The Aortic Valve: Structure, Complications and Implications for Transcatheter Aortic Valve Replacement

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Abstract

The aortic valve operates in a complex hemodynamic environment, opening and closing over 100,000 times a day. When complications arise such as aortic stenosis, prognosis can be very poor, leading to death within the first few years. Surgical valve replacement is currently the standard treatment for aortic stenosis. A thorough understanding of the anatomy and function of the native valve is imperative when developing a prosthetic replacement that can withstand the complex demands of the heart. This review focuses on the anatomy, structure and disease of the aortic valve and the implications for a transcatheter aortic valve replacement (TAVR). Current complications with TAVR such as major vascular bleeding, conduction disturbances and patient-prosthesis mismatch (PPM) can be overcome by reducing the delivery profile and through use of more accurate imaging technologies to work towards a fully functional and durable prosthesis.

Keywords

Heart valves, transcatheter, aortic valve replacement, valve structure, aortic valve disease

Introduction

The aortic valve directs a one way forward flow of blood from the left ventricle of the heart to the rest of the body with minimal regurgitation and pressure drop.[1] These delicate and thin leaflet structures are subjected to a lot of rapid tensile, shear and bending stresses, opening and closing approximately 100,000 times a day and about 3.7 billion times in an average life-span. Historically, they were considered to react passively to regulate blood flow to keep us alive. However, it is now readily becoming accepted that the aortic valve undergoes a series of complex operations at the cellular and molecular level to maintain their function in the extreme hemodynamic and mechanical environments.[2] When these valves are congenitally malformed, diseased or subjected to trauma, their function is compromised leading to complications such as heart failure and eventual death if left untreated. In severe cases, surgical replacement with a prosthetic valve is the gold standard treatment. Aortic stenosis (AS) is the most prevalent disease. However, 33% of patients over the age of 75 with severe symptomatic AS are refused surgery due to the increased risk related to age and left ventricular function.[3] Transcatheter aortic valve replacement (TAVR) enables patients to receive a prosthetic heart without the need for open heart surgery. Since the first human intervention in 2002, there have been over 50,000 TAVR procedures.[4, 5] However, these valves can introduce the patient to other complications such as major vascular bleeding and stroke. A correct understanding of the anatomy of the aortic root is therefore vital when considering the design of a prosthetic valve, particularly in the case of a transcatheter delivered valve which sandwiches the native leaflets between the stent and the aortic wall and may create an obstruction to flow. The following sections of this review focus on the aortic valve's anatomy, pathology, the existing surgical replacement valves available and the implications for a percutaneous heart valve.

Gross anatomy and location

The aortic valve consists of three semi-lunar shaped leaflets and three dilations known as the sinuses of Valsalva. It lies within the aortic root which bridges the left ventricle to the

ascending aorta.[6] The base of the valve leaflets lie just below the anatomical ventriculo-arterial junction on a virtual ring known as the basal attachment.[7] It is this anatomical location between the ventricle and aorta that surgeons use to suture a valvular prosthesis.[8] The sinuses interject with the ascending aorta at a ring known as the sinotubular junction. In two of the sinuses lie the coronary ostia which give rise to the right and left coronary arteries. Thus, the sinuses are regarded as the right and left coronary sinuses respectively, and the third sinus is the non-coronary (or posterior) sinus.[1] The sinuses have a scalloped or crown like border running from the basal attachment to the sinotubular junction to which the semi-lunar side of the leaflets attach, creating a hinge on which the leaflets flex. Cut-aways of the heart exposing the anatomical position of the aortic valve and of the aorta are shown in Figures 1 and 2 respectively.

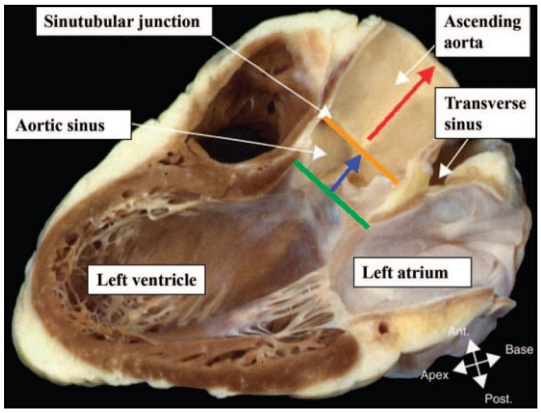

Figure 1. Anatomical position of the aortic valve in relation to the left ventricle, left atrium and ascending aorta of the heart. Green line shows the basal attachment of the aortic leaflets.[7]

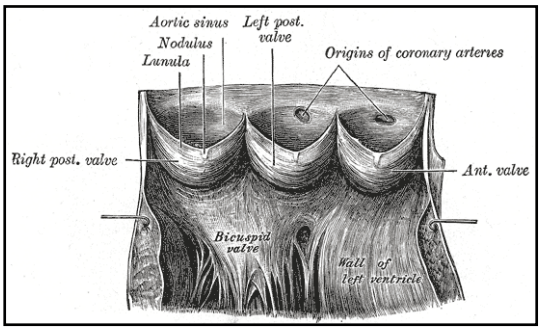

Figure 2. Cut away of the aorta showing the semilunar leaflets, sinuses of Valsalva and the coronary ostia.[9]

Three fibrous inter-leaflet triangles form between the leaflets and the basal attachment. The inter-leaflet triangle between the posterior and left leaflet are in fibrous continuity with the anterior leaflet of the bicuspid mitral valve (Figure 2). Thus a low placement of the valvular prosthesis within the left ventricular outflow tract (LVOT) may result in impingement on the mitral leaflet.[7] The triangle between the right and posterior leaflet is connected to the membranous part of the ventricular septum. In congenitally deformed valves, these triangles have been observed to be inadequately formed, providing a more annular shape than normal.[8, 10]

The leaflets can be considered to form part of a cylinder as they are flexed circumferentially but are flat in the radial direction. This enables them to easily reverse curvature during valve opening and closure.[1] The free edges of the leaflets come together at an angle of 120° to

prevent the back flow of blood.[11] The line of attachment where the leaflets come together distally is known as the commissures, which transfer the load from the leaflets to the aortic wall. The region where the free edges overlap is known as the coaptation region (or lunula), and forms due to a bend in the radial plane of the leaflets. This region functions to transfer the pressure load from the centre of the leaflets to the commissures.[1] Fibres form a thickened nodule at the centre of the free edges known as the node of Arantius which help to ensure full coaptation.

Valve dynamics

During ventricular systole, pressure in the left ventricle rises and overcomes the pressure in the aorta. This results in a rapid opening of the aortic valve with minimal resistance to blood flow. Blood reaches a peak velocity of approximately 1.35 ± 0.35 m/s in the first third of the cycle before decelerating and reversing flow. Ideally, the aortic valve would be required to open rapidly with minimal resistance. In a healthy valve, it typically opens in 20-30 ms. The deceleration reverses the pressure gradient, forcing the edges of the leaflets to come together and rapidly shut the valve with minimal regurgitation. The closing volume has been noted to be less than 5% of the forward flow. Whilst the pressure gradient across the open valve is less than 10 mmHg in a healthy valve, typical closing pressures are 80 - 100 mmHg.[12]

During forward flow some of the blood coils around the sinus edge, which then decelerates and forms eddy currents before returning to the mainstream flow. This action was first reported by Leonardo da Vinci in 1513 who observed vortices forming behind the leaflets of valves mounted on a glass model of the aortic root.[13] Similar experiments were carried out by Bellhouse and Talbot which agreed with da Vinci's findings on the role of the sinuses.[14] The vortices keep the leaflets afloat and create a pressure gradient on the lateral aspect of the leaflets in relation to the centre, pushing them together. If the sinuses were removed, the reversal pressure gradient of the mainstream flow is capable of valve closure but with less speed and efficiency. During diastole, when pressure in the ventricle drops below the aortic pressure, blood in the sinuses flows into the coronary arteries through the right and left coronary ostia.

The velocity profile of the blood flow through the aortic valve is laminar and typically flat although there is a slight skew caused by the orientation of the valve to the long axis of the left ventricle.[12] Although the aortic valve has generally been considered to react passively to the flow of blood, it in fact reacts dynamically to the hemodynamic changes during the cardiac cycle. For example, the base perimeter is largest at the end of diastole due to the LVOT and decreases by 9-22% at the end of systole.[1] The radius of the commissures also expands outwardly by 12% in systole and decreases by 16% in diastole.[15, 16] Additionally the leaflets are found to contract circumferentially during systole to increase the orifice area and extend radially during diastole to provide full coaptation.[17] It has been suggested that the design of the prosthetic aortic valve should be based on the dimensions of the valve at mid-diastole.[16]

Structure of the leaflets

The cellular constituents of the aortic valve can be divided into two types; the valvular endocardial cells (VEC) and the valvular interstitial cells (VIC). Together, these cells interact

in a complex hemodynamic and mechanical environment to regulate the valve.[18] The VEC encases all heart valves and serves as a non-thrombogenic barrier between the blood and leaflets. Their phenotypes have been found to be distinctly different from vascular endothelial cells. Additionally, they have been found to align perpendicular to the direction of shear stress whereas vascular endothelial cells are aligned parallel to the direction of flow.[18] VECs on the aortic and ventricular sides have also been reported to be intrinsically different. Calcification of the aortic valve originates from endothelial dysfunction and occurs on the aortic side of the leaflet.[2] It is possible that the greater shear stress exposed by the ventricular side increases the resistance of its VECs.

The VIC has characteristics between smooth muscle cells and fibroblasts and forms a network across the extracellular matrix (ECM) of the leaflets.[19, 20] It has been suggested that the VIC have several phenotypes including smooth muscle cells, myofibroblasts and fibroblasts. They exhibit contractile properties and regulate and synthesize components of the ECM.[2, 21] Contractile properties have been supported by evidence of α-smooth muscle actin expression when VICs were cultured in vitro. Additionally, they are involved in the inherent repair of the valve which is subjected to damage due to the complex hemodynamic environment and their absence in prosthetic valves may be a cause for structural failure.[18]

Due to their thin structure, the leaflets are practically avascular and obtain their nutrients from the surrounding blood. Interestingly, they have been found to be richly innervated, particularly on the ventricular side of the leaflet, apart from the lunula. Their significance is still not clearly understood but structural changes in response to neuromodulators may suggest adaptations to mechanical properties to cope with various pathologies such as hypertension.[22]

The ECM primarily consists of collagen, elastin and proteoglycans, each accounting for 60%, 10% and 20% of the dry weight of the valve respectively (Kunzelman et al.[23] cited by Flanagan and Pandit).[19] Collagen provides the valve leaflet with much of its mechanical strength whilst the elastin provides interconnections between the fibres and helps restore the collagen to its natural crimped state.[24] Proteoglycans are highly hydrophilic which act as shock absorbers during the dynamic changes in the valve.[2]

The leaflets of all valves are comprised of three layers; the fibrosa, spongiosa and ventricularis (atrioventricular valves also contain an atrialis layer which forms part of the spongiosa). These terms were first coined in 1931 by Gross and Kugel who carried out a thorough study on the topographical anatomy and histology of heart valves in an attempt to address mechanisms of valve failure.[25] The fibrosa is the thickest layer, consisting primarily of a dense network of type I collagen fibres arranged circumferentially. It appears to be the main loading bearer and extends throughout the whole of the tissue.[11] Collagen fibres have been found to be aligned circumferentially at the commissures which become more highly aligned in loading.

The ventricularis is a dense network of collagen and elastin fibres which face the ventricular chamber. The elastin fibres appear to be radially aligned which assists in reducing radial strains caused by fluid flow when the valve is fully open. Between the fibrosa and ventricularis is a watery connective tissue known as the spongiosa. This layer contains a high concentration of glycosaminoglycans and proteoglycans which are believed to lubricate the adjacent layers as they shear and deform relative to each other during leaflet flexure and pressurization.[1, 26]

Mechanical properties

Due to the circumferential and radial alignments of the collagen and elastin fibres, the valve leaflets have anisotropic and complex viscoelastic mechanical properties.[27] The structural deformation of the aortic valve can be divided into two mechanisms; flexure and tension.[28] Flexion occurs during leaflet opening and closure whilst tension occurs during full loading from the diastolic pressures. Loading aligns and straightens out the crimped collagen fibres along the direction of the force which results in an initial toe region as the collagen straightens out followed by a rapid linear response in a stress-strain graph (Figure 3a). The leaflets are significantly stiffer in the circumferential rather than the radial direction. In a study by Kalejs et al. the elastic modulus of human aortic valve was calculated to be 15.34 ± 3.5 MPa in the circumferential direction and 1.98 ± 0.24 MPa in the radial direction.[29]

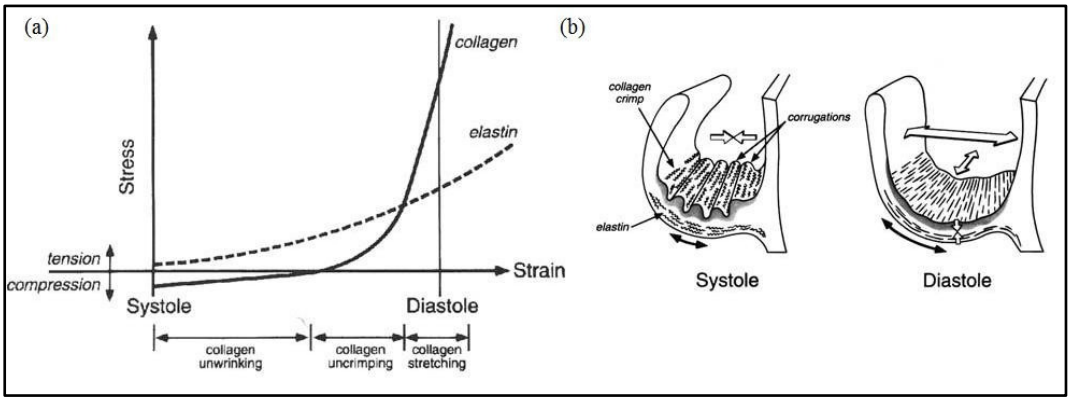

Figure 3. (a) Mechanical response of collagen and elastin during the cardiac cycle and (b) schematic representation of the aortic leaflet during systole and diastole.[30]

The leaflets are viscoelastic, meaning that their mechanical properties exhibit both elastic and viscous characteristics. In time dependant studies, the mechanical properties of aortic leaflets were found to be independent of strain rate. They were also found to exhibit continued stress relaxation but had negligible creep over a period of three hours.[11] Materials exhibiting stress relaxation have a gradual decrease in stress at a constant strain which is beneficial during the diastolic phase of the cardiac cycle. Creep is an undesirable characteristic since it would permit the leaflets to gradually stretch with time when subjected to a fixed load which could lead to a prolapsed leaflet.

In flexion tests, the ventricularis was found to support the leaflet in tension when flexed with the curvature of the leaflets, i.e. when the valve is open. The elastin fibres arranged radially in the ventricularis enable the leaflet to extend radially for full coaptation; enabling it to handle strains of 60%. However, the elastin in the fibrosa was shown to have minimal involvement in the radial or circumferential directions.[24] In a study by Mirnajafi et al., the flexural stiffness at the belly region of the aortic valve was found to be three times that of the commissures. It was also found to be higher when the commissures were flexed in the non-physiological reverse direction and decreased with increasing flexion angle in both directions. The decrease was attributed to local tissue buckling which reduced the effective thickness of the leaflet.[31]

Valvular diseases

Diseases of the heart valves compromise the normal valvular function leading to other complications to the surrounding structures. They may be caused by a variety of factors including congenital defects, age, lifestyle habits, trauma or infection. The following sections focus on the main valvular complications which arise from congenital deformations or due to degenerative disease.

Bicuspid aortic valves

Congenital valve defects range from a missing or complete closure of the valve as in aortic atresia, to sub-aortic or supra-valvular stenosis due to a narrowing of the left ventricular or aortic tract respectively, to poor formation of the valve cusps. The most common congenital abnormality is the bicuspid aortic valve (BAV), where two leaflets are fused together to form a single large leaflet. This occurs in 1-2% of the population and is more prevalent in males.[32] Certain characteristics define a BAV including leaflets of different sizes, a central raphe between the largest leaflet and a smooth leaflet margin even when diseased.[33] Difference in leaflet size occurs in 92% of BAV cases and most prevalent (86%) between the right and left coronary leaflets.[34] The disease is thought to be genetic since it is highly associated with other abnormalities of the aorta such as aortic coarctation. Additionally it has been hypothesised that a lack of microfibrillar proteins during valvulogenesis may disrupt full development of the valve leaflets as well as create a weakened aortic root structure.[35]

The incidence of patients with AS (a narrowing of the valve aperture) having a bicuspid, uni-cuspid or (rarely) quadri-cuspid valve[36] is particularly high.[1] The geometry of the valve has also been shown to play a role in leaflet calcification, thereby indicating a need to develop a valve with a native tri-leaflet design. Thubrikar noted that the greater the deviation from the normal design, the greater the number of valve replacements and the younger the patient needing replacement.[1]

As well as AS, congenital valvular abnormalities are also associated with aortic regurgitation, infective endocarditis, and aortic complications such as root dilation, aneurysms and dissection.[35] The occurrence of infective endocarditis in patients with BAV were found to range from 12% - 39% in surgical and autopsy studies.[34] Many patients with BAV have dilations of the aortic root, sinotubular junction, ascending aorta and aortic arch. These dilated structures lead to abnormal hemodynamics and shear stresses, which can accelerate calcific degeneration of the valve. BAV is commonly asymptomatic from birth and the patient can function normally for 50-60 years before symptoms arise. Symptoms detected from early childhood are generally due to severe valvular disease.

Aortic stenosis

Aortic Stenosis (AS) is a narrowing of the valve aperture, reducing the aortic valve area and increasing resistance to blood flow, thereby increasing the transvalvular pressure gradient. This obstruction increases the workload of the left ventricle leading to ventricular hypertrophy, although the ejection volume remains the same. In a random population study of

11,911 adults, the mass of the left ventricle was found to increase from 171.1 ± 70.1 g with a normal valve to 198.7 ± 80.9 g in patients with AS, suggesting ventricular hypertrophy.[37] The most common cause is calcific degeneration leading to stiffening and calcification of the tri-leaflet valve and restricting the motion of the leaflets. It can also be caused from Rheumatic fever due to inflammation of the leaflets although prevalence of this has decreased in developed countries.

Mechanisms of calcification in the valve seem to stem from disruption of the endocardium lining the aortic side which may be caused by increased mechanical stress or a decrease in shear stress. Additionally, the posterior leaflet is usually the first to be affected and this leaflet has a reduced shear stress compared to the left and right coronary leaflets due to the absence of the coronary ostia.[38] Calcific nodules form on the aortic side and at the base of leaflets and the histological process has been likened to atherosclerosis. Lipids are seen to infiltrate through the endocardial lesion and accumulate within the sub-endocardial and fibrosa layers. Low density lipoproteins are oxidised and are then taken up by macrophages to produce foam cells. Additionally, inflammatory cells such as macrophages and T-cells infiltrate through the lesion, releasing cytokines which remodel the extracellular matrix. A subset of myofibroblasts in the fibrosa layer has been shown to differentiate into an osteoblast phenotype which is capable of producing calcific nodules (Figure 4).

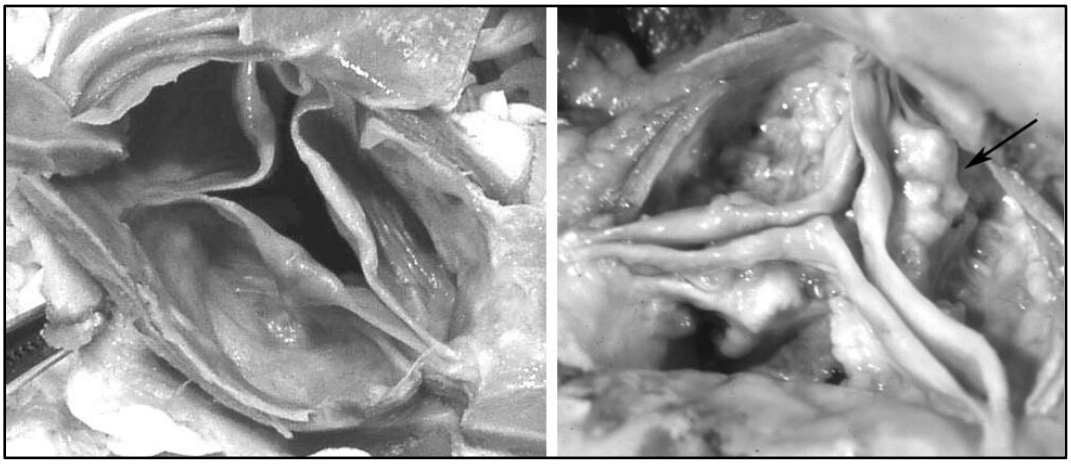

Figure 4. Photograph of a minimally diseased aortic valve and a severely calcified aortic valve. Arrow points to lipo-calcific changes to the aortic side although the commissures are spared.[38]

Based on the results of the Euro Heart Survey on Valvular Heart Disease, AS was prevalent in 33.9% of patients with a single native heart disease, making it the most common valvular disease in Europe and America.[39] The prevalence of AS increases with age and can be as high as 4.6% in people over the age of 75.[37] As the age of the population increases it is likely that the prevalence of AS is onset to increase annually. It is estimated that 3.5 million people in England will have AS by 2020, amongst which 4.3% would be classified as severe.[40]

AS may be symptomatic; exhibiting symptoms of angina, syncope or heart failure, or be asymptomatic.[41] In symptomatic or severe cases prognosis is poor, with death occurring in one to two years following symptom onset and the valve would require replacement through surgical intervention. The ACC/AHA guidelines grade severe AS occurring when the orifice area is less than 1.0 cm^2, the mean gradient is greater than 40 mmHg or the jet velocity is greater than 4 m/s.[41] In milder forms of AS with areas between 1 and 1.5 cm^2 and velocities between 3 and 4 m/s, surgery is considered if calcification is significant.[42] However,

approximately 30% of patients with severe AS over the age of 75 years do not undergo valve surgery due to technical complications such as a porcelain aorta, due to patient refusal, general frailty or serious comorbidity such as renal dysfunction.[43]

Aortic regurgitation

Aortic regurgitation (or insufficiency) is caused by abnormalities to the aortic leaflets or aortic root, resulting in a leakage of blood from the aorta to the left ventricle when the valve is closed. Before antibiotic treatment was available, the most prevalent cause of aortic regurgitation used to be Rheumatic fever. Nowadays, it is more commonly caused by insufficient leaflet coaptation due to calcific degeneration, congenital defects and infective endocarditis.[44-46] Other causes include trauma leading to perforations, cusp bending or a prolapsed leaflet.[47, 48] In chronic cases, the left ventricular volume leads to ventricular hypertrophy and recruitment of sarcomeres to accommodate the increase in volume.[32] Therefore a normal physiological stroke volume and ventricular diastolic pressure are maintained. Patients with chronic aortic regurgitation may be asymptomatic for decades.[49] Complex murmurs may be heard which include an early mid-systolic murmur as the left ventricle rapidly ejects the overload of blood and a holodyastolic murmur corresponding to early closure of the mitral valve in response to the increased left ventricular volume. A rumbling late diastolic murmur known as the Austin Flint murmur may be also heard corresponding to the partial or complete closure of the mitral valve during ventricular diastole due to the regurgitant jet flow from the aortic valve. In patients with acute aortic regurgitation, enlargement of the left ventricle does not occur to accommodate the extra volume. Consequently, there is a decrease in stroke volume which leads to tachycardia to increase the cardiac output. However, usually the increase in heart rate is insufficient to cope with the demand leading to pulmonary oedema (due to an increase in left atrial pressure) and cardiogenic shock.

Indications for valve replacement surgery

Generally, there are no effective treatments for AS or regurgitation except aortic valve replacement (AVR).[50] Additionally, there is no proof that medical treatment could prevent or delay valve disease.[40, 49] Balloon valvotomy could be used as a bridge to surgery to provide temporary relief of symptoms but is not recommended as an alternative to AVR. Patients with symptomatic severe AS and those with severe AS also undergoing other cardiac procedures such as coronary artery bypass graft (CABG) surgery have a poor prognosis following onset of symptoms and are indicated for aortic valve replacement.[49]

The severity of AS can be determined from diagnostic measurements to measure the effective orifice area (EOA), the jet velocity, the ejection fraction and transvalvular pressure gradients.

There are several approaches to determining the EOA of the stenosed valve. The most common method is the Gorlin formula (1) which is defined as:

$$\mathrm{A} = \frac{\mathrm{CO}}{\mathrm{HR} \cdot \mathrm{SEP} \cdot 44.3 \cdot C \cdot \sqrt{\Delta P}} \tag{1}$$

Where A is the orifice area of the valve (cm^2), CO is the cardiac output (cm^3/min), HR is the heart rate in beats/min, SEP is the systolic ejection period in seconds per heart beat, 44.3C is an empirical constant (C is assumed to be 1.0 for the aortic valve), and ΔP is the transvalvular pressure gradient in mmHg.

Another equation which is often used is the continuity equation (2), which states that the flow rate in the LVOT is equal to the flow in the vena contracta (VC).[51]

$$\mathrm{EOA} = \frac{\mathrm{A_{LVOT}VTI_{LVOT}}}{\mathrm{VTI_{VC}}} = \frac{\mathrm{SV}}{\mathrm{VTI_{VC}}} \quad (2)$$

Where A is the geometric area, VTI is the velocity time integral and SV is the stroke volume.

Either cardiac catheterization or Doppler echocardiography is used depending on whether the Gorlin equation or the continuity equation is used respectively. Doppler echocardiography would estimate the EOA based on the VTI at the vena contracta, which would give the smallest cross-sectional area of the stream. However, this method is likely to overestimate the severity of the AS which may lead to an unnecessary indication for valve replacement surgery. Patients with mild AS may be incorrectly indicated for valve replacement if they appear to have a high transvalvular gradient. An infusion of nitroprusside or dobutamine would increase the outflow and the calculated aortic area and only slightly increases the gradient, which would reduce the severity of the AS. In patients with severe AS, nitroprusside or dobutamine increases the gradient substantially but only mildly increases the area, if at all.

Surgical aortic valve replacement

History of valvular surgery

Surgery on the valve can be traced back to as early as 1912 when Dr. Theodore Tuffier, a French surgeon, used his finger to push the aortic wall to free the fused leaflets of a stenosed aortic valve.[52] Since then, initial attempts on valve repair before the introduction of the cardiopulmonary bypass (CPB) involved mitral valve commissurotomy through access from the atrial chamber. In 1948, Thomas Holmes Sellors used a tenotomy knife to perform the first pulmonary valvulotomy through the right ventricle.[53] Charles Hufnagel developed the first artificial valve based on a reciprocating ball in a cage which was inserted rapidly into the descending aorta to reduce the amount of blood flowing back into the ventricles due to aortic insufficiency.[54] Following the invention of the CPB machine, heart valve replacement in the anatomical position of the native valves rapidly took off. The first successful aortic valve replacement (AVR) was performed by Dr. Dwight Harken and colleagues using a ball-cage valve. In the same year, Dr. Albert Starr and Lowell Edwards implanted their own caged-ball valve in the mitral position.[55] It is important to emphasize that no artificial heart valve developed can ever replace the native aortic valve in terms of its adaptability to complex hemodynamic environments. Accordingly, repair or preservation of the diseased aortic valve should be considered wherever possible. The choice of valve depends on the age and well-being of the patient. Bio-prosthetic valves have a similar hydrodynamic function to the natural aortic valve but have a limited life expectancy. Mechanical valves are more durable but require constant anti-coagulation treatment. These valves are discussed in further detail below.

Mechanical valves

Mechanical heart valves typically have a longer lifespan than bioprosthetic valves; lasting approximately 25 years and so would not require frequent replacement as is the case with bioprosthetic valves. Since 1960, over 70 different mechanical heart valve designs have been developed.[56] Amongst the most common are the ball and cage valve, the tilting disc and the bi-leaflet (Figure 5). In the early 1950's, Charles Hufnagel developed a plastic tube with a ball occluder which functioned as a valve assist device to adequately control the flow of blood in the descending aorta of patients with aortic regurgitation. More than 200 valves were implanted in the descending thoracic aorta of patients, with some valves achieving 30 years of function with minimal wear.[57] The ball valve was modified by Dr. Albert Starr and Lowell Edwards who developed a cage made initially from Lucite with a silicone elastomer ball. The cage material was changed to stainless steel and then Stellite 21. The valve, known as the Starr-Edwards valve had a Teflon sewing ring which enabled suturing into the mitral position and later the aortic position.[55]

This valve design underwent several modifications to reduce thrombogenicity such as covering the struts with cloth to reduce metal contact with blood, having streamlined struts and a silastic shield. However, excessive rubbing of the ball against the sewing ring caused abrasion which increased haemolysis. Additionally, the valve had a high profile which was found to occlude the coronary ostia. Despite the initial complications, the Starr-Edwards valve demonstrated the feasibility of prosthetic valves and enabled them to draw up a design criteria. This covered several fundamental points including that the valve should be; a) chemically inert, b) biocompatible, c) atraumatic to blood and d) non-thrombogenic.[58] In 1965, a non-rotating disc valve known as the Kay-Shiley valve replaced the ball with a single disc to reduce the profile of the valves. Other similar designs emerged with Delrin discs, a poly-acetal homopolymer. However, high energy losses resulted from lateral flow of blood past the disc surface which led to poor hemodynamics such as high pressure drop and haemolysis. These valves were soon discontinued.

A tilting-disc valve was developed by Bjork-Shiley in 1969 and overcame the problems with the single-disc valve. The disc freely rotates between metal struts, which enable it to open by tilting at an angle of 60°. Originally this valve was made from Delrin, but this was soon replaced with Isotropic Pyrolytic Carbon (PyC) which had excellent hemocompatibility. In 1975, Bjork-Shiley replaced the flat disc with a convexo-concaved one to enable the disc to slide by 2 mm to create a larger orifice. However, the welded struts were found to fracture, leading to a product recall for the 70° valves in 1983 and the 60° valves in 1986.[59] Structural failure of the valve in the aortic position led to occlusion, severe acute regurgitation and death within minutes.

The most common tilting disc valve to date was developed by Dr Karl Hall and Robert Kaster, which was later known as the Medtronic Hall valve. It had a thin strut and a perforation in the middle of the disc as a guide, and an improved tilting angle of 75° in their aortic valves.[60] Early complications with this valve included friction and wear of the disc on the struts, and fracture of the struts caused by high mechanical loading during closure.

The bi-leaflet valve was developed by St. Jude Medical in 1977. It consists of two semi-circular flaps made from PyC with the hinges close to the centre of the orifice. This creates three orifices for blood to flow through, which increases the blood contact surface area but has a higher EOA than the tilting disc or ball and cage valves. The EOA was found to

increase from 1.5 - 2.1 cm^2 in the tilting disc to 2.4 - 3.2 cm^2 in the bi-leaflet valve.[60] The bi-leaflet is favourable due to its improved clinical performance; however some researchers have found the tilting disc valve to have superior hemodynamics if orientated to correspond to the eccentric profile of the normal blood flow.[61, 62]

A problem with the bi-leaflet valve was the hinge region which caused recirculation or stagnation of blood flow and elevated shear stresses which led to thrombus formation and haemolysis.[63] An interesting bi-leaflet valve which addressed this problem was the CardiaMed valve, previously known as the Jyros valve developed in Russia. This valve was designed with leaflets that continuously rotated 360° around the central axis of the valve housing with every heart beat. This enabled an even distribution of the blood flow across the prosthesis, allowing the parts to be washed to prevent thrombus formation. This feature of the valve also meant that the valve did not require orientation during the surgical procedure. However the objective performance criteria rate for thromboembolism following AVR was reportedly higher at 2.98% per year compared to 2% for the St. Jude valve.[64]

As mechanical valves are prone to thrombosis and embolism, patients fitted with a mechanical heart valve would constantly require anticoagulation therapy. Additionally, the noise produced by the leaflets can reduce patient quality of life. Failure of mechanical valves is largely caused by loading, material fatigue and cavitations. The failures led to several design modifications such as using PyC which exhibited excellent hemocompatibility and remains the material of choice for mechanical heart valves today.

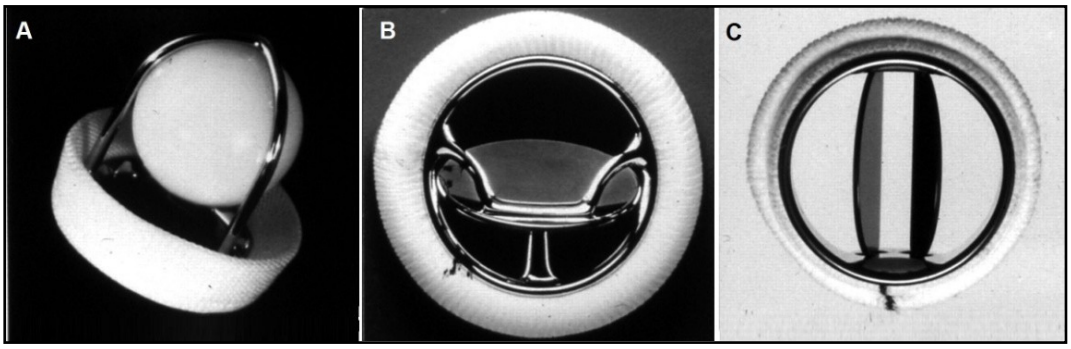

Figure 5. Mechanical heart valves: a) ball and cage valve, b) tilting-disc valve and c) bileaflet valve.[65]

Bioprosthetic valves

A bioprosthetic valve may either be an allograft (cadaver or Ross procedure) or more commonly, a xenograft (native or pericardium). The Ross procedure is a heart valve replacement procedure popular with surgeons for neonates and children. It involves replacing the diseased aortic valve with the patient's own pulmonary valve (pulmonary autograft) and replaces the pulmonary valve with an aortic or pulmonary allograft. There are three techniques to this method; subcoronary implantation, aortic root replacement or aortic root inclusion. The benefits of this procedure are that the pulmonary autograft can grow with the patient and will not induce an immunological response. Additionally, less demand is expected on the allograft in the pulmonary position. However, two surgical procedures are performed and a highly skilled surgeon is required to perform the operation. Common complications with this procedure include aortic dilation and insufficiency, due to an increased diameter of the sinotubular junction. Dilation was more commonly reported with the root replacement

technique which was attributed to an abnormality of the pulmonary valve in patients with congenital aortic valve disease.[66]

The most common xenografts are porcine aortic valves which may be stented or stentless, and bovine pericardial valves. A stented valve would incorporate a metal wire folded to typically form three prongs which serve as an attachment site for the commissures of the valve. The entire wire frame would be covered in Dacron to enable suturing of the tissue to the stent. A stentless valve is one where the valve has been excised from the animal with the conduit intact. Stentless valves have a hemodynamic advantage over stented valves as they provide a greater EOA due to the absence of the stent. The blood is also subjected to less shear stress and so the chances of haemolysis due to rupture of the blood cells is reduced. However pericardial valves are more easily mass produced as there is no problem with supply.[67]

The first popular pericardial valve was the Ionescu–Shiley Pericardial Xenograft valve which was developed in 1971 and marketed in 1976. This valve used bovine pericardium sutured onto a titanium stent which was covered with a Dacron fabric. Although having superior hemodynamics compared to other prosthesis, a series of early structural failures lead to its withdrawal in 1987, negatively impacting in pericardium as a material of choice. It was later realised that the valves had abrasive tears due to the fabric-tissue interface and due to the leaflets calcifying.[67] These problems were overcome with the Carpentier-Edwards bovine pericardial valve in 1980 by stitching the pericardium to the inside of the Dacron fabric rather than around it, using flexible stent posts and by removing the sutures that were put in place for commissural alignment.

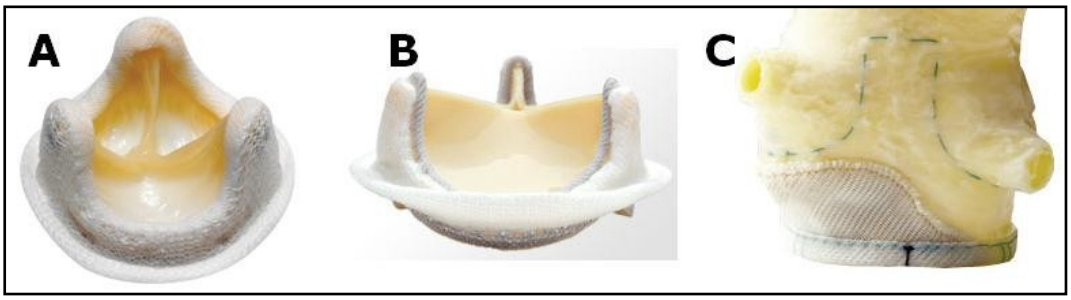

Figure 6. Bioprosthetic valves: a) Medronic Hancock II Porcine Valve, b) Edwards Pericardial Valve and c) Edwards Prima Plus Stentless Porcine Prosthesis.

Biological valve prostheses have excellent hemodynamics compared to mechanical valves due to their anatomical structure. However, they are prone to calcification and thus have a shorter life span than mechanical valves. Valves and pericardium excised from species need to be sterilized and preserved. The most common treatment adopted for the preservation of these tissues is their fixation in glutaraldehyde, a five-carbon atom dialdehyde.[68] The method of fixation varies substantially. Some bioprosthetic valves are fixed at 0 mmHg or low pressures whereas others are prepared at 80-100 mmHg closing pressures. It was observed that when a high pressure fixation is adapted, the pericardium loses its natural collagen crimp structure which increases it's stiffness.[1] This problem could be avoided by fixing the tissue under dynamic pressures. Glutaraldehyde fixation has also been found to reduce the GAG concentration in valvular leaflets during flexural fatigue, which would compromise the structure of the spongiosa layer and may contribute to tissue deterioration and calcification.[69]

Other fixation methods including photo-oxidization and decellularization have been considered although the long term effects of these treatments still needs to be determined.[70, 71] There are two main causes of bioprosthetic valve failure; mechanical and chemical influences. Pericardium and xenografts are prone to calcification particularly in regions exposed to high stress which leads to eventual stiffening of the leaflets. However, the highest cause of failure come from mechanical stresses alone, indicating the importance of nailing valve design.[72] Other causes of failure included stent rigidity, the level of pressure applied to glutaraldehyde fixation and anisotropy between leaflets.

Tissue engineered valves

Tissue engineering is a field in regenerative medicine which aims to restore and maintain the function of living tissues through the applied understanding of engineering and biological sciences. They have found particular success in skin grafts for burn victims. The perceived advantages of tissue engineered heart valves (TEHV) compared to other valve replacement options include non-thrombogenicity, infection resistance and cellular viability. It is particularly exciting in children and young adults where the possibility exists of a valve capable of growing, remodelling and repairing itself as the patient grows.[30] However their design has remained challenging and their success depends on advancements in material science and culturing techniques. There have been several TEHV approaches predominately to the pulmonary valve including decellularization[73, 74], biodegradable scaffolds, in-vivo[75] and hybrid TEHVs[76].

Decellularization involves removal of the cellular contents of a native heart valve, keeping only the ECM component. This approach has the benefit of decreasing the immunogenicity response, enabling xenografts to be suitable in humans. Additionally, the matrix should have the desirable mechanical and structural integrity for use as heart valves. However, decellularizing the matrix can lead to alterations to the collagen structure, GAG content and ECM which may influence the mechanical properties.[77] The matrix can also be reseeded either through coating with a bioactive substance or by seeding with autologous cells, although cells have been found to leach out once implanted in vivo. The use of a decellularized matrix is also limited since it requires relatively healthy valves which would be more suited for allografts.

Biodegradable scaffolds are commonly employed in tissue engineering due to the vast availability of synthetic materials with biodegradable properties. The most widely used synthetic polymers are polyglycolic (PGA) and polylactic acid (PLA), although natural scaffolds such as chitosan have also been considered. The basic idea behind these scaffolds is to create a template on which the matrix can synthesize. This requires a careful balance in controlling the rate of scaffold degradation with the rate of matrix synthesis so that the cells remain seeded on a structurally stable material. However, the final matrix has been found to have a lower mechanical strength to the biodegradable scaffold.[78] Scaffolds are then harvested with autologous cells, allogenic cells or stem cells such as mesenchymal stem cells (MSC) which should then proliferate to VECs and VICs. Additional signals such as cytokines, hormones and growth factors and mechanical stimuli such as bioreactor systems are often adopted to improve tissue growth.[19]

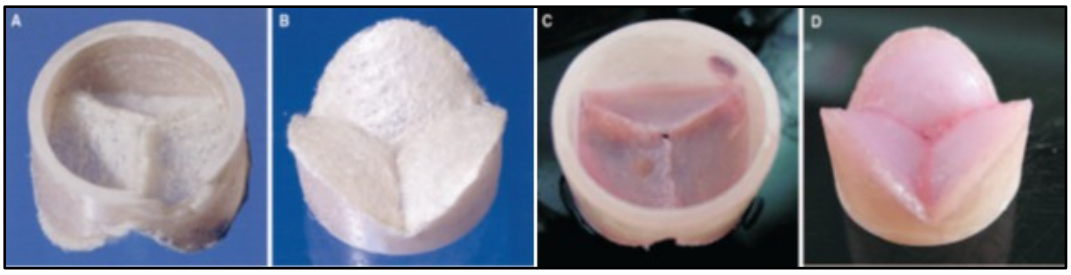

Figure 7. Photographs of autologous tissue engineered valve (a) non-woven PGA scaffold coated with P4HB from the (a) aortic and (b) ventricular sides. (c) and (d) after 4 weeks of culturing. Adapted from Mol et al.[78]

Polymeric valves

Polymeric heart valves (Figure 8) combine the durability of mechanical valves with the hydrodynamic function of bioprosthetic valves.[80] They have a huge advantage in that they can be manufactured to various shapes and sizes.[81] In a comparative study of a polyurethane valve with a mechanical and bio-prosthetic valve, the former was found to have superior hemodynamics compared to the bio-prosthetic valve. Additionally, incidence of thrombogenicity was lower than in the mechanical valve.[80] Polymeric valves have been around for over 50 years but failed to gain popularity due to their initial poor characteristics. In fact, one of the earliest prosthetic heart valves was a mitral polyurethane valve with a Teflon chordae tendineae which was implanted in a 44 year old woman in 1959.[82] Many of the earlier polymeric valves used polymers which were prone to calcification and early degradation which prohibited their widespread use. Consequently they were only used in short term 'Bridge to Transplantation' devices such as in total artificial hearts and left ventricular assist devices.

It was the introduction of polyurethane, a two-phased microstructure of hard and soft segments which escalated their use as biomaterials. Biomer was the first polyurethane stable enough to be coined as a 'biomaterial' and used to form the pump diaphragm of the Jarvic 7 total artificial hearts.[83] Biomaterial polymers such as silicone, polytetrafluoroethylene (Teflon) and polyvinyl alcohol have also been considered as alternative materials to heart valves.[79, 84] However, much of the focus has been on thermoplastic polyurethanes (TPU) which have shown potential due to their excellent mechanical properties and bio-stability. Advanced material science has enabled development of these polymers with improved biostability and durability. Initially these polymers had polyester soft segments which were prone to hydrolysis and oxidation. The two-phase microstructure of TPU has enabled researchers to improve biostability by modifying the soft segments or through chemical substitutions to their structure.[81]

Improving the stability of polyurethanes often involves incorporating silicone into the polymer chain. In 1999, Gunatilake et al. developed a polymer with silicone microdiols which gave it superior biostability in relation to other TPUs. This polymer is now marketed by Aortech International Plc (Rogers, Minnesota) under the name Elast-Eon™ and is used in the development of heart valves as well as insulation for pacemaker and defibrillator leads.[85-88] Another group have developed a polycarbonate urethane with polyhedral oligomeric silsesquioxanes (POSS) nanoparticles which they aim to develop thin enough for use in TAVR.[89] Polymeric valves have vast manufacturing possibilities including dip-coating, film casting and injection molding. They are promising in the field of percutaneous technologies

due to the ability to control their thickness and create leaflets thin enough for low profile TAVR.

Unlike the native valve and pericardium, polymeric materials are strain rate dependant and this feature could affect the valve performance and durability if not accounted for in valve design. For example, the leaflets could stiffen at increased heart rates which could increase opening times or prevent smooth coaptation during diastole.

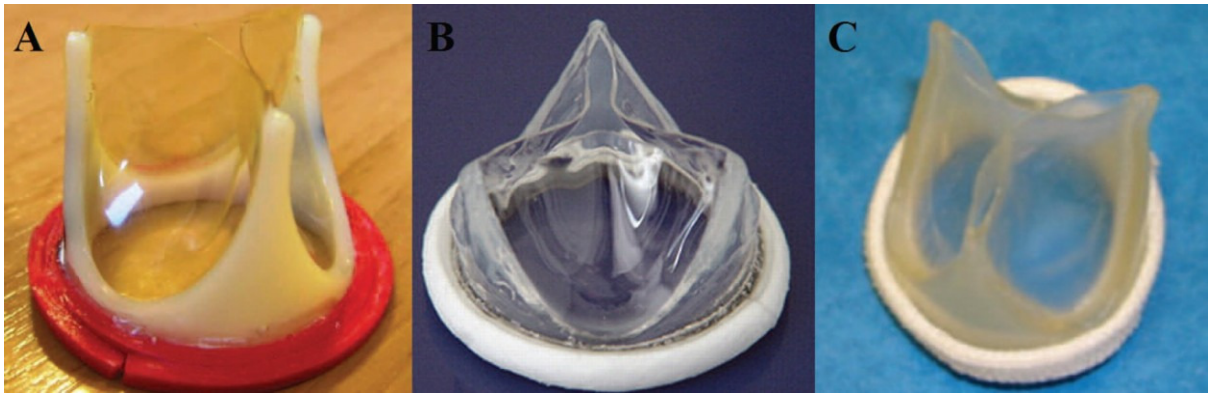

Figure 8. Polymeric heart valves; (a) polymeric valve designed by the University of Strathclyde with Elast-Eon leaflets (b) the ADIAM Polycarbonate urethane valve[90] and the (c) POSS-PCU valve developed at University College London.[91]

Complications with AVR and Implications for TAVR

Almost a third of patients with severe AS over the age of 75 years are turned down for AVR as the surgical procedure is deemed too risky or due to technical complications such as a porcelain aorta, where the aorta is too calcified to allow suturing of a valve.[43] The mortality rate from 2004 to 2008 for AVR alone and with CABG was estimated to be 2.8% and 5.3% respectively.[50] AVR is also not practical in neonates and children who would need frequent replacement as they grow, and current bioprosthetic and mechanical valves are too large for implantation. Although the Ross Procedure is successful, this technique is technically challenging and involves replacing an otherwise healthy pulmonary valve.

In 1992, Andersen et al. demonstrated the feasibility of TAVR by deploying a porcine aortic valve sutured and crimped into a balloon expandable stent.[91] A decade later, Cribier and colleagues deployed a transcatheter valve in a patient suffering calcific AS, severe leg ischemia and cardiogenic shock but was denied surgery by several surgeons. Immediately following the procedure, the transvalvular pressure gradient dropped from 30 mmHg to 6 mmHg and there was an improvement from 14% to 17% in the left ventricular ejection volume.[92] The major benefit of TAVR is that the valve is deployed over the native valve percutaneously without the need for open heart surgery and CPB, enabling patients who are refused surgery due to high risk or technical complications to receive valvular replacement. There are two leading valves in the market today; the Edwards SAPIEN valve by Edwards LifeSciences and the CoreValve Prosthesis by Medtronic Inc.

TAVR was previously only indicated in inoperable high risk patients with severe AS, having a EuroScore ≥20 or an STS PROMS score ≥10. There is now an increasing drive to perform TAVR in operable high and intermediate risk patients and these outcomes are being assessed in both the PARTNER II and SURTAVI trials.[93, 94] However, there are still many complications that need to be overcome before TAVR should be considered in lower risk

patients, which include paravalvular leakage, stent migration, major vascular complications, conduction disturbances and stroke.[95-97]

The distal end of the valvular prosthesis is often positioned below the basal attachment and the large diastolic pressures can cause it to migrate into the LVOT. Although rare, late stent migration and rotation can occur if the calcific nodules on the native valve are not sufficient to anchor the stent, which can lead to paravalvular leakage or obstruction of the LVOT.[98, 99] Conversely, although calcific nodules are necessary for stent fixation, their location particularly at the aortic wall and valve commissures can be a determinant for paravalvular leakage (PVL).[100] PVL can also occur if there is an annulus-prosthesis mismatch due to prosthesis under-sizing.[101] Balloon post-dilation is often practiced immediately following TAVR to minimise PVL although over-dilation can lead to poor leaflet apposition, cerebral vascular events or rupture of the aortic annulus.[95, 102, 103] This can be prevented by ensuring the balloon is not larger than the maximum diameter of the aortic valve.[101]

Over-sizing can also increase the risk of conduction abnormalities due to the compression of the atrio-ventricular (AV) conduction node or the His bundles. Bleiziffer et al. reported a 2-fold increase in risk for new onset AV-block if the aortic annulus was at the lower end of the recommended size for a specific prosthetic size and a 4-fold increase in risk with the CoreValve than the Edwards SAPIEN valve.[104] There is also an increase in conduction disturbances if the stent is positioned too deep into the LVOT. Muñoz-García et al. found a CoreValve implantation depth of $\geq$ 11.1 mm into the LVOT could be an early indicator of the need for a pacemaker and recommend an optimal implantation depth of 6 mm.[105]

Alternatively, positioning the valvular prosthesis supra-annularly can cause coronary ostia occlusion, affirming the need for accurate positioning. As TAVR is largely non-invasive, the procedure is dependent on imaging techniques such as trans-oesophageal (TEE) and trans-thoracic (TTE) echocardiography. TEE can however under-estimate the aortic valve area due to the ellipsoidal nature of the annulus, leading to patient prosthesis mismatch (PPM). Better imaging such as the use of multi-slice (or multi-detector) computed tomography (MSCT) or planimetry has been shown to more accurately predict the aortic annulus.[106-108] Accurate imaging is also necessary for patient selection and for determining the most suitable delivery route to take. MSCT can provide enhanced three-dimensional reconstructed images to assess the degree of arterial tortuosity, calcification and of the aortic root and is commonly adopted in pre-procedural assessment.[109, 110]

The current size of transcatheter valves in their collapsed state has been shown to contribute to major vascular complications following retrograde delivery through the femoral arteries.[97] Calcific debris can also be dislodged from heavily sclerotic arteries during the delivery procedure, which can lead to stroke or silent cerebral ischemia.[111] Consequently, it is desirable to decrease the size of the delivery catheter to provide a less invasive and traumatic access vessel to the aorta. This can be achieved by enabling delivery to a peripheral artery through a minimal or fully percutaneous incision. However this requires the valve to be collapsed into a smaller sheath and current percutaneous valves formed from porcine or bovine pericardium are too thick to enable this, having thicknesses of 200-400 μm.

Conclusions

The aortic valve is often considered to be a passive structure, opening and closing as a result of pressure changes. It in fact responds in an intricate and dynamic manner to flow changes during the cardiac cycle by structurally adapting to the complex hemodynamic environment. Their ability to dynamically adapt to changes creates an obstacle in prosthetic valve design to overcome problems including durability, thrombogenicity, haemolysis and calcification. Deviating from the native tri-leaflet design of the valve leads to changes in mechanical and hemodynamic responses of the valve, which can increase shear stress, commissural and belly stresses and strains on the leaflet free edge. Therefore it is imperative that considerations are made to minimise leaflet stresses and create outflow patterns that mimic the native valve.

Polymeric valves combine the hemocompatibility of bioprosthetic valves with the durability of mechanical valves, providing an optimal material of choice, as well as providing enough stability to not necessitate anti-coagulation treatment. Polymers also have vast manufacturing options to produce various valve designs. Thus they can be optimally designed to crimp into a small vessel with minimal structural damage to the leaflets. An ultra-thin synthetic leaflet material is hoped to overcome the complications related to the current femoral arterial access by enabling a lower profile delivery though a peripheral artery. Prosthetic valve development will never identically replicate the characteristics of the native valve. However the goal is to work towards a fully functional and durable prosthesis, capable of regulating the one way flow of blood through the heart.

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