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STRUCTURAL HEART DISEASE (RJ SIEGEL AND NC WUNDERLICH, SECTION EDITORS)

Pathology of the Aortic Valve: Aortic Valve Stenosis/Aortic Regurgitation

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Abstract

Purpose of Review This discussion is intended to review the anatomy and pathology of the aortic valve and aortic root region, and to provide a basis for the understanding of and treatment of the important life-threatening diseases that affect the aortic valve.
Recent Findings The most exciting recent finding is that less invasive methods are being developed to treat diseases of the aortic valve. There are no medical cures for aortic valve diseases. Until recently, open-heart surgery was the only effective method of treatment. Now percutaneous approaches to implant bioprosthetic valves into failed native or previously implanted bioprosthetic valves are being developed and utilized. A genetic basis for many of the diseases that affect the aortic valve is being discovered that also should lead to innovative approaches to perhaps prevent these disease. Sequencing of ribosomal RNA is assisting in identifying organisms causing endocarditis, leading to more effective antimicrobial therapy.
Summary There is exciting, expanding, therapeutic innovation in the treatment of aortic valve disease.

Keywords Aortic stenosis · Aortic regurgitation · Calcific degeneration · Bicuspid aortic valve · Rheumatic valve disease · Endocarditis · Transcatheter aortic valve implantation (TAVI) · Aortic valve replacement · Myxomatous degeneration · Endocarditis · Non-bacterial thrombotic endocarditis (NBME)

Introduction

Hemodynamically significant aortic valve disease, in one form or another, is a relatively common disorder. The lesions may be congenital, acquired, or both. There are few causes of aortic stenosis, with age-related calcific disease, congenitally bicuspid valve, and post-inflammatory (rheumatic) disease being the most common. In contrast, there is a long list of diseases that result in aortic regurgitation; these may be inflammatory, such as syphilis and Behçet's disease, or non-inflammatory such as Marfan syndrome or other collagen vascular diseases. There is no medical or surgical cure for aortic valve disease; however, effective methods of valve repair and replacement exist and percutaneous approaches to treat aortic valve disease are being utilized with increasing frequency. Aortic valve disease may be congenital or acquired, or a combination of both. Structural abnormalities present at birth, such as a congenitally unicuspid valve, may be associated with stenosis and/or regurgitation early in life. Other abnormalities, such as a congenitally bicuspid aortic valve, may be present without any hemodynamic consequences early in life, only to then become hemodynamically significant later. With aging, morphologic changes occur in both the normal and abnormal aortic valves. Over time, the aortic valve becomes thicker and stiffer due to fibrosis and calcification. In addition, the aortic root widens and myxomatous degeneration of the valve cusps may occur resulting in significant aortic regurgitation. Clinically significant aortic valvular heart disease is becoming more common as our population grows and becomes more aged. Calcification is seen in more than one quarter of individuals over 65 and more than half of those over 85 [1]. Calcific aortic stenosis is the most common valve disease requiring surgery. Currently, there is no long-lasting effective medical treatment for aortic valve diseases.

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Anatomy of the Aortic Valve

In order to recognize and understand the pathology of the aortic valve, it is critical to recognize and understand the normal anatomy of the valve. A *normal valve* can reasonably be defined as a thin, mobile, tissue structure that allows free flow of blood in one direction and prevents reflux of blood in the opposite direction. Anatomically, the aortic valve is located between the left ventricular outflow tract and the tubular portion of the aorta. The normal aortic valve has three cusps (also called leaflets)—right, left, and posterior or non-coronary. The cusps are roughly similar in size; in adults, the average cusp measures 25–26 mm in width [2]. The cusps are separated by *commissures*. Each cusp has a base, which affixes to the aortic wall, and a free edge; the free edges come together or *coapt* when the valve is closed. There is a space bounded by the cusp's free edge, base, and the wall of the aorta referred to as the *sinus of Valsalva*, or simply *aortic sinus*. Of note, there is a redundant surface of the valve between the free edge and line of closure; incidental horizontal defects or fenestrations may be seen in this location. On the ventricular side of each cusp, in the middle along the line of closure, is a central nodule known as the *nodule* (*or node*) *of Arantius*. Papillary, whisker-like fronds may project from the nodules called *Lambl's excrescences* or *Yater's whiskers* (Fig. 1). Fenestrations, nodules of Arantius, and Lambl's excrescence may become more prominent with age but are typically not of clinical significance. Above the aortic valve is a tapered ridge of aorta referred to as the *sinotubular junction*. It is worth noting that the base of the left and posterior aortic cusps are in fibrous continuity with the anterior leaflet of the mitral valve. Pathology such as infective endocarditis may spread between the two adjacent valves along this structure.

The aortic valve cusps are composed of three layers: *fibrosa*, *spongiosa*, and *ventricularis* (Fig. 2). The fibrosa, composed of dense collagen, is the main structural component of the valve. The ventricularis, comprised of numerous elastin fibers, provides the valve's elasticity. In between the fibrosa and ventricularis, the spongiosa, composed of collagen, proteoglycans, and mesenchymal cells, functions as the "shock absorber" of the cusp [3].

Fig. 1 Gross photograph of the left ventricular outflow tract. The metal probe is entering the posterior sinus of Valsalva. Note the fenestrations on the posterior aortic cusp (*yellow dotted circle*) and the prominent Lambl's excrescence at the line of closure (*yellow arrow*)

Aortic Stenosis

Most cases of aortic stenosis are the result of cusp pathology. The three most common causes of aortic stenosis are (1) age-related calcific degeneration, (2) congenitally bicuspid (or unicuspid) aortic valve, and (3) post-inflammatory valvular disease (e.g., rheumatic disease) [4, 5]. The mechanisms of stenosis in these three conditions are fibrosis, calcification, and/or commissural fusion.

Age-Related Calcific Degeneration

The congenitally normal tricuspid aortic valve undergoes a calcific degenerative process with age that has been referred to as age-related aortic stenosis, senile aortic stenosis, aortic stenosis of the elderly, aortic sclerosis, and more. The aortic valve opens and closes about 100,000 times each day. In an 80-year-old person, the valve has opened roughly 2.9 billion times, chronically exposing the valve to complex shear forces that result in progressive degeneration. In a prospective population-based study, the prevalence of aortic stenosis in octogenarians was found to be 9.8% [6].

In age-related calcific degeneration, there is progressive deposition of calcium phosphate mineral affecting all the three cusps. Grossly, there is dense nodularity of the outflow surface that heaps up and may fill the sinuses of Valsalva (Fig. 3a). The cusps become anchored to the valve annulus, which impairs cusp mobility. The cusps are separate; commissural fusion is absent or minimal. Hence, significant regurgitation is uncommon. Histologically, there is nodular calcification originating in the fibrosa layer of the cusp. In severe cases, calcification is transmural; the valve is distorted but the three-layer architecture of the cusp is somewhat recognizable, at least focally. Inflammation, lipid, and ulceration with granulation tissue may be seen. The calcium phosphate mineral may undergo chondrous or osseous metaplasia, forming cartilage and bone, sometimes even with marrow elements [7]. Localized amyloid deposition may also be present [8, 9].

Congenitally Bicuspid Aortic Valve

Congenitally bicuspid aortic valves are present in 1–2% of the population and are the most common cause of isolated aortic stenosis in individuals age 50–70 [5, 10, 11]. These valves function normally at birth and undergo a similar degenerative process involving fibrosis and calcification as valves with three cusps. However, with advancing age, the vast majority

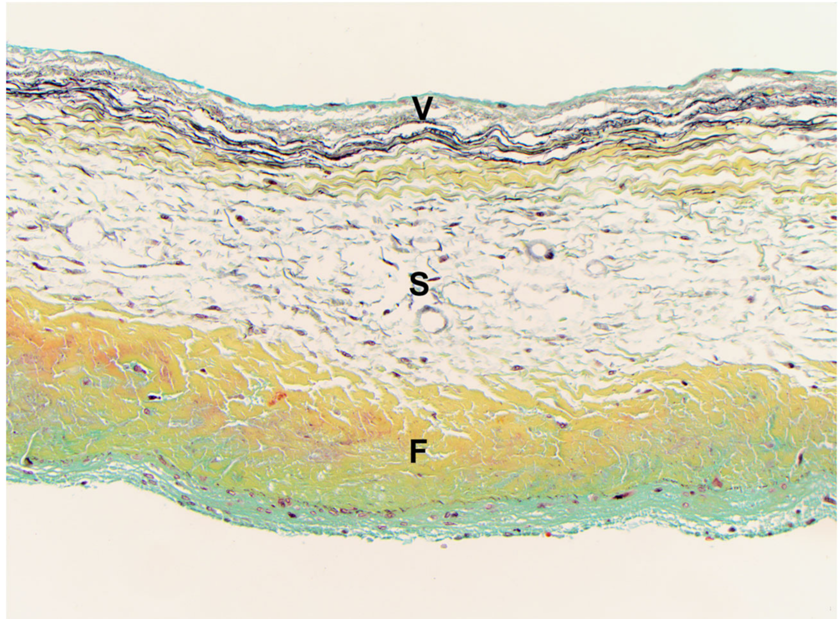

Fig. 2 Movat pentachrome stain highlighting the three-layer architecture of the aortic valve cusps. The ventricularis (*top*, *V*) has numerous elastin fibers whereas the fibrosa (*bottom*, *F*) is composed of dense fibrosis. The spongiosa (*middle*, *S*), composed of loose connective tissue, proteoglycans, and mesenchymal cells, acts as the "shock absorber" of the valve. × 200

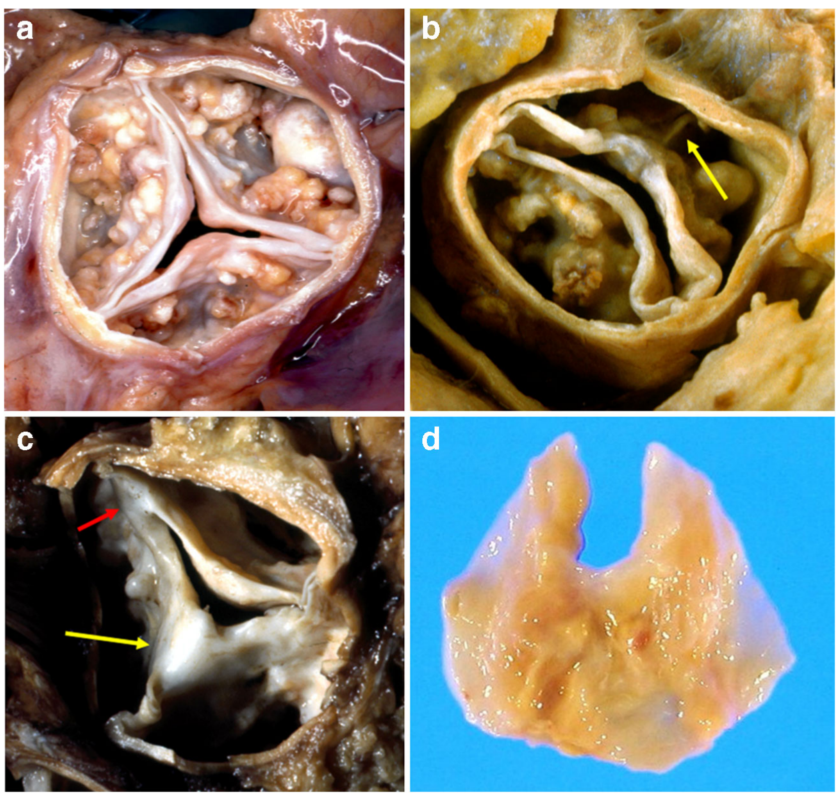

Fig. 3 Examples of aortic valve pathology. **a** Age-related calcific degeneration; note the nodular calcification on the outflow surface of the valve. **b** Congenitally bicuspid aortic valve with calcific degeneration; two relatively equal-sized cusps are present—one anterior and one posterior. A small raphe is present on the anterior cusp (*yellow arrow*). The raphe is midline and runs perpendicular to the free edge of the valve. **c** "Acquired" bicuspid aortic valve in rheumatic valve disease; the right and left aortic cusps are fused due to post-inflammatory scarring (*yellow arrow*). The result is a stenotic valve with two functional cusps. In contrast to congenitally bicuspid aortic valve, the conjoined cusp has about twice the surface area of the remaining cusp and its free edge is V-shaped. In this example, mild commissural fusion can also be seen involving the right and posterior cusps (*red arrow*). **d** Congenitally unicuspid aortic valve; unicuspid valves may have one commissure (*unicommissural)* or no commissures (*acommissural*, not shown)

will become stenotic—about 10–15 years earlier than is typical of age-related calcific degeneration in aortic valves with three cusps. The precise mechanisms underlying the pathology are yet a matter of some debate. However, a genetic basis of the disease is widely accepted. The prevalence of bicuspid aortic valve in first-degree relatives of individuals with congenitally bicuspid aortic valves is approximately 9% [12, 13]. Furthermore, congenitally bicuspid aortic valves are associated with some genetic syndromes, including Turner syndrome, Marfan syndrome, Loeys-Dietz syndrome, and familial thoracic aortic aneurysm syndromes (Table 1) [14–17]. Congenitally bicuspid aortic valve may be associated with aortic dilatation [18]. In addition, echocardiographic studies have shown that first-degree relatives of individuals with congenitally bicuspid aortic valves have an increased prevalence of dilated aortic root [19].

The congenitally bicuspid valve is composed of two cusps relatively similar in circumference, although rarely equal. The cusps may be anterior and posterior, in which case both coronary ostia override the anterior cusp. Alternatively, the cusps may be left and right, in which case the coronary ostia override the left and right cusps respectively. Frequently, one of the cusps will have a prominent ridge on the middle of the outflow surface known as a raphe (Fig. 3b). The raphe is perpendicular to the aortic wall and usually does not extend all the way to the free edge of the cusp. The raphe is thought to represent the site of failed cusp division; as such, the cusp with the raphe is often referred to as the *conjoined cusp*. Nodular calcific and fibrotic degeneration tends to be more pronounced at the raphe. Histologically, the stenotic congenitally bicuspid aortic valve looks no different than a three-cusped aortic valve with age-related calcific degeneration. That said, osseus and chondrous metaplasia appear to be more common in congenitally bicuspid valves, however [20].

Less frequently, a stenotic valve may be congenitally unicuspid. Invariably, patients with unicuspid valves become symptomatic earlier than individuals with bicuspid valves. Unicuspid valves may have a single commissure (unicommisural) or no commissure (acommissural) (Fig. 3d). These valves also may or may not have a raphe. Rarely, aortic valves are congenitally quadricuspid; these valves usually result in aortic regurgitation, rather than stenosis, however [21].

Table 1 Genetic syndromes associated with congenitally bicuspid aortic valve

Syndrome	Genetic defect(s)
Turner	Monosomy X
Marfan	FBN1 mutations
Loeys-Dietz	TGFBR1, TGFBR2 mutations
Familial TAAD	ACTA2, MAT2A mutations
DiGeorge	22q11.2 deletion
Andersen-Tawil	KCNJ2 mutations
Larsen	FLNB mutations
Kabuki	KMT2D, KDM6A mutations
Isolated bicuspid aortic valve	NOTCH1 mutations

TAAD thoracic aortic aneurysm and dissection

Post-inflammatory Aortic Stenosis

The prototypic post-inflammatory valve disease is chronic rheumatic heart disease. In developed countries, the pathologist almost never sees acute rheumatic fever. However, chronic inflammation and scarring may lead to valvular stenosis with or without concomitant regurgitation. Isolated post-inflammatory aortic valve disease is rare [22]; the mitral and/or other valves are usually also affected.

Gross features of post-inflammatory aortic stenosis include cuspal thickening, calcification, and commissural fusion (Fig. 3c). Cusps may fuse resulting in a functional or *acquired* bicuspid aortic valve. This may be difficult to distinguish from a congenitally bicuspid valve, particularly when a raphe is present. However, in the latter case, the valve cusps are of roughly equal size; in the former case, the fused post-inflammatory cusps will generally be about twice as large as the non-fused cusp and will have a "v"-shaped free edge.

Histologically, post-inflammatory valve disease is characterized by prominent neovascularization, varying degrees of chronic inflammation, and diffuse effacement of the normal 3-layer architecture (i.e., fibrosa, spongiosa, ventricularis) of the valve by fibrosis with or without calcification [23]. Calcific degeneration, whether age-related or in the setting of congenital valve disease, first and mostly involves the fibrosa; therefore, some preservation of the 3-layer architecture should be maintained. Infective endocarditis may also result in prominent neovascularization and architecture effacement. However, these changes are usually focal, whereas in rheumatic-type disease they are diffuse. Diffuse fibrosis may also be seen in radiation-induced valve disease; in contrast to rheumatic-type disease, chronic inflammation and neovascularization are typically absent [24].

Aortic Regurgitation

Aortic regurgitation may be the result of abnormalities either of the aortic valve or of the aortic root. Mechanisms of aortic regurgitation include dilation of the aortic valve annulus, cusp prolapse, retraction of the cusps by scar, and cusp perforation [25, 26]. Cuspal causes of aortic regurgitation include post-inflammatory valve disease, infective endocarditis, congenitally bicuspid aortic valve, connective tissue disease, and iatrogenic causes, such as valvuloplasty (Table 2).

Table 2 Causes of aortic regurgitation

Cuspal causes	Aortic causes
Post-inflammatory changes (e.g., rheumatic disease)	Aortic medial degeneration (hypertension, age-related)
Infective endocarditis	Connective tissue disorder
Congenitally bicuspid aortic valve	Aortic dissection
Iatrogenic (e.g., valvuloplasty)	Aortitis
Cusp prolapse	

Post-inflammatory Valve Disease

Rheumatic-type post-inflammatory aortic valve disease often results in mixed aortic stenosis and regurgitation. As previously discussed, post-inflammatory scarring results in fibrosis, calcification, and commissural fusion of the aortic valve cusps. The result is cusp immobility that not only obstructs flow, causing stenosis, but also fixes the valve orifice in an open position, allowing regurgitation [25].

The healing phase of other inflammatory diseases, including ankylosing spondylitis, Behçet's disease, and syphilis, may also cause aortic regurgitation [27–29]. In ankylosing spondylitis, there is fibrosis of not only the aortic cusps but also the aortic wall of the sinuses of Valsalva. The anterior leaflet of the mitral valve may be affected as well. In syphilis and Behçet's disease, regurgitation is largely the result of aortic root dilatation following aortitis.

Infective Endocarditis

Infective endocarditis is the incorporation and proliferation of microorganisms in the valvular endocardium. The aortic valve is the most common valve affected [30]. The organisms, acute inflammation, and thrombi coalesce to form vegetations on the valve cusps. This process can lead to destruction of the valve tissue that may result in regurgitation. Patients with pre-existing valvular disease, such as rheumatic disease or congenitally bicuspid aortic valve, are at increased risk for developing endocarditis. However, affected individuals may or may not have pre-existing valvular or structural heart disease [31]. Additional risk factors include advanced age [32], intravenous drug use [33], and poor dentition [34].

Vegetations in endocarditis are often large, verrucous, and friable. Fungal vegetations tend to be larger than bacterial vegetations. The sheer bulk of the vegetation may result in valvular dysfunction. However, tissue necrosis caused by the infection may lead to ulceration and perforation. The infection may spread to involve the aortic root and the area of the atrioventricular node. Hence, the development of pericardial effusion or heart block in a patient with aortic valve endocarditis is an ominous finding. In addition, because the aortic valve is in fibrous continuity with the anterior leaflet of the mitral valve, aortic valve endocarditis may easily grow to involve the mitral valve as well.

Microscopically, the vegetations of active infective endocarditis are composed of platelet and fibrin thrombi and degranulating neutrophils. Organisms may be readily apparent or may be difficult to identify without special stains. Gram stain is helpful to both visualize and characterize the organisms. Grocott methenamine silver (GMS) stain is also very useful, as it stains both fungal and bacterial organisms. These stains fail to reveal microorganisms in about 25% of cases [30]. Once healed, there is overlap between histologic appearance of remote infective endocarditis and rheumatic valve disease. This includes effacement of the valve tissue 3-layer architecture by fibrosis and neovascularization. These changes, however, are focal in infective endocarditis rather than diffuse, as in rheumatic-type disease.

Bacterial and fungal cultures of blood or fresh tissue may be used to definitively identify organisms during the acute phase. However, cultures may fail to grow organisms in approximately 30% of cases [35], particularly if performed following the administration of antibiotics. In culture-negative cases, sequencing of 16S ribosomal RNA, either by polymerase chain reaction (PCR) or next-generation sequencing (NGS), may identify the culprit organism and can be performed on formalin-fixed paraffin-embedded tissue [36•, 37]. One series demonstrated this technique to have a sensitivity and specificity of 67% and 91%, respectively [38]. *Staphylococcus* and *Streptococcus* species are most commonly the causative organisms [30]. Common causes of culture-negative infective endocarditis include *Coxiella burnetii* (Q fever), *Bartonella* species, and *Tropheryma whipplei* [39].

Another form of endocarditis without infection, known as marantic endocarditis or, more properly termed, non-bacterial thrombotic endocarditis (NBTE), is a condition affecting individuals with a hypercoagulable state, such as patients with advanced-stage cancer. The lesions are usually first detected at autopsy. The vegetations in NBTE consist of platelets and fibrin and are only loosely attached to the valve surface. Accordingly, these vegetations clinically manifest as embolic phenomena rather than valvular dysfunction [40].

Myxoid Degeneration

Myxoid (aka myxomatous) degeneration is a pathologic process of the valve tissue that may be the cause or result of aortic regurgitation. Myxoid degeneration can be an isolated age-related process or may be associated with aortic medial degeneration (Erdheim's cystic medionecrosis), aortic aneurysms, and/or aortic root dilatation. Systemic hypertension accounts for the majority of these cases. Less common etiologies include diseases of connective tissue, such as Ehlers-Danlos syndrome, Marfan syndrome, and Loeys-Dietz [41]. Grossly, the valve appears thin and translucent. Histologically,

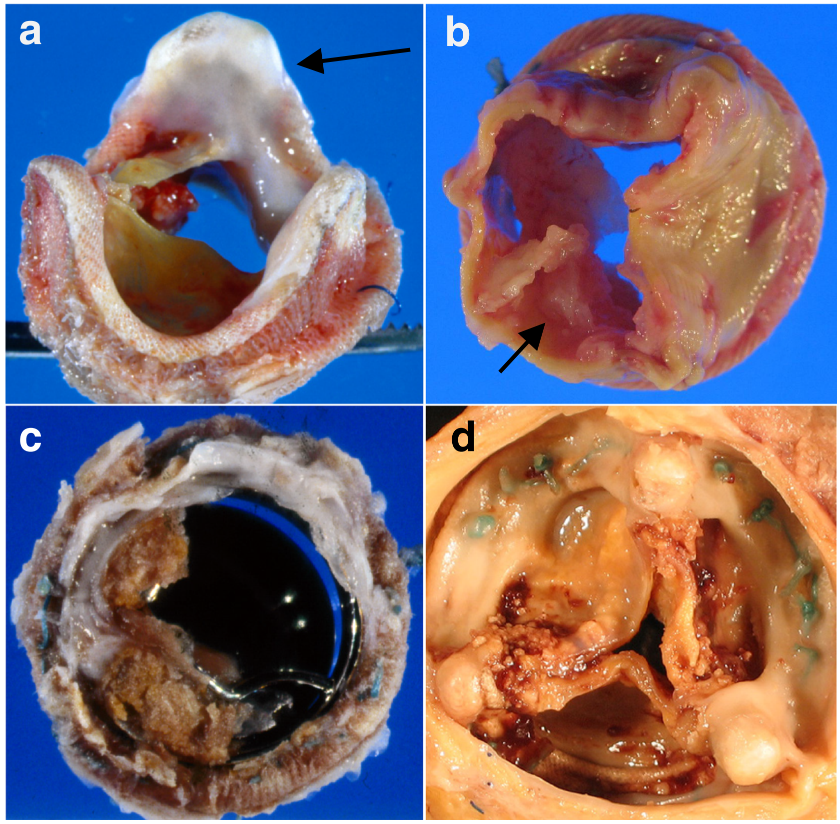

Fig. 4 Prosthetic valve pathology. **a** A bioprosthetic valve with significant pannus overgrowth involving the strut and commissure (*black arrow*). **b** Bovine pericardial valve with endocarditis; note the friable vegetation on the inflow surface of the valve (*black arrow*). **c** A single leaflet tilting disc mechanical valve with endocarditis and occlusive vegetation. **d** Calcific degeneration of a bovine pericardial valve. Note the nodular calcification of the leaflets. Pannus can also be seen on the sewing ring and struts

there is disruption of the valvular fibrosa and increased mucopolysaccharide in the spongiosa [42].

Pathology of Prosthetic Aortic Valves

The first mechanical prosthetic valve was implanted the aortic position by Dwight Harken in the early 1960s [43]. Around the same time, Donald Ross implanted the first aortic valve allograft [44]. Since then, there have been numerous technological advances in the implementation and design of prosthetic valves. Pathologic evaluation of prosthetic valves requires knowledge of the prosthetic valve anatomy. No matter the design, whether mechanical or tissue-based, surgically implantable prosthetic valves have several parts in common: (1) an occluder, (2) a sewing cuff, and (3) a superstructure that anchors or guides the occluder. Attention must be paid to all three components. A thorough pathologic examination of a prosthetic valve involves gross examination, radiography, and histology [45]. Specimens should be photographed and radiographed prior to extensive manipulation to ensure defects are genuine and not introduced by the examiner. Commonly observed pathologic findings include thrombosis, infection, tissue overgrowth (aka pannus), structural/mechanical failure, and tissue deterioration (Fig. 4).

Mechanical valves have the advantage of durability at the cost of blood compatibility—anticoagulative therapy must be initiated to prevent thrombosis. The most widely used mechanical valves employ a ball-in-cage design (e.g., Starr-Edwards), a single leaflet tilting disc (e.g., Bjork-Shiley, Medtronic-Hall), and a bileaflet tilting disc (e.g., St. Jude). Structural deterioration is not a common finding in modern mechanical valves; valve failure is usually the result of interference of the moving parts by thrombus or tissue overgrowth, resulting in functional stenosis or regurgitation. Thrombus is an important pathologic finding even in the absence of valve failure, however, as the sequela of thromboemboli (e.g., stroke) may be clinically significant.

Tissue valves, or bioprosthetic valves, are made from animal or human tissue that is preserved in glutaraldehyde and mounted on a fabric covered fixation ring or stent. Common tissue valves include cadaveric homografts, porcine

Table 3 Causes of prosthetic aortic valve failure

Surgical aortic valve replacement	Transcatheter aortic valve implantation (TAVI)
Structural deterioration (e.g., calcification)	Incomplete expansion
Thrombosis	Compression
Infective endocarditis	Late embolization
Pannus overgrowth	All the pathology also seen with surgical valve replacement (left)

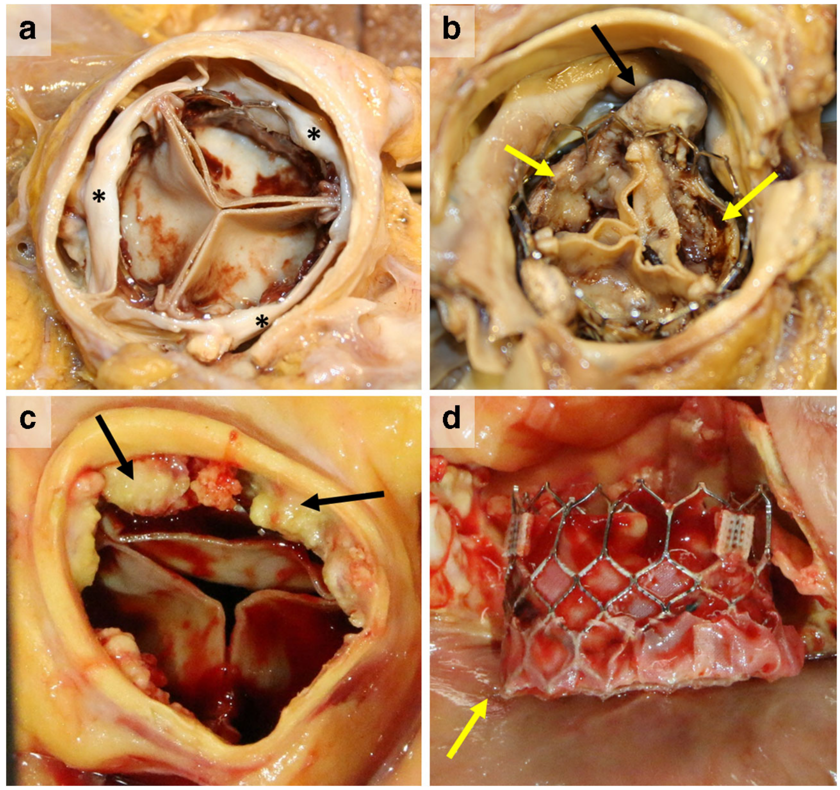

Fig. 5 Transcatheter aortic valve implantation. **a** The native valve is not replaced, but rather the prosthetic valve is implanted in the lumen. Note the native valve cusps (*asterisks*) pressed up against the wall of the aortic root. **b** The native valve was replaced with a bioprosthetic valve that failed. A transcatheter valve was implanted within the surgically implanted valve (valve-in-valve procedure); note the struts of the surgically implanted valve (*black arrow*). The new valve shows prominent leaflet thrombosis (*yellow arrows*). **c**, **d** This transcatheter valve was implanted too proximally due to obstructive aortic atherosclerotic plaques (*black arrows*). As a result, the bottom of the stent was compressing the myocardium (*yellow arrow*) in the area of the conduction system, resulting in heart block

xenografts, and bovine pericardial valves. While more blood-compatible than mechanical valves, bioprosthetic valves are less durable. In time, a similar calcific degenerative process that affects native heart valves occurs in tissue valves as well. This process occurs more rapidly in children than in adults [46]. The mineralization may limit cusp mobility or cause cuspal tear. The result can be stenosis and/or regurgitation.

In addition to surgical valve replacement, bioprosthetic aortic valves may be implanted via catheter. Transcatheter aortic valve implantation (TAVI, aka transcatheter aortic valve replacement), first performed in 2002 [47], is a minimally invasive or percutaneous method of delivering a bioprosthetic valve into the aortic position. The native valve is not actually replaced; the compressed bioprosthesis is introduced into the orifice of the aortic valve and expanded, functionally replacing the native valve. This technique may also be used within previously implanted failed bioprosthetic valves, referred to as a "valve-in-valve" procedure. All of the pathology common to surgically implanted valves, such as structural degeneration (e.g., calcification), thrombosis, infection, and tissue (pannus) overgrowth, may be seen in transcatheter valves [48]. However, there are also pathologies specific to transcatheter valves that are generally not seen with surgical prosthetic valves, such as valve compression and late embolization [49] (Table 3). Pathologic examination of transcatheter valves must include an assessment of morphologic features related to deployment, such as the completeness of expansion and relationship of the valve to adjacent structures, if present. For example, a valve implanted too proximally may cause complete or partial heart block (Fig. 5). A valve implanted too distally may occlude the coronary ostia. Incompletely expanded valves may have varying degrees of leaflet immobility. Severe leaflet immobility may result in failure of coaptation and regurgitation. Less severe immobility, however, may result in relative blood stasis and leaflet thrombosis. In some cases, leaflet thrombosis may be the cause of leaflet immobility [50•].

Conclusion

Aortic valve disease is an important group of potentially fatal conditions with increasing prevalence as our population expands and ages. Fortunately, innovative, less invasive interventions are being developed to address these not uncommon conditions. A thorough knowledge of the anatomy and pathology of the aortic valve and aortic root region is necessary if optimal therapeutic results are to be obtained.

Compliance with Ethical Standards

Conflict of Interest Gregory A. Fishbein and Michael C. Fishbein declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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