for mechanically better graft material. In a recent study from our research group (Tremblay et al., 2009), we have carefully compared, using the same testing protocol, the mechanical behaviour of various material that can be used as replacement and/or patching materials either from synthetic or biological sources. We showed that both healthy and dilated AA are significantly less stiff than any of the replacement materials tested: fresh and glutaraldehyde fixed human pericardium, commercially available Peri-Guard bovine pericardium (Synovis, St. Paul, MN) and Gelweave Dacron grafts (Sulzer Vascutek, Renfrewshire, Scotland). At physiological strain, our results showed that Dacron is 25 and 18 times stiffer than healthy and dilated AA. To put these results in context, pressure values that would stretch healthy tissue by 25% will only stretch a Dacron graft by 9%. When looking at the other graft materials, none of them are getting even close to the mechanical properties of the native tissue, healthy or dilated.

Combining our findings with the ones found in the literature, there is no doubt that significant differences in mechanical properties of graft materials and human ascending aortic tissue exist. There is still much work that needs to be done in designing replacement materials to better mimic the mechanical behaviour of native tissues while being durable, thromboresistant and easy the handle for the surgeon.

CONCLUSION

The factors that cause dilation of the AA are still lively debated. It is believed that the hemodynamic forces have an impact on the initiation and progression of the disease. To date, unfortunately, no clinical study has been able to directly connect hemodynamic data with structural remodelling leading to changes in tissue mechanical properties. Combining hemodynamic and structural remodelling data can potentially unveil the underlying pathogenesis mechanisms or significantly converge towards more specific mechanisms and providing alternative treatments to surgery.

While clinicians and experimentalists are investigating the disease initiation and progression process, surgical procedures using replacement materials have remained consistent in the use of a few biomaterials. However, we have shown in this review that there is still significant room for improvements and efforts for designing replacement materials that mimic the mechanical behaviour of native tissues. This will greatly improve graft function from which patients will benefit.

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