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

Mitral Valve Pathology

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Abstract
Purpose of Review This review describes numerous pathologic entities that cause structural abnormalities of the mitral valve. Different pathologic entities involve different components of the so-called mitral apparatus: atrial wall, annulus, leaflets, chordae, papillary muscles, and/or left ventricular free wall. These abnormalities can cause valvular stenosis, regurgitation, or both.
Recent Findings Currently, in addition to open-chest surgery to replace or repair the damaged mitral valve, there are less invasive percutaneous approaches to address mitral valve dysfunction. These include narrowing the orifice, clipping the leaflets, and inserting bioprostheses percutaneously.
Summary Understanding the structural abnormalities discussed in this review is essential for choosing the optimal therapeutic intervention for mitral valve disease.

Keywords Mitral valve · Mitral regurgitation · Mitral stenosis · Endocarditis · Rheumatic heart disease · Valve repair · Myxomatous degeneration · Myxoid degeneration · Floppy valve disease · Mitral valve prolapse

Introduction

The structure of the mitral valve is unlike that of the other cardiac valves. The mitral valve only has two rather than three leaflets. The mitral valve has six components that affect its function: the left atrial wall, an incomplete annulus, leaflets, chordae tendineae, papillary muscles, and the left ventricular free wall. There are few causes of mitral stenosis, post-inflammatory/rheumatic disease and congenital malformations being the most common. On the other hand, there are many structural abnormalities of the components of the mitral valve that can result in mitral regurgitation. Dilation of the left atrium, annulus, or left ventricle; myxoid change of the leaflets and chordae; and other changes in the leaflets or papillary muscles can make the mitral valve leak. The causes of such changes include congenital malformations, infection, numerous collagen-vascular diseases, ischemic heart disease, and heart failure to name the most common. Until recently, open-heart surgery with replacement of the valve was the only surgical option. More recently, open-chest and percutaneous repair of the valve can be accomplished. The pathology of the mitral valve discussed in this chapter will, to some extent, dictate the therapeutic approach.

This article is part of the Topical Collection on *Structural Heart Disease*

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Mitral Valve Anatomy

The structure responsible for modulating blood flow between the left atrium and left ventricle is complex, and is not simply a "valve." Indeed, the term "mitral apparatus" [1] has been aptly applied to this structure that actually has six components: the posterior wall of the left atrium, an annulus, two asymmetric leaflets, chordae tendineae, papillary muscles, and the left ventricular wall [Fig. 1]. Abnormalities in one or more of these structures may cause the valve to leak or become stenotic. Left atrial dilatation can result in displacement of the posterior leaflet of the valve, resulting in regurgitation.

The annulus, or valve ring, is an incomplete band of dense collagen between the left atrium and ventricle that surrounds the posterior leaflet. There is no true annulus around the anterior leaflet that is in fibrous continuity with the aortic valve and aortic wall. The annulus is somewhat elastic and

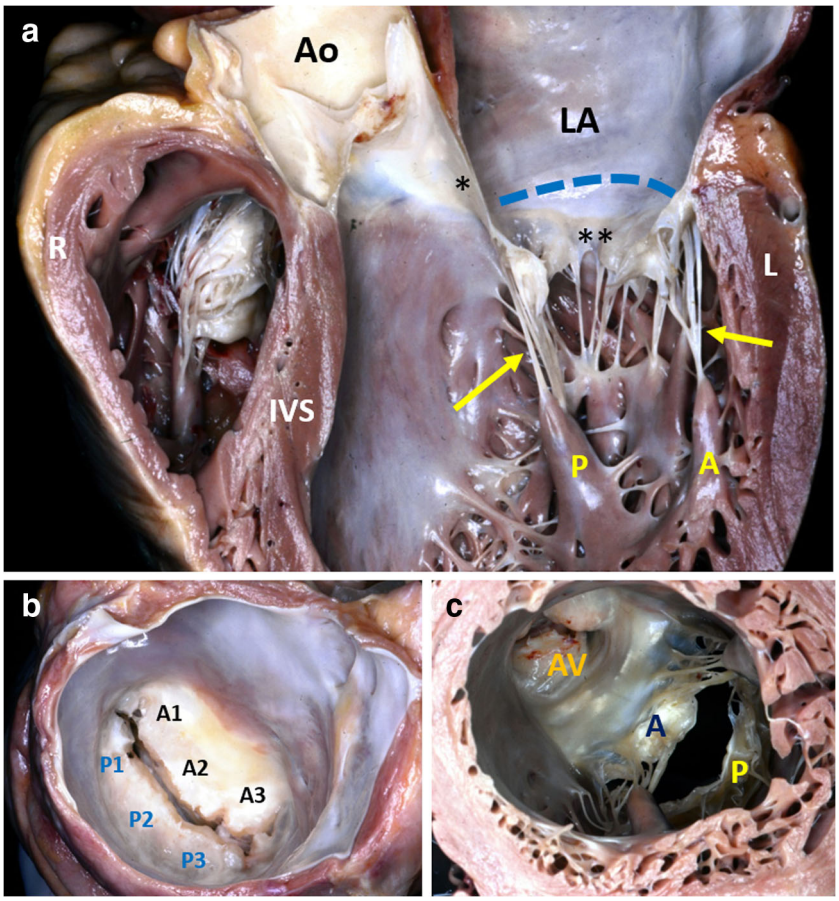

Fig. 1 Mitral valve anatomy. **a** Gross photograph of the heart cut along the long axis of the left ventricle. The mitral apparatus consists of the posterior wall of the left atrium (LA), an annulus (*blue dotted line*), anterior (*) and posterior (**) leaflets, chordae tendineae (*yellow arrows*), posterior (P) and anterior (A) papillary muscles, and left ventricular wall (L). Other structures seen from this view include the right ventricular free wall (R), the aorta (Ao), and the interventricular septum (IVS). **b** View of the mitral valve from the left atrium (inflow surface). Conceptually, the anterior and posterior leaflets can be subdivided into three segments, A1 A2 A3 and P1 P2 P3, respectively. c View of the mitral valve from the left ventricle (outflow surface). The anterior mitral leaflet (A) is continuous with the aortic valve (AV), whereas the posterior mitral leaflet (P) attaches to the left ventricular wall

distensible that allows contraction during systole. Unfortunately, this compliance also allows the ring to stretch if the atrium or ventricle is dilated, contributing to regurgitation [2].

The ring may also calcify, most often in patients with hypertension, renal failure, or certain connective tissue diseases. Calcifications are more common in women, the elderly, and in association with obesity in women [3, 4]. This calcification can limit the contraction of the annulus resulting in mild mitral regurgitation (MR), or the calcific nodules may rarely extend onto the valve leaflets and cause valvular stenosis [5]. Atrial fibrillation is also more common in individuals with a calcified mitral annulus [4].

The two quite different valve leaflets are responsible for anatomic closure of the valve orifice. The posterior leaflet is longer and narrower than the anterior leaflet, which is more "fan-shaped." Accordingly, the anterior leaflet is more mobile and swings between the septum during diastole, and the left ventricular free wall during systole. The posterior, longer leaflet, surrounds 2/3 of the annulus [6] while the anterior leaflet is responsible for the other 1/3. The leaflets have a layered structure: a prominent layer of collagen, the fibrosa, a thinner layer of basophilic extracellular matrix, the spongiosa, a layer with elastic fibers on the atrial side, the atrialis, and a covering layer of endothelial cells on all surfaces. The fibrous continuity between the anterior leaflet and the aortic root may be altered in a number of congenital malformations of the heart, particularly transposition of the great vessels. The valve leaflets are victim to a variety of pathologic changes to be discussed. The valve leaflets are tethered to the papillary muscles by string-like fibrous strands, the chordae tendineae. Most chordae attach to the edges of the leaflets, but other chordae attach to the undersurface, or ventricular surface, of the leaflets. The chordae subdivide and anastomose as they approach the valve leaflets. Approximately half the chordae from each leaflet attach to each of the two papillary muscles. With age, the valve leaflets and chordae may be thickened by fibrous tissue and show some degenerative changes.

The two papillary muscles and underlying left ventricular free wall are the muscular portions of the mitral apparatus. The papillary muscles arise from the apical to mid-third of the ventricular wall. The posteromedial papillary muscle, as its name implies, takes origin adjacent to the posteroseptum, while the anterolateral papillary muscle is not in close apposition to the interventricular septum. There is considerable variation in the structure of the papillary muscles: the anterior usually has one large "head," while the posterior more often has multiple "heads" [Table 1] [7].

Table 1 Causes of mitral regurgitation

Myxomatous degeneration
Rheumatic heart disease
Infective endocarditis
Connective tissue disease
Congestive heart failure
Cardiomyopathy
Papillary muscle dysfunction/rupture
Drug-induced valvular disease
Congenital malformations

Myxomatous Degeneration

Myxomatous disease of the mitral valve is reported to have an incidence of 2.4–5%, and is the most common cause of mitral regurgitation in older patients [8]. The gross abnormality consists of elongation and stretching of the leaflets and chordae tendineae. The valve may have a thickened, gelatinous, scalloped appearance [Fig. 2]. The affected chordae are stretched and attenuated, and are prone to rupture. Myxomatous degeneration may cause superior displacement of one or both mitral leaflets into the left atrium, referred to as mitral valve prolapse. Other names for this clinical entity include Barlow syndrome, floppy valve syndrome, ballooning degeneration, billowing leaflet syndrome, and mucinous degeneration [9]. The histopathology is characterized by architectural changes in the leaflets consisting of fragmentation of collagen with an increase in extracellular proteoglycans and subsequent fibrosis [Fig. 3] [10]. Classically, a midsystolic click is heard by auscultation; however, the diagnosis is currently made by echocardiography. Cardiac complications include infective endocarditis, and mild to severe mitral regurgitation. Less well-understood manifestations include stroke and sudden death [11]. While the risk of stroke and sudden death appear to be increased in patients with myxomatous degeneration of the mitral valve, the degree of risk is controversial [12–14]. Myxomatous degeneration of the mitral valve may be a primary isolated abnormality, or found in association with other connective tissue diseases such as Marfan syndrome and pseudoxanthoma elasticum [Tables 2 and 3] [15, 16].

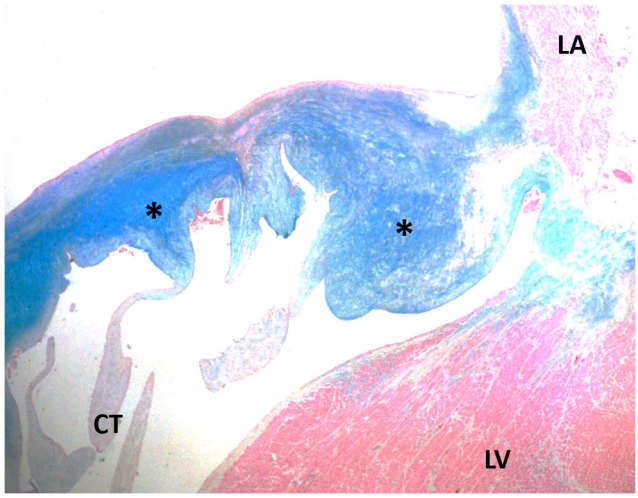

Fig. 3 Histologic section showing myxomatous degeneration of the mitral valve. There is an increase in proteoglycans and subsequent fibrosis (*) in the valve tissue, as highlighted in *blue* by the Masson trichrome stain. This section also shows the muscle, staining *red*, of the left atrial (LA) and ventricular (LV) myocardium. Chordae tendineae (CT) can also be seen

Post-inflammatory Mitral Valve Disease

While there are many causes of mitral valve regurgitation, there are relatively few causes of mitral stenosis. Very large vegetations, usually with fungal endocarditis, may obstruct the orifice of the valve. Rarely, calcification from the annulus may grow onto the leaflets, and even tophaceous gout involving the mitral valve has been reported to cause stenosis [17]. However, by far and away, "rheumatic" disease is recognized worldwide as the most common cause of mitral stenosis. Rheumatic fever (RF) is an autoimmune reaction to untreated *Streptococcus pyogenes*, a Gram-positive bacteria causing throat infection in susceptible children and young adults. The major sequela is rheumatic heart disease (RHD), a fibroinflammatory process that tends to affect the mitral valve.

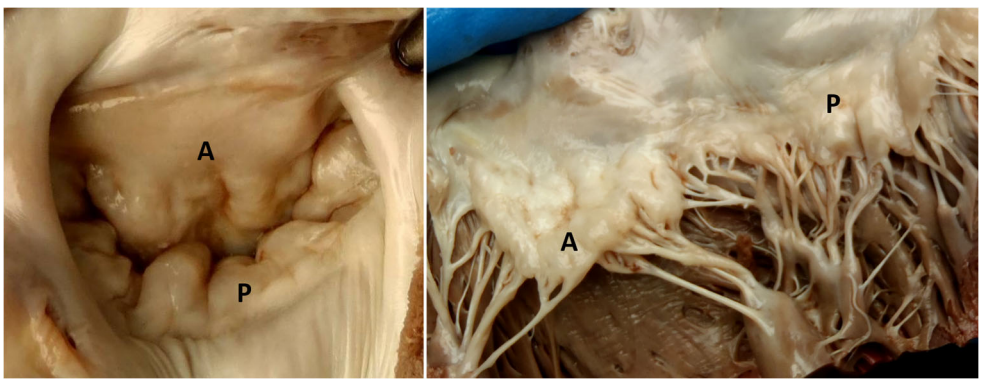

Fig. 2 Gross appearance of myxomatous degeneration of the mitral valve—views from the left atrium (*left*) and the opened left ventricle (*right*). The anterior (A) and posterior (P) leaflets appear thickened, redundant, and scalloped. There is stretching and thinning of the chordae tendineae

Table 2 Syndromic causes of myxomatous degeneration

Syndrome	Major related genes	Estimate prevalence of MVP
Marfan	*FBN1*	25–45%
Ehlers-Danlos	*COL5A1*, *COL5A2*	6%
Loeys-Dietz	*TGFBR1*, *TGFBR2*	21%
Aneurysms-osteoarthritis	*SMAD3*	45%
Hypertrophic cardiomyopathy	*MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*	3%
Osteogenesis imperfecta	*COL1A1*, *COL1A2*	Unknown
Pseudoxanthoma elasticum	*ABCC6*	Unknown

MVP mitral valve prolapse

Susceptibility to RF and RHD has a genetic basis, involving both HLA (human leukocyte antigen) and non-HLA-related genes [18]. It is thought that other inflammatory diseases, both infectious and non-infectious, may result in characteristic valve lesions of rheumatic disease. Hence, currently, when the pathologist sees the typical lesion pathologically, the preferred diagnostic term is "post-inflammatory" valve disease. Such valves have abnormalities of the valve leaflets and chordae tendineae. The classic lesion is diffuse thickening, fusion, and shortening of the chordae, with diffuse fibrosis of the valve leaflets and fusion of the valve commissures. Calcification of the leaflets is often present [Fig. 4]. The shortened chordae appear to pull up the papillary muscles so that their tips are closer than usual to the valve leaflets [19, 20]. Accordingly, in rheumatic disease, the stenosis is not only at the valvular level, but also at the subvalvular. Because the commissures are fused, the valve orifice may be fixed in a partially narrowed, yet stuck-open position, so a combination of stenosis and regurgitation to varying degrees is observed clinically. The histopathology is nonspecific with fibrosis, calcification, and myxoid change. Blood vessels are not seen in a normal mitral valve, so the neovascularization that is present indicates prior inflammation of the valve leaflets. Secondary effects include left atrial enlargement and changes in the left ventricle. If the stenosis is severe, the left ventricle may be small and atrophic. If there is ample regurgitation, the left ventricle will be dilated and there will be an increase in left ventricular mass. Eventually, the increased left atrial pressure will cause changes to the pulmonary vasculature and parenchyma, and changes in the right heart related to pulmonary hypertension. In RHD, other cardiac valves may be affected; but by far, mitral valve abnormalities are most common.

Valvular changes have been reported in other "rheumatologic" diseases, but are usually mild and nonspecific, associated with mild mitral regurgitation clinically [21]. Classical rheumatoid nodules have been described in patients with rheumatoid arthritis [22]. Mitral valve prolapse has been reported in polymyositis [23]. The changes of ankylosing spondylitis that usually involve the aortic root may extend down into the anterior leaflet of the mitral valve resulting in inflammation, fibrosis, and the characteristic subaortic bump with mild mitral regurgitation [24].

The acute valvular lesion of systemic lupus erythematosus, fibrinous verrucae on the undersurface of the leaflets, Libman-Sacks endocarditis, has been well recognized for many years. With current therapy, this acute inflammatory lesion of the mitral valve is rarely seen, and long-term consequences are even more unusual, but mitral regurgitation has been reported [23].

Table 3 Causes of mitral stenosis

Rheumatic heart disease
Infective endocarditis
Severe mitral annular calcification
Storage diseases
Drug-induced valve disease

Infective Endocarditis

As its name suggests, infective endocarditis is inflammation of the endocardial lining of the heart due to infection. Usually, the valve leaflets are the primary site of infection, but the mural endocardium may also be involved, or may be the only site of infection. From experimental studies, it appears that the damage to the endothelium with resulting thrombotic vegetations form the milieu for bacterial colonization. Hemodynamic factors play a role as endocarditis is much more common on valves with structural abnormalities [23]. Vegetations form on the line of closure. The bacteria and associated inflammation invade and destroy the valve and chordae tissue, usually resulting in valvular regurgitation. Very large vegetations rarely cause stenosis. Portions of the vegetations break off, and the resulting septic emboli wreak havoc in affected organs. Intracardiac complications include ring abscess formation that can result in conduction abnormalities, or the infection can spread out through the annulus causing pericarditis [25].

Healed infective endocarditis, that is, endocarditis that is cured with antibiotics, often leaves structural change. There may be diffuse fibrosis mimicking rheumatic disease (hence, post-inflammatory disease), ruptured chordae, valve perforations, and aneurysm formation in tissue weakened by the infection [26].

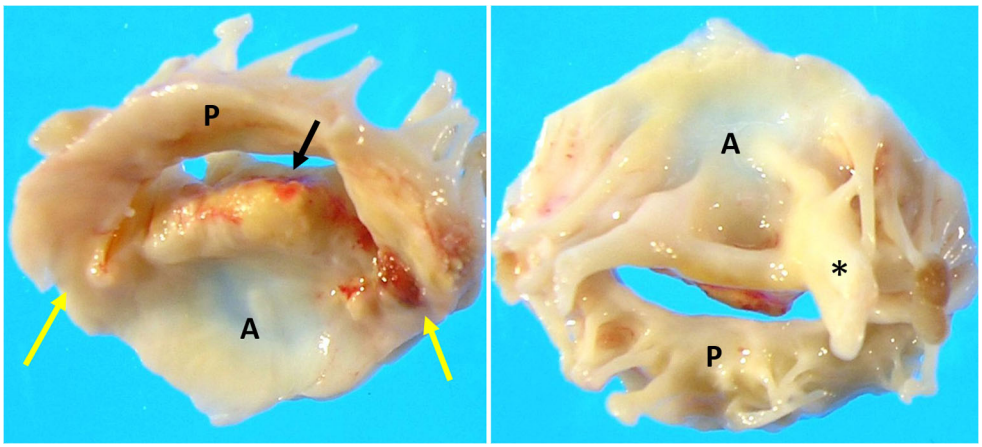

Fig. 4 Mitral stenosis secondary to post-inflammatory scarring—views of inflow (*left*) and outflow (*right*) surfaces. In this example of rheumatic valvular disease, the anterior (A) and posterior (P) mitral leaflets are fused at the commissures (*yellow arrows*). The chordae are shortened and fused (*). There is fibrous thickening of the leaflets with calcification (*black arrow*)

Countless organisms have been reported to cause endocarditis. Bacteria are the most common organism, with streptococci and staphylococci accounting for 80% of the cases [27]. Fungal infections are less common, but increasing in prevalence, as fungal organisms are more frequently encountered in illicit drug use, immunosuppressed patients, and individuals on antibiotics [28]. In patients in whom the infection cannot be controlled medically, or who have severe destruction of the valve, surgery to remove part or all of the valve is an option [29].

Non-bacterial thrombotic endocarditis (or endocardiosis), NBTE, is a term to describe platelet-fibrin deposits without inflammatory cells on the line of closure of a cardiac valve. By definition, there is no infection and no destruction of the underlying valve tissue [Fig. 5] [30]. NBTE has been called "marantic" endocarditis, a term used to describe wasting or cachexia that is often afflicting the unfortunate affected individual. The vegetations of NBTE are typically found in association with a variety of malignancies, especially adenocarcinomas. NBTE is also seen in patients with disseminated intravascular coagulation (DIC) and hypercoagulable states. Systemic emboli may occur, but are often undiagnosed in the seriously or terminally ill patients that are most often affected. In the overwhelming majority of cases, the diagnosis of NBTE is first made at autopsy.

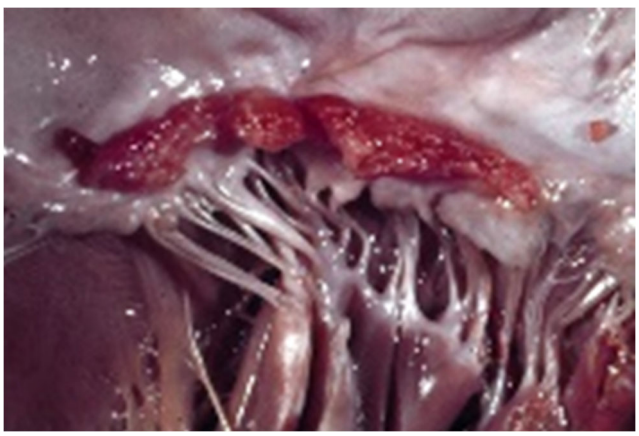

Fig. 5 Non-bacterial thrombotic endocarditis (NBTE), also called *marantic endocarditis*. Sterile vegetations consisting of platelets and fibrin characteristically deposit along the line of closure of the valve leaflet. There is no inflammation, infection, or destruction of the underlying valve tissue

Congenital Malformation of the Mitral Valve

The mitral valve apparatus may be malformed as part of complex congenital heart lesions such as atrioventricular (AV) canal, single ventricle, transposition of the great arteries, and heterotaxy syndrome, or any other rare situations. For the purposes of this manuscript, only the more prominent isolated congenital lesions of the mitral valve will be addressed.

One relatively minor abnormality of the mitral valve is a cleft in the anterior leaflet. While this defect is common as part of an AV canal malformation, it can occur alone as well, and it may be a cause of mitral insufficiency that is usually not severe [31]. Usually, the cleft is accompanied by abnormal chordae that attach to the site of the membranous septum rather than the papillary muscle.

Parachute mitral valve is a cause of mitral stenosis characterized by the presence of only a single papillary muscle in which chordae from both leaflets attach. The leaflets themselves and chordae are usually normal. The convergence of all the chordae into one papillary muscle narrows the valve orifice.

In anomalous mitral arcade, there is a fibrous tissue bridge between two papillary muscles continuous with the anterior leaflet of the valve. The valve commissures are not well developed and the chordae are short. Clinically, there may be an obstruction or regurgitation.

In a double-orifice mitral valve, there is an opening present within one of the leaflets of the mitral valve with chordae from the edge of the defect connecting to the underlying papillary muscle [32].

The Mitral Valve in Coronary Artery Disease

As indicated earlier, the mitral valve apparatus includes muscular components, namely the papillary muscles and the supporting left ventricular free wall. Acute myocardial infarction involving a papillary muscle may cause papillary muscle rupture, usually a fatal complication. Rupture is said to more often involve the posterior papillary muscle, which more often has a single vascular supply without much collateral flow [33]. Rupture of the papillary muscle adds a hemodynamic stress, severe mitral regurgitation, to a ventricle that has lost some of its functional myocardium, which is why this is so often a fatal event. If the papillary muscle infarction does not rupture, the muscle is replaced by fibrous tissue that does not contract. Thus, papillary muscle dysfunction occurs resulting in mitral regurgitation.

So-called secondary mitral regurgitation occurs in the presence of a mostly structurally normal valve apparatus. Usually in the setting of congestive heart failure from many causes, the ventricular cavity dilates, changing the geometric relationship of the papillary muscles such that they no longer contract in the proper plane, resulting in mitral regurgitation. The valve annulus can also dilate in heart failure that also may contribute to mitral regurgitation [34•].

Drug-Induced Mitral Valve Disease

As early as the 1960s, it became known that certain medications could cause valvular heart disease, when methysergide, a drug used to treat migraine headaches, was discovered to cause fibrosis of cardiac valves. While aortic valve involvement was more common, mitral valve involvement by a fibrosing process was also described [35]. Similar fibrosis that encased, but did not destroy, affected cardiac valves was noted with ergotamine therapy, also for migraine headaches [36]. Mitral regurgitation was the most common functional abnormality. Similar valvular abnormalities were observed with the ergot-derived dopamine receptor agonists, pergolide and cabergoline, used in the treatment of Parkinson's disease [37].

Additional widespread concern was raised by reports of severe valvular heart disease associated with the use of fenfluramine and phentermine, fen-phen, drugs approved by the FDA as appetite suppressants for the treatment of obesity. The initial report on July 8, 1977, included 24 women who presented with cardiovascular symptoms or a heart murmur. Mitral regurgitation was one of the functional abnormalities related to the thick, dense, fibrous tissue that covered the valve leaflets and chordae [38]. By September of 1997, the FDA had received notice of 144 cases of valvulopathy associated with fen-phen use. Similar reports with the use of fenfluramine or dexfenfluramine alone also emerged [39]. Uncontrolled echocardiographic studies suggested that 30–38% of users of fen-phen had valvular heart disease, but the true frequency was probably less than 10% [40, 41]. The findings mimic those that occur on the right side of the heart in the carcinoid syndrome. The exact mechanism is not completely understood; the common denominator appears to be some modulation of the central serotoninergic system [42].

Mitral Valve Replacement/Repair

Until recently, valve replacement was the only surgical treatment for mitral regurgitation. Then, mitral valve repair evolved to remove redundant tissue and replace ruptured chordae, thus preserving most of the native valve tissue without having to place an artificial valve. Most recently, less intrusive percutaneous methods have evolved by which the mitral valve annulus can be constricted by a device placed in the coronary sinus, or the leaking valve leaflets can be sutured or clipped together. In experimental studies in a porcine model, complete encapsulation and endothelialization of the clips occurred in as early as 4 weeks, and in 100% of clips by 17 weeks [43].

In contrast, transcatheter treatments for mitral stenosis have existed for over three decades [44, 45]. Percutaneous mitral balloon valvotomy has been a viable alternative to surgical commissurotomy in some patients with favorable mitral valve morphology [46]. It is only recently, however, that transcatheter mitral valve "replacement" has existed as an alternative to surgical valve replacement. Initially reserved for high-risk patients, transcatheter heart valve (THV) procedures may one day supplant surgical valve replacement altogether. The bioprosthetic valve, mounted on a compressible stent, is deployed via catheter and either self-expands or is press-fit into position. The term transcatheter valve "replacement" is a misnomer, as no valve is removed during the procedure; the THV is simply implanted in the lumen of the previous, failed valve. In the mitral position, this technique has gained popularity as an alternative to surgical valve replacement of a failed bioprosthetic valve. The so-called valve-in-valve procedure was first performed in humans on failed aortic bioprosthetic valves [47] and mitral bioprostheses shortly thereafter [48]. The THV can be introduced retrograde, via a transapical approach, or antegrade, via a transseptal approach. The former requires a minimally invasive "mini"-thoracotomy, whereas the latter is performed percutaneously. THV implantation into the native mitral annulus presents additional challenges, as the mitral apparatus anatomy is more complex than the round annulus of a bioprosthetic valve. Nevertheless, transcatheter native mitral valve "replacement" is performed, currently in patients with severe mitral regurgitation who are at high or prohibitive surgical risk [49•].

Conclusion

A wide range of structural abnormalities of different etiologies can affect the function of the mitral valve. In the not so distant past, there were few options for addressing mitral valve dysfunction. Currently, valves can be replaced or repaired surgically. In addition, a number of different percutaneous interventions are available. An understanding of the abnormal structure of the mitral valve is critical in choosing the optimal therapeutic approach for affected individuals.

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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