Surgical solutions for complex aortic root pathology

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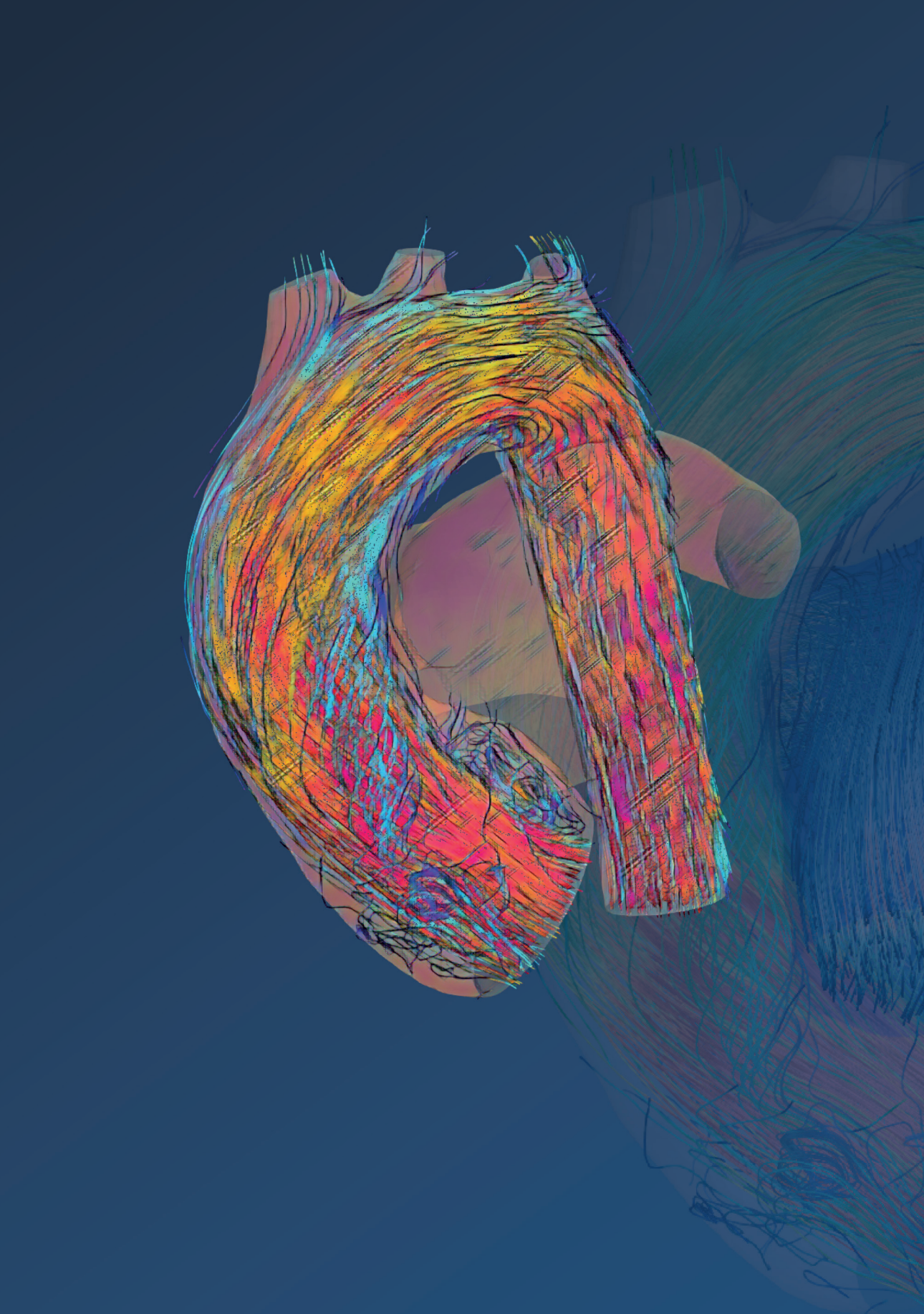

GENERAL INTRODUCTION

CHAPTER 1

THE HEART

The heart is the first functioning organ during human embryology and continues to beat over 2 billion times during an average humans' lifetime. It consists of four chambers: 2 atria and 2 ventricles (Figure 1). Functionally, it can be divided into the 'right' sided heart, which receives blood from the body and pumps it to the lungs for oxygenation, and the 'left' sided heart, which receives oxygenized blood from the lungs and distributes it to the rest of the body. Although its function is simple – to distribute oxygenated blood to the rest of the body – the functional and structural components underlying this action are far from simple. Several processes are working simultaneously to achieve adequate cardiac function. Electric conduction needs to be optimal to provide synchronized contractions of both atria and, sequentially, the ventricles; contractility of the myocytes in the ventricular wall needs to be sufficient to overcome the hearts afterload; and the valves in the heart must facilitate easy forward flow, while preventing backward flow of blood. All these components must function optimally and in close cooperation with systemic factors such as vascular resistance and fluid status. In addition, they need to be able to adjust to altering systemic demands, for example during physical activity or illness. Any failure in one of these components will affect all other processes, eventually resulting in less efficient cardiac function and, ultimately, heart failure.

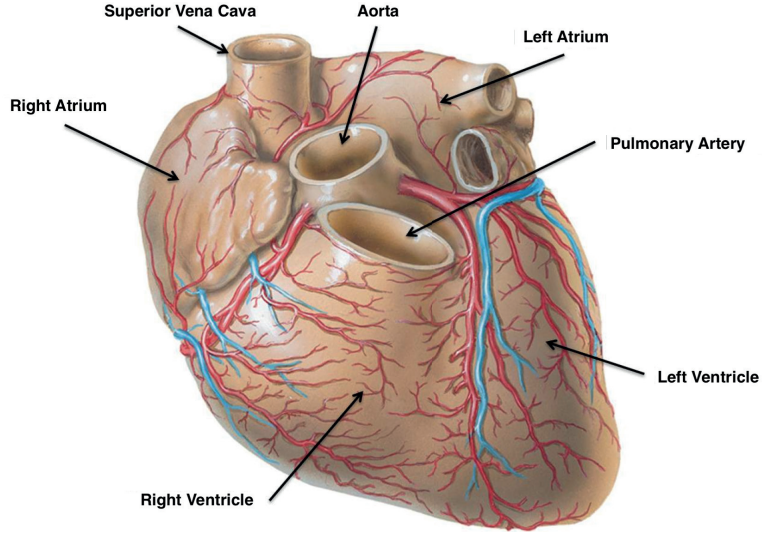

Figure 1. The human heart. *Adapted Netter illustration used with permission from Elsevier Inc.*

The aortic valve and root

The aortic valve is located between the left ventricle and the aorta. Its function is to permit unrestricted ejection of blood from the left ventricle, and prevent backflow once ventricular ejection stops. Rather than a simple trapdoor, the aortic valve is a complex three dimensional apparatus consisting of 3 semilunar cusps – or leaflets – three sinuses – the sinuses of Valsalva – the interleaflet triangles, and the sinotubular junction. These structures combined are called the aortic root. The sinuses are dilated pouches at the most proximal part of the aorta. The leaflets are suspended in these sinuses, giving them its crown-like shape (Figure 2). Out of two of these sinuses, the left and right coronary arteries originate. The three cusps and sinuses are named after these respective coronary arteries, resulting in left-, right- and non-coronary cusps and sinuses. The interleaflet triangles are the parts at the ventricular side between the hinges of the valve leaflets with its lower border at the nadir of the leaflets. Finally, the sinotubular junction is located at the highest point of the attached leaflets, the commissures, and marks the junction between the sinuses of the aortic root, and the tubular ascending aorta. The close relation between all these components can be explained by the embryonic development of the left (and right) ventricular outflow tract.

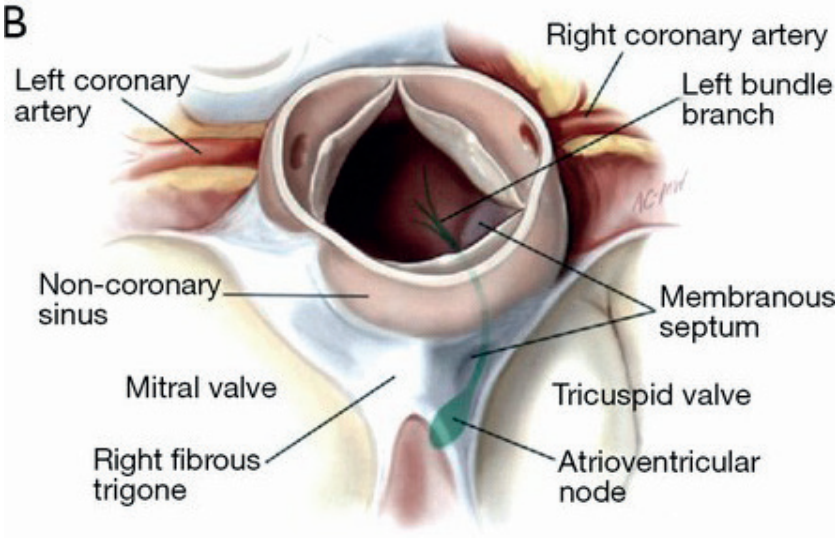

Figure 2. The aortic root and surrounding structures. *Adapted from Carpentier et al., 2010.*

Embryonic development of the left ventri-cular outflow tract and aortic valve complex

The ventricular outflow tracts can be divided into three parts: the most proximal part, consisting of the ventricular part of the outflow tract; the middle part, starting at the hinges of the valve leaflets and extending up to the sinotubular junction; and the distal part, the intrapericardial part of the aorta from the sinotubular junction to the pericardial lining. By the 4th week of gestation, the primordial heart has a tubular shape, consisting of 2 layers; the primary myocardium and endocardium. During the process of cardiac looping, the primary myocardium secretes 'cardiac jelly', which forms endocardial cushions at the outflow (and inflow) portion of the looped cardiac tube. Fusion of these two primary endocardial

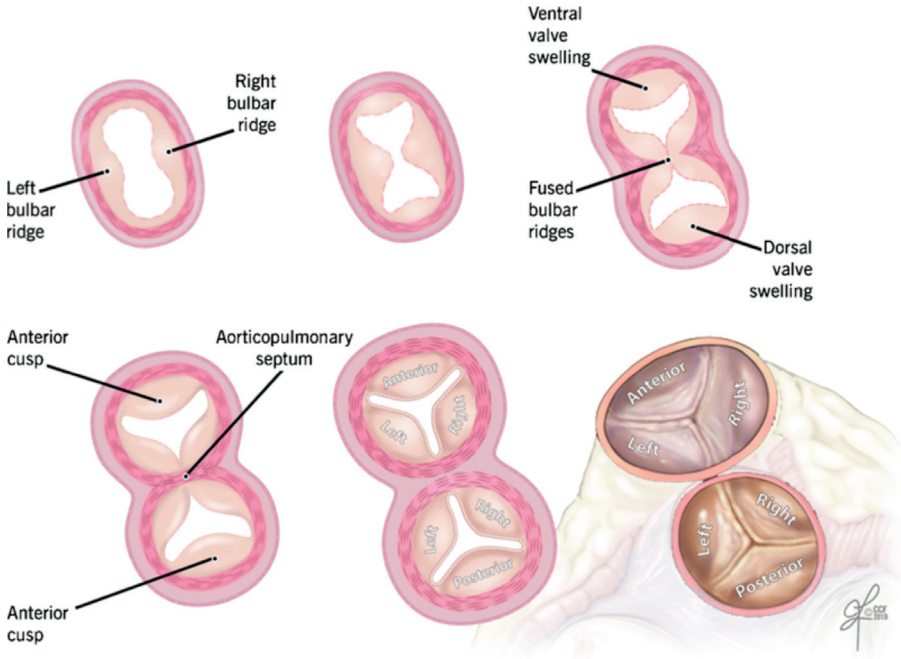

Figure 3. Development of the aortic and pulmonary valve leaflets. *Reproduced with permission*

cushions results in a separation of the left and right sided outflow tracts. This fusion starts in the distal part of the outflow tract and progresses proximally. Simultaneously, two intercalated cushions form at the middle part of the outflow

tract, at the remaining two quadrants of the original common trunk. It is the location of these intercalated cushions that determine the location of the arterial valve apparatus in the outflow tract [1,2].

The lateral margins of the primary cushions do not fuse, resulting in what will become the left and right leaflets of the aortic and pulmonary valves (Figure 3). The intercalated cushions will become the non-coronary (posterior) cusp of the aortic valve, and anterior leaflet of the pulmonary valve. The valve leaflets are formed by a process in which the endocardial cushions are excavated, with simultaneous ingrowth of non-myocardial cells which form the arterial wall of the sinuses. As the myocardium moves proximally, these tissues fill the gaps between the semi-lunar shaped leaflets, and will thin, ultimately forming the interleaflet triangles.

These processes, which form the outflow tract including the aortic root, show how interrelated all these structures are, and that failure in one of these processes, or one of these structures, can result in aortic valve disease and ventricular outflow tract obstructions.

Histology of the aortic valve leaflets

As shown previously, the aortic valve apparatus is a three dimensional structure. When observed from the aortic side, the three leaflets each cover 120 degrees of the circumference of the aortic root wall. The free margins of the valve leaflets, the coaptation areas (or lunulae) of the respective leaflets, appose to provide a tight seal. In the middle, where all three leaflets meet, there is a small thickening, the nodule of Arantius. This nodule demarcates the middle of the free margin. Small fenestrations in the coaptation area are often present, but do not impact valve competence.

Histologically, three distinct layers can be observed in the leaflets: the lamina fibrosa at the aortic side, the lamina spongiosa in the middle and the lamina ventricularis on the ventricular side. The lamina fibrosa consist of circumferentially orientated collagen fibers, which diverge from the commissures towards the middle of the leaflets, where they intertwine and form a dense honeycomb figuration. This thick and dense layer contributes most to the structural strength of the leaflets. Collagen fibers from the fibrosa curve inward into the sinus wall where they interdigitate with elastic and muscular layers of the sinus wall, sharing the mechanical stress during valve closure[3].

The central lamina spongiosa is thicker at the basal part of the leaflet, and thins or even disappears towards the free margin. It is rich in proteoglycans and glycosaminoglycans, which allow smooth sliding of the other layers. Furthermore, the proteoglycans act as a shock absorber during valve opening and closure.

The lamina ventricularis is primarily composed of radially orientated elastin fibers, giving the leaflet its elasticity. A continuous layer of endothelial cells cover the layers of the valve leaflets from the sinuses and continue into the endocardium on the ventricular side.

The endothelial cells are aligned circumferentially, perpendicular to the direction of blood flow. This is in contrast to endothelial orientation in the rest of the vascular system [4]. Even when cultured with a matrix parallel to flow, valvular endothelial cells were oriented perpendicular to the flow. This suggests that underlying fiber direction is not responsible for endothelial orientation [4]. Biaxial forces, rather than shear stress might be responsible for the orientation of endothelial cells in the aortic valve leaflets [5]. Furthermore, valvular endothelial cells may be important in regulating interstitial cell phenotype and extracellular matrix synthesis [6].

Valvular interstitial cells (VIC's) regulate and synthesize the extracellular matrix (ECM). They are predominantly smooth muscle a-actin-positive cells and fibroblasts. Continuous remodeling of the valve is achieved by synthesis of ECM components. This plays an important role in coping with the wear and tear during the valve's lifetime. Valvular interstitial cells have shown to be able to change their phenotype [7]. This alteration in VIC phenotype (e.g. into osteoblastic VIC) may play an important role in the pathogenesis of (senile) valvular diseases.

Stress/strain properties of the aortic valve

The aortic valve leaflets are subject to several forces during each cardiac cycle: shear stresses, leaflet strain (both radially and circumferentially), mechanical pressure, and bending forces. The ventricular side of the leaflets is subject to laminar shear stresses with a high velocity as a result of ventricular ejection, but the arterial side of the leaflets are subject to low-velocity multidirectional shear stresses. As a result of these forces, the valve leaflets stretch during diastole and shorten during systole, more so in the radial direction than circumferentially[8]. This interaction between stress and strain on the valve leaflets is shown in Figure 4. At the beginning of systole, the elastin fibers stretch with minimal stress while

the collagen fibers start unwrinkling. At end-systole with increasing stress on the valve leaflets, the collagen fibers are uncrimped and take the load of diastolic pressure, with high stress and minimally increasing strain. As described in the previous section, this high stress is shared with the wall of the sinuses of Valsalva through the interdigitated collagen fibers, resulting in an inward motion of the commissures during diastole. At the end of the cardiac cycle, the inverse occurs as pressure on the leaflets minimizes and the elastin fibers recoil the leaflet.

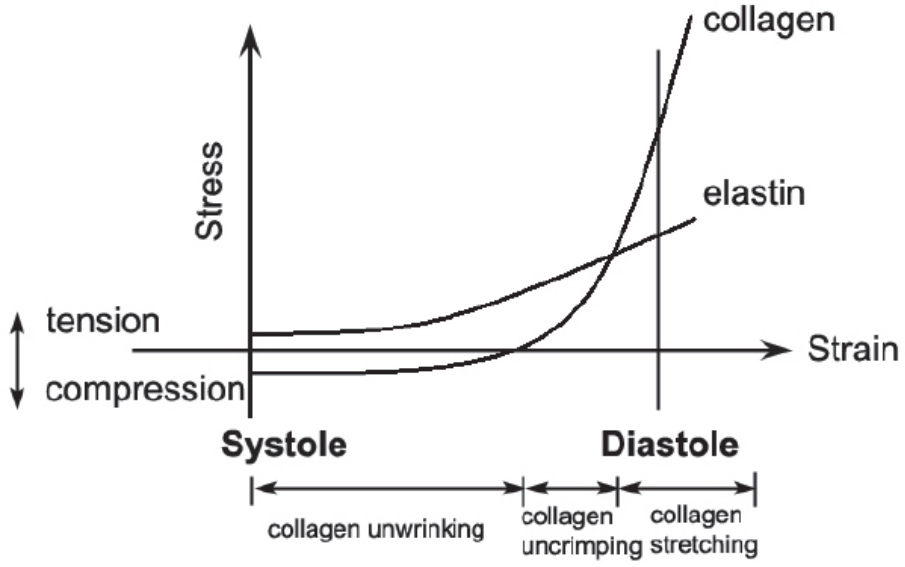

Figure 4. Stress/strain properties of the aortic valve. *Reused from Schoen FJ, Levy RJ. Journal of Biomedical Materials Research. 1999 Dec 15;47(4):439–65, with permission.*

Dynamics of the aortic root during the cardiac cycle

The aortic root is a dynamic structure, which changes during the cardiac cycle. Studies in canine aortic roots with markers placed at the leaflets and sinus wall, analyzed with fluoroscopy, show movement of these structures during the cardiac cycle [3]. The direction of these movements depends on the type of tissue forming these structures. In the sinuses, at the level of the commissures, the compliant characteristics of smooth muscle cells in the aortic wall result in a passive, outward direction during systole as a result of increased pressure [3]. At end-systole and during diastole, outward pressure on the aortic wall decreases, and pressures on the aortic valve leaflets increase, resulting in a decrease in diameter

at the level of the commissures [3]. Functionally, these changes in diameter have several consequences. More space between the leaflets and sinus wall prevents obstruction of the coronary arteries during systole. Furthermore, vortex formation in the sinuses improves coronary blood flow[9], and may also exhibit an inward force on the valve leaflets, facilitating easier valve closure [10-12].

The diameter at the base of the valve leaflets reaches its maximum during early systole, enabling easy valve opening. During systole, the diameter decreases as the ventricular wall, in which the leaflets are suspended, contracts. At end of systole, just before coaptation of the valve leaflets, the diameter of the base of the aortic valve is minimal, facilitating easy valve closure. During diastole, this diameter increases again [13]. The normal ratio between annular diameter and the diameter at the level of the sinotubular junction is 1.15 / 1 in diastole.

AORTIC VALVE DISEASE

Prevalence and etiology

Aortic valve disease is the second most common valvular disease in the general population of developed countries and its prevalence increases with age. [14] Aortic valve stenosis is more common than aortic valve regurgitation. A population-based study in North-America showed an increasing prevalence of aortic valve stenosis from 0.02% in persons aged between 18 and 44, to 2.8% in the population over 75 years of age [14]. Within patients who undergo valve intervention, aortic valve stenosis is the most common disease, accounting for over half of the interventions [15].

Aortic valve disease in neonates and children

Congenital aortic valve stenosis represents approximately 5% of congenital cardiac malformations [16]. The most common congenital anomaly is a bicuspid aortic valve, with a prevalence of ~1–2% [17]. Often, one or more commissures are absent or severely underdeveloped; this can be accompanied by underdevelopment of the left ventricular outflow tract. In neonates with critical aortic valve stenosis, adequate systemic and coronary blood flow is dependent on a patent ductus arteriosus, which necessitates early intervention.

Noncritical aortic valve stenosis is often the result of a malformed valve (e.g. a bicuspid valve) [18]. Patients with severe stenosis often present early in life due to (severe) symptoms. However, patients with less severe stenosis go through a latent phase in which progressive stenosis occurs, but symptoms are absent or mild. These patients may present later in life as disease progression results in the presentation of symptoms.

In order to maintain left ventricular ejection, the left ventricle will become hypertrophic as a compensatory mechanism to the higher pressure needed to pass blood through the stenotic valve. Depending on the severity of LV hypertrophy secondary to aortic valve stenosis, coronary perfusion of the hypertrophic ventricular wall may be insufficient. This can lead to relative ischemia of the endocardium, resulting in endocardial fibroelastosis. This further diminishes ventricular function and is a surgical challenge to remove, often with poor outcomes.

Isolated congenital aortic valve regurgitation due to absence or under development of a valve leaflet is very rare, with an incidence of 0.3% of congenital heart disease. [19]. It is, however, associated with several congenital heart diseases, such as tetralogy of Fallot and ventricular septum defects. Furthermore, connective tissue diseases may result in aortic valve regurgitation due to dilatation of the aortic root.

Aortic valve disease in the adult

The most common causes of aortic valve stenosis in developed countries is senile degeneration. In developing countries, rheumatic valve disease plays a more important role. In senile degeneration, progressive calcification of the valve leaflets leads to progressive sclerosis and stenosis. This calcification is mostly seen at the areas with most flexion of the leaflets, i.e. the coaptation line and the valvular attachment in the sinus wall [20]. Furthermore, stiffening of the valve leaflets reduces their elasticity and limits proper leaflet coaptation, resulting in some degree of valve regurgitation. Approximately half of the patients operated for aortic valve stenosis have a bicuspid valve. Although the exact mechanism of valvular calcification remains unclear, several factors are thought to influence its initiation and progression. Among these are the development of VIC's to the osteoblastic type due to stress, specific signaling pathways, and lipid and macrophage accumulation which resembles the process of atherosclerosis [21].

Patients with aortic valve stenosis can remain asymptomatic for a long time, as compensating mechanisms of the heart can cope with the increased mechanical demands for quite some time. In response to the increased ejection pressure, the myocardium of the left ventricle will become hypertrophic. By the time the compensating mechanisms fail, severe symptoms become present and patients' life expectancy is considerably impaired (Figure 5).

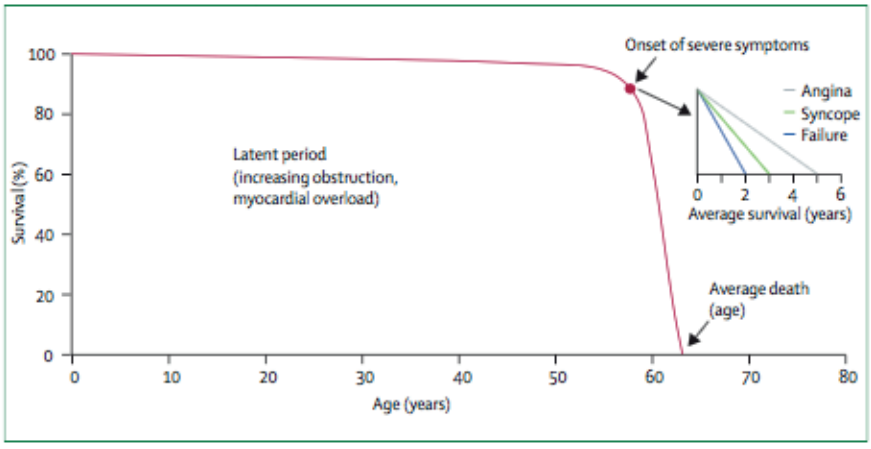

Figure 5. Survival of patients with aortic valve stenosis over time. *Adapted from Ross et. al. With permission)*

Aortic valve regurgitation can have several causes, depending on which part of the apparatus is affected. As previously mentioned, calcific disease, as well as bicuspid valves can lead to regurgitation due to decreased leaflet pliability resulting in inadequate coaptation. Furthermore, connective tissue diseases which lead to aortic root or ascending aorta dilatation (or even dissection or rupture) pull the commissures outward, resulting in malcoaptation of the valve leaflets. In these circumstances, the valve leaflets can still be normal, which may enable valve repair.

Infective endocarditis of the aortic valve is a life-threatening condition which requires urgent care. Destruction of the leaflets, as well as surrounding tissues, results in acute aortic valve regurgitation which can result in cardiac decompensation.

Rheumatic valve disease is characterized by fibrous leaflet thickening, often with fusion of one or more of the commissures. It has become rare in Western countries, but still remains an important cause in developing countries. Isolated aortic valve stenosis in rheumatic disease is uncommon, as it is often combined with mitral valve stenosis.

Treatment of rare causes of aortic valve disease, such as tumors, trauma and drug-induced aortic valve disease, depends on the reparability (e.g. removal of a fibroelastoma) of the valve. If a durable repair is not deemed possible, the valve needs to be replaced.

SURGICAL TREATMENT OPTIONS FOR AORTIC VALVE DISEASE

Several treatment options are available for the diseased aortic valve. Since the first (documented) aortic valve operation performed in 1912 by the French surgeon Theodore Tuffier[22], in which he pushed the aortic wall through a stenotic valve in a 26-year old male, many improvements have been made.

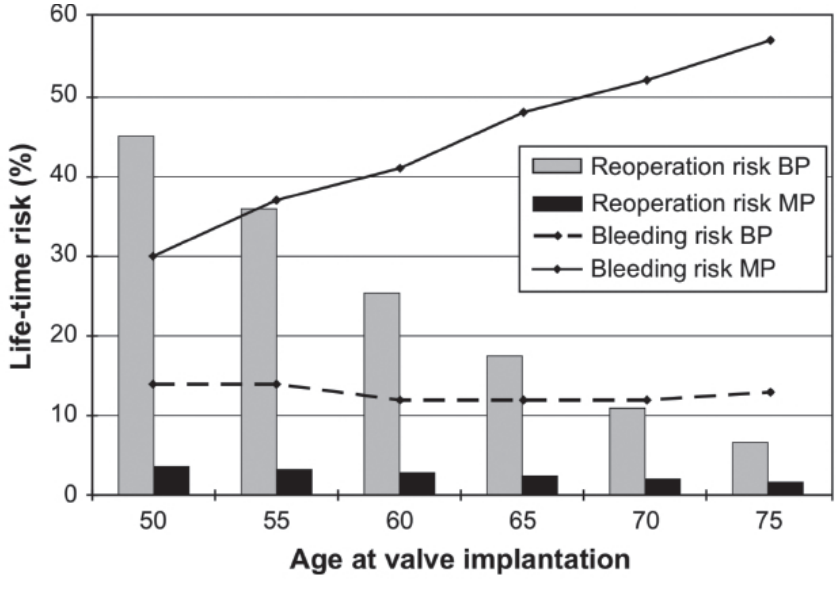

Figure 6. Lifetime risks of reoperation and bleeding after AVR with mechanical and bioprostheses. BP, Bioprostheis; MP, mechanical prosthesis. *Reused from Van Geldorp et al., JTCVS 2009;137:881-6, with permission.*

Depending on the underlying mechanism of failure, the valve and/or root can be repaired or replaced. An individual assessment of the valve leaflets needs to be made, in order to decide whether a valve repair is considered durable. In general, calcific disease of the valve leaflets is not suited for valve repair. When the valve or root needs to be replaced, several prostheses are available. Valve prostheses can be categorized in mechanical and biological prostheses. Within the biological prostheses, a further distinction between prostheses with and without a stent can be made. Furthermore, patients' own pulmonary valve (the pulmonary autograft), and human donor aortic valves (allograft) can be used to replace the aortic root.

Mechanical prostheses

Modern mechanical prostheses are composed of 2 semicircular leaflets rotating in struts attached to the valve housing. They are designed to last a lifetime, which is their biggest advantage, although replacement is still needed in approximately 5% after 10 years [23]. The thrombogenicity of these prostheses necessitates lifelong anticoagulant treatment with vitamin K antagonists. This puts patients at higher risks for bleeding events, although with strict (home) monitoring, these risks can be minimized.

Stented biological prostheses

Stented bioprostheses are the most commonly used aortic valve prostheses, especially in older patients [24]. Several stented biological prostheses are available. They can be categorized in pericardial prostheses and porcine valves. In pericardial valves, treated bovine, porcine or equine pericardium is mounted on a frame to construct valve leaflets, whereas in porcine valves, the aortic valve itself is mounted on a stent. As a result of these stents, the geometric orifice area, and consequently the effective orifice area (EOA), of stented valves is reduced.

Stentless bioprostheses

Stentless bioprostheses were developed to maximize the EOA thereby improving hemodynamics. Furthermore, it was believed that the more natural way the leaflets were incorporated in these prostheses would help improve their longevity. Studies have shown that left ventricular mass regression occurs faster after stentless valve replacement compared to stented valves, but that this difference disappears 1 year after prosthesis implantation [25]. Because of their larger EOA, stentless

prostheses are valuable options in patients with a small aortic annulus, and they facilitate larger prostheses during future transcatheter valve-in-valve procedures. Furthermore, some of these prostheses can be used as a root replacement in patients with an indication for aortic root replacement.

Homografts

Human donor valves (homografts or allografts) were introduced in the 1960's, and its successful orthotopic use was first described by Ross in 1962 [26]. Aortic and pulmonary homografts are procured from suited post-mortem donors and heart transplant recipients. They are generally sterilized with antibiotics and subsequently cryopreserved. As the number of available homografts is limited, and durability has shown to be comparable with some bioprostheses [27], the use of aortic homografts is limited, and mainly reserved for patients with extensive endocarditis affecting the surrounding tissues. Pulmonary homografts in the aortic position have shown to have a very limited durability [28].

Pulmonary autograft (Ross procedure)

Also introduced by Ross [29], the patient's own pulmonary root can be used to replace the aortic root. The pulmonary root is then replaced with a cryopreserved pulmonary homograft. Hemodynamics of the pulmonary autograft closely resemble that of a native aortic root. Furthermore, its capability to grow is a huge advantage in children, as replacement of the autograft due to growth of the child is not necessary. The valve leaflets of the autograft have shown to adapt well to the increased pressure in the systemic circulation compared to the pulmonary circulation. However, although the autograft wall thickens, the autograft stiffness is reduced compared to native aortic root walls, which may lead to dilatation in the long run [30]. The most often mentioned downside of this procedure is that it creates a dual valve problem for a single valve disease. Furthermore, technical difficulties limit its use to experienced centers.

Transcatheter aortic valve replacement

Since the first transcatheter aortic valve replacement (TAVR) in 2002 [31], the role of TAVR within aortic valve replacement is still being explored. In high-risk patients, TAVR is accepted as an alternative to surgery [32]. In the short term, TAVR seems

a reasonable alternative to surgery in the older (³75 years) intermediate- and low-risk patients with severe stenosis of their tricuspid aortic valve [33-36]. Long-term data, especially regarding structural valve deterioration, are still lacking and need to be awaited before its definite role in these patients can be established. The NOTION 2 trial, analyzing TAVR versus SAVR in all-comer patients between the age of 18 an 75 years is currently enrolling, and its outcomes need to be awaited to see if TAVR has a role in younger patients.

Valve sparing root replacement and aortic valve repair

In selected patients, the aortic valve may be preserved and surgically repaired. This depends on the size and pliability of the valve leaflets and surface of coaptation between the leaflets. If the valve is insufficient due to dilatation of the aortic root and/or ascending aorta, the valvular function can be restored by means of valve sparing root replacement.

Treatment options in aortic valve disease in neonates and children

As mentioned, critical aortic valve stenosis requires early intervention. Depending on the severity of outflow tract hypoplasia, a management strategy will be made which will in- or exclude the left ventricle. Often, (intra-uterine) balloon dilatation of the stenotic valve will be the first intervention, and growth of the left ventricle and outflow tract can sometimes be awaited. Balloon expansion of the stenotic aortic valve can result in subsequent regurgitation. However, this is generally well tolerated and postpones surgical intervention to later in life. In too severely hypoplastic left ventricles, a strategy towards a univentricular heart, in which the right ventricle provides both pulmonary and systemic circulation, will be adopted. When valve replacement is necessary, the Ross procedure, with our without LVOT enlargement using a Konno incision, provides a valuable solution, as the pulmonary autograft is capable of growing with the child. Replacement of the aortic valve with valve prostheses is often suboptimal, but may be required in specific situations, such as the inability to perform a Ross procedure due to a non-suited pulmonary valve. Furthermore, other indications for oral anticoagulation in older children, such as an existing cardiomyopathy, may plead in favor of mechanical valve replacement, provided an adequately sized prosthesis can be implanted.

Outline of this thesis

Aortic valve and root disease comes in many forms. This thesis is focused on complex aortic root pathology and the surgical possibilities that are available and the accompanying challenges that need to be overcome. Outcomes after aortic root surgery in complex root pathology, both in children and adults, will be presented and discussed, focusing on biological solutions. The data presented in this thesis can help patients, cardiologists and cardiac surgeons in their choice of therapy in complex aortic root disease.

Part 1 of this thesis is focused on the use of the pulmonary autograft in patients who need aortic root replacement (the so-called Ross procedure). Neonates and small children with concomitant left ventricular outflow tract obstruction next to their aortic valve stenosis require aortic root replacement with concomitant enlargement of the left ventricular outflow tract. One way to achieve this with the use of the pulmonary autograft is the so-called Ross-Konno procedure, in which the interventricular septum is incised to widen the outflow tract. In Chapter 2, the Ross-Konno technique and long-term outcomes are described. When no outflow tract obstruction is present, aortic root replacement with the pulmonary autograft remains a valuable option, especially in adolescents and younger adults. In Chapter 3, outcomes after root replacement with the pulmonary autograft are reported. In Chapter 4, a modified technique of the Ross procedure is presented in which the pulmonary autograft is reimplanted into a vascular graft to prolong its durability.

Part 2 of this thesis is focused on a biological stentless aortic root prosthesis, called the Freestyle prosthesis. This porcine aortic root can be used to replace the aortic valve and root for several indications. In Chapter 5 long-term outcome data on this prosthesis, with a special focus on the expected trajectory for each patient to aid in their choice of prosthesis, are presented. The Freestyle prosthesis can be used in several root pathologies, one of which is the challenging condition of infective endocarditis of the aortic root and surrounding structures. In Chapter 6, surgical techniques for this complex surgery are presented and outcomes in this high-risk patient group are discussed. In Chapter 7, outcomes after aortic root replacement using the Freestyle prosthesis are compared with outcomes after aortic root replacement using a composite mechanical prosthesis. Both

advantages and disadvantages of both types of prosthesis are discussed, and outcomes in a matched cohort are presented. Finally, in Chapter 8, clinical outcomes after reintervention on a Freestyle prosthesis that need to be replaced are reported. Both the underlying modes of failure and the types of reintervention are discussed with their respective procedural challenges and outcomes.

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