

# Etiologic Classification of Degenerative Mitral Valve Disease: Barlow's Disease and Fibroelastic Deficiency

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Barlow's disease and fibroelastic deficiency are the two dominant forms of degenerative mitral valve disease and have unique differentiating characteristics on clinical and echocardiographic assessment. Preoperative differentiation of patients by both cardiologists and surgeons is important because the techniques, surgical skill, and expertise required to achieve a repair vary among these etiological subsets. Barlow's patients often have multiple complex lesions, thus high rates of repair are only likely to be achieved by a reference mitral valve repair surgeon. In contrast, many forms of fibroelastic disease should be repaired at a high rate by experienced general cardiac surgeons. In this article, we highlight the differentiation of Barlow's disease and fibroelastic deficiency.

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Degenerative mitral valve disease refers to a spectrum of conditions in which morphologic changes in the connective tissue of the mitral valve cause structural lesions that prevent normal function of the mitral apparatus. Degenerative lesions, such as chordal elongation, chordal rupture, leaflet tissue expansion, and annular dilation typically result in mitral regurgitation due to leaflet prolapse. Degenerative mitral valve disease is recognized as an important cause of cardiovascular morbidity and mortality.<sup>1</sup> Although mitral valve prolapse with severe mitral valve regurgitation is a common indication for surgical referral, differentiation into the specific degenerative process that results in the mitral regurgitation has generally been less emphasized. Differentiating degenerative mitral valve disease, specifically Barlow's disease from fibroelastic deficiency, is, however, important because key aspects of surgery may depend on this distinction. This review focuses on the classification of degenerative mitral valve disease, with a specific emphasis on the differentiation of Barlow's disease from fibroelastic deficiency (Table 1).

## Historical Perspective

Although the syndrome of a midsystolic click and systolic murmur, now known as Barlow's disease, was first described in 1887 by Cuffer and Barbillon,<sup>2</sup> it was not until the 1960s that these findings were recognized to be due to mitral valve prolapse. Although some early workers, such as Griffith in 1892<sup>3</sup> and Hall in 1903,<sup>4</sup> had suggested they were caused by mitral regurgitation, the prevailing opinion until the early 1960s was that these murmurs were "innocent" and caused by pleuro-pericardial adhesions or extracardiac disease.<sup>5</sup> The theory of pericardial or extracardiac origin was challenged by Reid in 1961, who, again, suggested that mitral regurgitation was the cause of midsystolic murmurs and that the click probably arose from sudden tautening of previously lax chordae.<sup>6</sup> Barlow and colleagues validated Reid's theory in 1963; using cine ventriculography, they were able to demonstrate conclusively the presence of mitral regurgitation in seven patients with midsystolic murmurs.<sup>7</sup> Barlow and colleagues were therefore the first to provide direct evidence that the murmur and click were due to mitral regurgitation. However, they wrongly ascribed the findings to fibrosed chordae due to rheumatic valve disease and recommended that patients be placed on antibiotic therapy against rheumatic fever.<sup>7</sup> Barlow later presented his findings at Johns Hopkins Hospital, where Criley<sup>8</sup> correctly interpreted the mechanism of regurgitation as excessive posterior leaflet motion into the atrium during

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**Table 1** Key Differences Between Barlow's Disease and Fibroelastic Deficiency at Time of Surgical Presentation

|                                  | <b>Barlow's Disease</b>                                                                                                                                                                                                                  | <b>Fibroelastic Deficiency</b>                                                                           |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Pathology                        | Myxoid infiltration                                                                                                                                                                                                                      | Impaired production of connective tissue                                                                 |
| Typical age                      | Young (<60 years)                                                                                                                                                                                                                        | Older (60+ years)                                                                                        |
| Duration of known mitral disease | Several years to decades                                                                                                                                                                                                                 | Months                                                                                                   |
| Long history of murmur           | Usually                                                                                                                                                                                                                                  | No                                                                                                       |
| Familial history                 | Sometimes                                                                                                                                                                                                                                | No                                                                                                       |
| Marfanoid features               | Sometimes                                                                                                                                                                                                                                | No                                                                                                       |
| Auscultation                     | Midsystolic click and late systolic murmur                                                                                                                                                                                               | Holosystolic murmur                                                                                      |
| Echocardiography                 | Bulky, billowing leaflets, multi-segmental prolapse                                                                                                                                                                                      | Thin leaflets, prolapse of single segment, ruptured chord(s)                                             |
| Surgical lesions                 | Excess tissue, thickened and tall leaflets, chordal thickening or thinning, chordal elongation or rupture, atrialization of leaflets, fusion, fibrosis or calcification of chords, papillary muscle calcification, annular calcification | Thin leaflets, thickening and excess tissue (if present) limited to prolapsing segment, ruptured chordae |
| Mitral valve repair              | More complex                                                                                                                                                                                                                             | Less complex                                                                                             |

systole, a phenomenon he termed *mitral valve prolapse*. By the mid 1960s, the syndrome was recognized to be of a degenerative rather than rheumatic etiology because myxoid degeneration was found on histological examination of explanted valves. The macroscopic features of the Barlow valve were described and included voluminous thickening of the leaflets, and elongation, thickening, or thinning of the chords.<sup>9,10</sup> It was also appreciated that left ventricular dysfunction coexisted in up to 80% of patients with the syndrome, leading some workers to suggest that the valve degeneration was secondary to a cardiomyopathy.<sup>11</sup> With the introduction of 2-dimensional echocardiography, the echocardiographic features of mitral valve prolapse were defined, and, in the early 1980s, this modality superseded cineangiography as the tool of choice for diagnosing mitral valve prolapse. Barlow and Pocock later coined the term *billowing mitral leaflet syndrome* to describe the billowing of mitral leaflets as seen on echocardiography.<sup>12</sup> It is not clear when the eponym was first used to describe the disease, but references to Barlow's syndrome appeared in the medical literature as early as 1974.<sup>13</sup> Carpentier and colleagues characterized the surgical lesions seen in Barlow's disease<sup>14</sup> and were the first to differentiate it from another category of mitral valve prolapse where there was no billowing or excess tissue.<sup>14</sup> Carpentier used the term *fibroelastic deficiency* to describe this other degenerative process, which was generally associated with thinned and ruptured chordae, and typically involved a single segment of the posterior leaflet (P2).

## Barlow's Disease

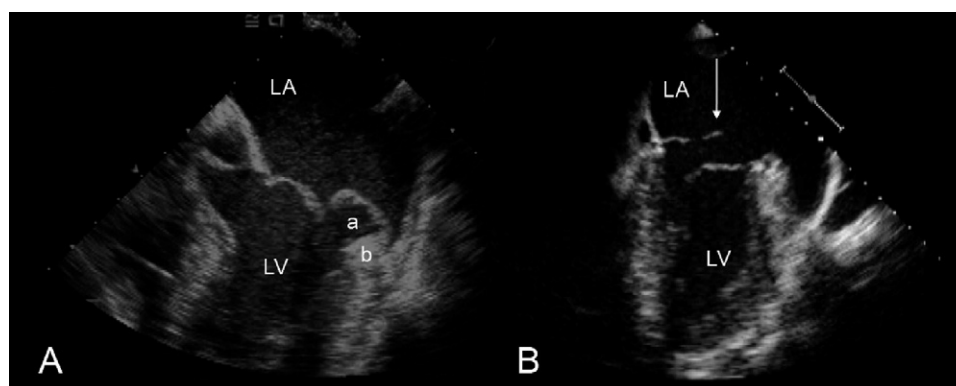
Barlow's disease is a degenerative mitral valve disease in which myxoid infiltration of the valve results in a myxomatous-appearing valve that is remarkable for excess thickened leaflet tissue. Chordae are sometimes thin but more commonly are thickened, fused, or even calcified. Chordal elongation is more frequent than rupture. The etiology is unknown; although some cases have a significant genetic or

familial component,<sup>15,16</sup> the majority of cases are sporadic. The pathological hallmarks are myxoid infiltration, which destroys the 3-layer leaflet architecture, and also collagen alterations seen on histological examination.<sup>17</sup> This myxoid infiltration is responsible for the thick, redundant leaflets seen in Barlow's disease. Because the infiltration affects the entire valve, billowing and/or prolapse of multiple segments of the valve are common findings.

## Clinical Assessment

Patients with Barlow's disease are typically young (age < 40 years), more often women, and asymptomatic at first presentation, having been found to have a murmur on physical examination. Many patients are then followed up by an internist or primary care doctor for an interval of several years before being referred for cardiologic assessment. On first presentation to the cardiac surgeon, most patients will therefore have a long history of a cardiac murmur. Some patients may have a family history of mitral valve prolapse. Surgical referral is often triggered by declining ventricular function, onset of atrial fibrillation, or the development of symptoms including palpitations, fatigue, dyspnea, and presyncope. Ventricular arrhythmias, syncope, angina, endocarditis, and cerebrovascular accidents are less common presentations. Patients with longstanding disease and left ventricular dysfunction may present with symptoms of heart failure. The recognition that clinical events and reduced life expectancy can occur in asymptomatic or minimally symptomatic patients with severe mitral regurgitation has led some workers to recommend surgical intervention before the onset of symptoms, arrhythmias, or ventricular dysfunction.<sup>18</sup> Patients are typically around 50 years of age at the time of surgical intervention,<sup>19</sup> although they can be of any age.

General physical examination is often unremarkable, but some patients have extracardiac signs, such as skeletal abnormalities, suggestive of a *forme fruste* of Marfan's syndrome.<sup>20</sup> The auscultatory findings in Barlow's disease were well char-



**Figure 1** Echocardiographic differentiation of degenerative disease. (A) Barlow's disease with posterior leaflet prolapse (transgastric, 4-chamber view): Note both leaflets are thick, bulky, and billowing. There is a displacement of the insertion of the posterior leaflet toward the atrium (a). Annular calcification (b) is also evident. (B) Fibroelastic deficiency with P3 prolapse (transgastric, 2-chamber view). Leaflets are thin and do not have billowing or redundancy. A ruptured chord (arrow) is visible. LA = left atrium; LV = left ventricle.

acterized in the 1960s<sup>21,22</sup> and classically include a mid to late systolic click and a high-pitched, late, systolic murmur. Interventions that decrease left ventricular end-diastolic volume, such as the valsalva or administration of nitrates, will increase the murmur of Barlow's and result in an earlier click, due to a more redundant mitral apparatus. Interventions that increase end-diastolic volume or afterload (for example, squatting, handgrips) make the murmur softer and shift the click to a later phase of systole. However, clinical findings are variable, and many patients do not fit classical descriptions.

## Echocardiography

Echocardiography is the gold standard for preoperative diagnosis and differentiation of degenerative mitral valve disease. Transthoracic echocardiography provides sufficient diagnostic information in a majority of patients. Transesophageal echocardiography provides clearer images and is necessary when transthoracic images are of insufficient quality. Three-dimensional echocardiography is an increasingly utilized research tool—preliminary data are exciting,<sup>23</sup> and this technology will likely simplify echocardiographic differentiation of degenerative mitral valve disease. From the surgical perspective, echocardiographic assessment of the Barlow's valve should (1) confirm the diagnosis of moderate to severe mitral regurgitation; (2) confirm Carpentier type II and often associated type I valve dysfunction<sup>24</sup> and identify which leaflet(s), and which segments of leaflets, prolapse or billow; and (3) delineate the primary lesions (excess leaflet tissue, chordal and leaflet thickening, chordal elongation and rupture) and secondary lesions (calcification, annular dilation).

Barlow's disease will usually show billowing of the body of one or both leaflets with prolapse of the margin of either or both leaflets. Regurgitation results from the marginal prolapse and not from billowing of the leaflet body. If the prolapse is due to chordal elongation, the regurgitation typically occurs in the mid to late phase of systole as opposed to holosystole in the case of chordal rupture. The valve is typically large, with elongated and redundant billowing leaflets; leaflets are bulky and thickened (Fig. 1A). Leaflet thickness in

diastole measured by M-mode echocardiography often exceeds 3 mm. Another common feature is displacement of the insertion of the posterior leaflet away from the ventricular crest and toward the atrium, creating an out-pouching at the leaflet base (Fig. 1A [a]). Severe annular dilation is typical. Annular or subannular calcification is less common but can be present in advanced disease (Fig. 1A [b]). Multiple segments of the valve are often prolapsing, although sometimes a single, prolapsing segment may be seen.<sup>25</sup>

## Surgical Lesions

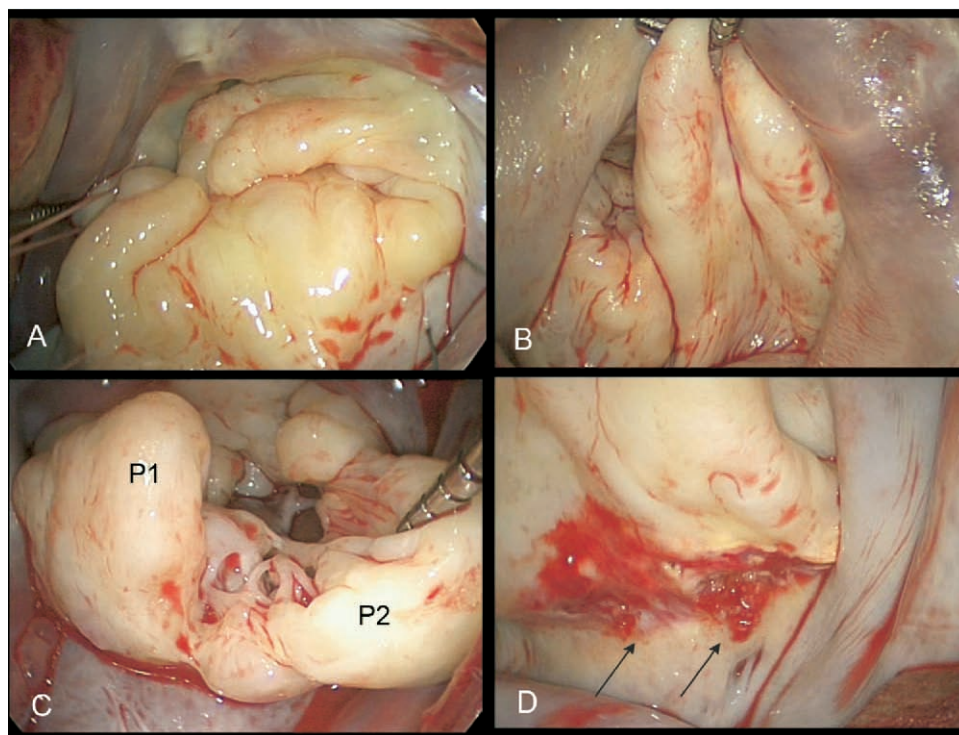
The most striking differences between Barlow's disease and all other causes of mitral regurgitation are the size of the valve and amount of excess tissue (Fig. 2A). Barlow's valves are often gigantic with the anterior leaflet sized at 38 mm or greater,<sup>19</sup> a finding unique to Barlow-type disorders. The height of the posterior leaflet not infrequently exceeds the septolateral diameter of the annulus (Fig. 2B). Multiple segments are thickened and present with excess tissue. Typically, chordal elongation results in multisegment prolapse, but chordal rupture may also be present. Chords may be thin but are often thickened and in advanced stages can become fused and retracted (Fig. 2C), leading to restriction of leaflet motion.

The annulus is always dilated in Barlow's disease, and it is not uncommon to encounter severe posterior annular dilation in relation to the true size of the anterior leaflet. Atrialization of the posterior leaflet with pseudodisplacement of its insertion away from the true annulus may be seen. Fissures at the base of the leaflet with microthrombi and calcifications are another feature commonly seen in Barlow's disease (Fig. 2D). Calcifications of portions of the annulus as well as the anterior papillary muscle and associated chordae may also be found.

## Implications for Repair

All lesions present should be corrected to restore not only valve competency but also a normal valve geometry and satisfactory line of closure. Because excess tissue is the hallmark

**Figure 2** Surgical lesions in Barlow's disease. (A) Large valve with redundant, thick, bulky leaflets. (B) Tall, posterior leaflet with tip rising to anterior annulus. (C) Calcified anterior papillary muscle (surgical picture of Fig. 1A): chords are fused and matted, causing restriction of P1/P2 junction. (D) Atrialization of the base of the posterior leaflet. Note the blurring of the junction between atrium and leaflet with fissures and microthrombi (arrows).



lesion of Barlow's disease, leaflet resection and restoration of the normal relationship of leaflet and annular dimension are usually central to the surgical strategy. Simply correcting marginal prolapse without resection leaves the lesion (of excess tissue) uncorrected and may predispose to systolic anterior motion and also recurrence of mitral regurgitation. If resection is not undertaken, such as in neochordoplasty, excess tissue should be positioned in a manner such that it does not contribute to the functional area of the valve. Congenital clefts, though not a characterizing feature of Barlow's disease, often require closure to effect an adequate repair. After reduction of excess tissue, chordal lesions should be corrected. It is important that appropriate support is restored to all areas fed by elongated chords to prevent a residual or recurrent prolapse. Support is restored by resection of prolapsing segments, chordal transfer, application of neochordae, or papillary muscle–repositioning techniques. Ruptured chordae are dealt with by similar techniques. The sliding plasty technique<sup>26</sup> may also be used to restore appropriate tension on mildly elongated chordae. Areas of leaflet and chordal calcification or fusion should be resected to restore mobility of the leaflet(s). Annular dilation is addressed by annular plication and annuloplasty. Annular decalcification is required for areas of extensive calcification. Finally, because Barlow's disease is typically associated with large valve size, we have found that the use of large annuloplasty rings facilitates a successful repair and may help prevent the complication of systolic anterior motion.<sup>19</sup>

## Fibroelastic Deficiency

In contradistinction to Barlow's disease, connective tissue deficiency, rather than excess, appears to be the main patho-

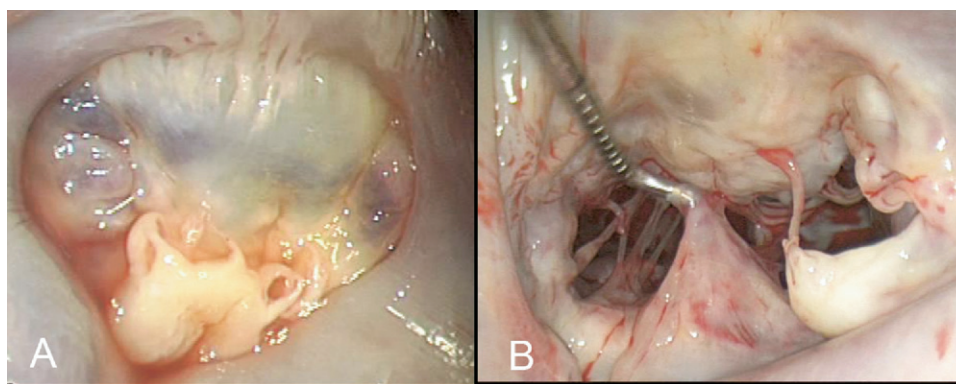
logical mechanism in fibroelastic deficiency.<sup>17</sup> Impaired production of connective tissue, with deficiency of collagen, elastins, and proteoglycans, results in thinning of leaflet tissue. The 3-layer architecture of the leaflet tissue is preserved. Secondary pathological change in prolapsing segments may result in myxoid deposition with resultant thickening and expansion, but this process is usually limited to the prolapsing segment.<sup>27</sup> Histologically, elastic fiber alterations are more prevalent in fibroelastic deficiency compared with Barlow's disease.<sup>17</sup> The etiology of the connective tissue deficiency in fibroelastic deficiency is unknown but may be age related. Rupture of thin, deficient chords is the usual mechanism of regurgitation in affected patients.

## Clinical Assessment

Patients with fibroelastic deficiency are typically asymptomatic until time of chordal rupture. In contrast to Barlow's disease, patients with fibroelastic deficiency are of middle or advanced age and report a short history of shortness of breath or fatigue. They do not usually have a long history of a murmur. In some instances, the patient may report precisely the time of onset of symptoms, coinciding to the time of chordal rupture. General physical examination is typically unremarkable. A harsh, holosystolic murmur radiating to the axilla is classically found. Signs of left heart failure may be present.

## Echocardiography

In fibroelastic deficiency, echocardiography usually shows a single, prolapsing segment, sometimes with a visible ruptured chord (Fig. 1B). Although the middle scallop of the posterior leaflet (P2) is the most often involved, any valve segment of the anterior or posterior leaflet may be affected.



**Figure 3** Surgical lesions in fibroelastic deficiency. (A) Prolapse of P2 due to multiple ruptured chordae; the leaflet tissue is thickened compared with other segments. Note the translucency of anterior leaflet, and normal height and thickness of P1 and P3, in contrast to findings in Barlow's disease (see Fig. 2). (B) Prolapse of P3 with ruptured chord (surgical picture of Fig. 1B); P3 is thickened, and the P2 (hook) and P1 segments are thin and of normal height.

The valve leaflets are thin and do not show redundancy or billowing. Annular dilation is less pronounced than in Barlow's disease, and calcification is typically absent. The regurgitation usually occurs throughout systole.

### Surgical Lesions

Chordal rupture is the classical lesion of fibroelastic deficiency (Fig. 3). One or more chords, usually to a single segment, are ruptured, causing prolapse of the unsupported segment. Nonruptured chords are often thinned. Leaflets are thin, sparse, and of normal height, the exception being the prolapsing segment, which may display thick and excess tissue (Fig 3A). The average ring size of patients with fibroelastic deficiency is 32 mm.<sup>28</sup> Annular dilation is present but less prominent than in Barlow's disease. Annular calcification is unusual but may occur in elderly patients because of coexisting senile annular degeneration.

### Implications for Repair

Because the primary lesion is chordal rupture, correcting the segmental prolapse resulting from the ruptured chord is always required. This lesion may be repaired by a variety of techniques including limited resection of the prolapsing segment, chordal transfer, implantation of neochordae or edge-to-edge suture to the corresponding area of the opposing leaflet. Excess tissue, if present, should be resected, although one must be cautious not to be too aggressive, because the residual noninvolved tissue is usually thin and sparse such that overzealous resection risks restricted motion of the reconstituted leaflet. Although leaflet and ring sizes are generally smaller than in Barlow's disease, systolic anterior motion remains a potential complication, so it is important to shorten excessively tall segments and not undersize annuloplasty rings.

### Other Degenerative Diseases

Degenerative mitral valve disease can be part of any syndrome of connective tissue disease. The degenerative mitral valve process seen in Marfan's syndrome—a connective tis-

sue disorder frequently associated with mitral regurgitation—is pathologically similar to Barlow's disease. Like Barlow's, Marfan's shows high levels of myxoid infiltration with excess tissue. There is, however, a tendency for more elastic fiber alterations in Marfan's valves, which is similar to the elastic fiber alterations present in extracardiac Marfan tissues.<sup>17</sup> From a surgical perspective, the Marfan valve is quite similar to the Barlow valve. For this reason, some have suggested that Barlow's disease is a *forme fruste* of Marfan's.<sup>29</sup> Other connective tissue diseases, such as Ehlers-Danlos syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum, and genetic disorders like Turner's syndrome, may also be associated with a Barlow-type mitral valve disease.

Sometimes, degenerative disease may affect exclusively the mitral valve annulus, causing a type I dysfunction—the etiology of such degeneration limited to the annulus is not understood, but in some cases may possibly be secondary to tachyarrhythmias or senile degeneration.

Not all patients who fit criteria for degenerative mitral valve disease can be clearly categorized on echocardiography or surgical inspection as Barlow or fibroelastic deficiency; sometimes the valve may share features of both syndromes.<sup>17</sup> Some valves may represent a *forme fruste* of Barlow's disease and will demonstrate myxoid infiltration on subsequent histological examination. Some presumed degenerative valves may be found on histology to have a nondegenerative origin such as rheumatic disease. Some degenerative disease will, however, remain unclassified.

### Implications of Degenerative Disease Differentiation

As cardiovascular specialists move toward more liberal surgical referral of asymptomatic patients with severe mitral valve regurgitation, the determination of likelihood of a mitral valve repair as opposed to a mitral valve replacement has taken on additional significance. Indeed, the current American College of Cardiology/American Heart Association Guidelines for Management of Patients With Valvular Heart

Disease<sup>30</sup> emphasize that an asymptomatic patient with chronic, severe mitral regurgitation should only be referred to experienced surgical centers where the likelihood of successful repair, without residual mitral regurgitation, is more than 90%. The proper differentiation of the degenerative disease process is a critical step in the referral process, as well as the surgical counseling a patient should receive.

## Surgical Implications

Differentiation of degenerative disease is a useful step for the reconstructive mitral surgeon, because the etiology and resulting lesions help define the techniques required to achieve a successful repair. For example, if the echocardiogram shows severe Barlow's disease with bileaflet multi-segmental prolapse and annular calcification, it follows that techniques such as posterior leaflet resection, sliding leaflet plasty, annular decalcification, chordal transfer or substitution, papillary muscle sliding, and large-ring annuloplasty will be required to achieve a repair. Unless the surgeon is well versed in such techniques, attempts at repair are unlikely to be successful. Also, such a repair will require a long period of aortic clamping and cardiopulmonary bypass. In our own series, the average cross-clamp time for a Barlow repair is 3 hours, reflecting the complexity of these reconstructive procedures.<sup>19</sup> After studying the preoperative echocardiogram, the surgeon should have a mental plan as to how he is going to achieve a repair. The lesions should also influence the incision proposed for the operation. For example, it is less likely to achieve a successful repair on a complex Barlow's (Fig. 2A) with a totally videoscopic port access approach; and, in such a case, it may be more prudent to recommend a median sternotomy or larger lateral thoracotomy, whereas a simple P2 prolapse has been shown to be reliably reparable through a variety of minimally invasive approaches. The distinction of etiology and reparability is particularly important for surgeons offering minimally invasive techniques, because young patients who seek such techniques are often asymptomatic patients with Barlow's disease.

## Referral Implications

It is sobering to note that despite a consensus in the cardiovascular community and an abundance of supporting data in the literature on the superiority of mitral valve repair over mitral valve replacement, mitral valve replacement for degenerative disease remains prevalent. To ensure a patient ends up with a mitral valve repair, rather than replacement, it is important that both cardiologists and surgeons familiarize themselves with the nuances of etiology and associated lesions in Barlow's valve disease versus fibroelastic deficiency, and also with the surgical complexity and skill required to repair various lesions. Although it is neither practical nor necessary to refer all patients with degenerative mitral valve disease to expert mitral surgeons, individual patients could be matched to the appropriate level of surgical expertise most likely to affect a repair. The surgeon and cardiologist should study the clinical scenario and preoperative echocardiogram to ascertain whether they are dealing with Barlow's disease or

fibroelastic deficiency. Barlow valves, when identified, should trigger referral to mitral valve repair surgeons skilled in such repairs.

## Assessment of Prognosis and Outcomes

It remains difficult to ascertain the true long-term durability of mitral valve repair because of poor classification of patients into appropriate etiologies, lesions, and dysfunctions.<sup>31</sup> Correct differentiation of etiologies and lesions is necessary to enable audit of the quality and durability of a center's mitral repairs and also for outcomes research. Surgeons committed to mitral repair must audit their repair rates and outcomes to ensure they are delivering their expected level of care—such audit can only be usefully done if stratified by etiology or lesions.<sup>32</sup> Surgeons should be able to quote their repair and residual regurgitation rates separately for Barlow's and fibroelastic deficiency to patients and referring cardiologists.

Although degenerative mitral valve repair has been undertaken for over 30 years, the long-term outcomes of degenerative mitral valve repair remain poorly defined because of lack of accurate differentiation. Although available data suggest that patients with bileaflet prolapse have a higher recurrence rate of moderate to severe mitral regurgitation and reoperation,<sup>33-35</sup> data cannot robustly differentiate outcomes according to etiology. It is not known, for example, whether Barlow's disease with repair restricted to the posterior leaflet has a similar outcome to fibroelastic deficiency with posterior leaflet prolapse, and whether differing repair techniques have differing outcomes. Differentiation of degenerative disease in future outcomes research is critical to further clarify the durability and results of mitral valve repair.

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