Althoug once rheumatic fever and its consequences were the major cause of valvular heart disease in the developed world, this disease has become exceedingly rare today. As a consequence, mitral stenosis (MS), which is usually caused by rheumatic fever, has also become rare. In fact, MS is most commonly found in the United States in patients who have emigrated here from areas where rheumatic fever is still endemic. Nonetheless, ≈1500 balloon mitral valvotomies (BMVs) were performed in the United States last year, which provides a rough index of severe disease prevalence. The following is a review of the current understanding and management of this disease.

Etiology

Although the attack rate for rheumatic fever is roughly equal among genders, MS is 2 to 3 times more common in women. It is generally believed that the M protein antigen held in common between the heart and group A hemolytic Streptococcus results in an autoimmune attack of the heart in response to streptococcal infection.\(^1\) What factors cause susceptibility to the illness remain unclear. Likewise, factors responsible for the decline in MS incidence in developed countries are also obscure. Although the decline may be due in part to the introduction of antibiotics, a fall in the attack rate of rheumatic fever began well before antibiotics were widely available.\(^4\)

Once begun, the rheumatic process leads to inflammation in all 3 layers of the heart: endocardium, myocardium, and pericardium. However, the disease primarily affects the endocardium, leading to inflammation and scarring of the cardiac valves. Although the process is punctuated by acute episodes of rheumatic fever, chronic inflammation and scarring continue well after the last attack, leading to severe valve damage years later. The mechanism of this chronic process is debatable and is thought to be due either to a continuing low-grade rheumatic process or to hemodynamic stresses on the now-injured valve. Elevated C-reactive protein levels, indicative of ongoing generalized inflammation, are found in many patients before BMV, which supports an inflammatory origin for MS.\(^5\) Although all of the cardiac valves may be involved by the rheumatic process, the mitral valve is involved most prominently and in virtually all cases. Stenosis of this valve occurs from leaflet thickening, commissural fusion, and chordal shortening and fusion.

Occasionally, mitral annular calcification rather than disease of the valve leaflets and chordae tendineae is the cause of mitral stenosis. Annular calcification appears to be closely related to aortic and aortic valve calcification, which have recently been associated with atherosclerosis rather than with rheumatic fever.\(^6\) Other exceedingly rare causes of MS include use of anorectic drugs and carcinoid syndrome.

Pathophysiology

The normal mitral valve orifice is 4 to 5 cm\(^2\), which essentially creates a common chamber between left atrium and left ventricle in diastole. In very early diastole, there is a brief, small gradient between left atrium and left ventricle, which rapidly dissipates (Figure 1A) so that pressure in the 2 chambers is equal for most of the filling.\(^7\) As the mitral orifice narrows in MS, it curtails free flow of blood from left atrium to left ventricle, and a pressure gradient develops between the 2 chambers (Figure 1B).\(^7\) This pressure gradient is added on to left ventricular diastolic pressure, which results in increasing left atrial pressure that eventually leads to left atrial enlargement and pulmonary congestion. As stenosis severity worsens, flow restriction limits left ventricular output. Pulmonary congestion and reduced cardiac output mimic left ventricular failure. Although it is generally believed that left ventricular contractility is normal in most cases of MS, the issue of a “myocardial factor,” ie, left ventricular damage cause by rheumatic fever, has often been raised without unanimity.\(^8\)–\(^10\) Although ejection phase indexes of left ventricular function are reduced in approximately one third of patients with MS, decreased preload from impaired filling and increased afterload secondary to reflex vasoconstriction (secondary to reduced cardiac output) are usually the causes of reduced left ventricular function rather than impaired contractility.\(^11\) However, in developing nations where rheumatic inflammation appears to be very aggressive, true contractile impairment may be present.

Because it is primarily the right ventricle that generates the force necessary to drive blood across the stenotic mitral valve, MS causes right ventricular pressure overload. In severe MS, pulmonary vasoconstriction in addition to left atrial hypertension produces severe pulmonary hypertension, which leads to right heart failure.
Diagnosis

History and Physical Examination

In mild disease (Table 1), the patient may be entirely asymptomatic. With worsening stenosis, the symptoms of dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea occur, although many patients may remain asymptomatic despite very high left atrial pressure. Lymphatic hyperfunction in such patients may help prevent pulmonary congestion and its attendant symptoms. Increasing left atrial pressure may result in hemoptysis as pulmonary venous hypertension results in rupture of anastomoses between bronchial veins. The enlarged left atrium may impinge on the left recurrent laryngeal nerve, causing hoarseness (Ortner’s syndrome). In some patients, the new onset of atrial fibrillation (AF) may be the first clue that MS is present. In other patients, the physiological stress of pregnancy may cause symptoms for the first time.

The physical examination of the patient with MS is characteristic and usually diagnostic. In advanced disease, the pulse pressure may be reduced, which indicates reduced stroke volume. There may be typical “mitral” facies with plethoric cheeks punctuated by bluish patches, a condition probably related to impaired cardiac output. Neck vein elevation is seen if there is right heart failure. Lung examination may demonstrate rales.

Cardiac examination finds a right ventricular lift if pulmonary hypertension has developed. A diastolic thrill may be palpated in the left lateral decubitus position. There is increased intensity of the S1 that occurs because the transmitral gradient holds the mitral valve open for all of diastole, so that ventricular systole closes the mitral valve from a long moment arm. In far-advanced disease, S1 may become soft because the valve is so diseased it neither opens nor closes well. The pulmonic component of the second sound will be increased in intensity if pulmonary hypertension is present. After S2, the mitral valve opens with a snap. The distance from S2 to the opening snap is a good clue to MS severity. The higher the left atrial pressure (and the more severe the stenosis), the sooner the mitral valve opens.

A low-pitched mitral rumble follows the opening snap and may be punctuated by presystolic accentuation if the patient is in sinus rhythm. A high-pitched blowing murmur (Graham Steell) may be heard at the cardiac base. Although often this murmur is thought to be secondary to the pulmonic regurgitation of pulmonary hypertension, in reality the murmur is more often due to concomitant aortic regurgitation. In patients with pulmonary hypertension, other findings may include a tricuspid murmur, hepatomegaly, ascites, and edema.

Laboratory Diagnosis

Although the ECG and chest radiograph provide support for the diagnosis of MS, today the echocardiogram forms the diagnostic mainstay (Figure 2). Echocardiography is used to establish the anatomy of the valve, confirming a typical “rheumatic” or “hockey stick” appearance. Stenosis severity is determined in 3 ways. First, the valve area can be planimetered directly. Second, Doppler interrogation of the valve can establish the pressure gradient, where gradient = 4 \( \frac{v^2}{d} \) and \( v \) = transmitral flow velocity. Third, valve area may be obtained by the pressure half-time technique. This empirical device divides the constant 220 by the time it takes for transmitral flow velocity to decrease from peak velocity to that velocity divided by the square root of 2. The more severe the MS, the slower the emptying into the left ventricle and the longer the pressure half-time will be, which enlarges the denominator and reduces the calculated valve area.

Suitability of valve anatomy for BMV is also assessed during echocardiography. In addition, disease of the other cardiac valves, pulmonary artery pressure (in the presence of even mild
Moderate to severe

<table>
<thead>
<tr>
<th>Severity</th>
<th>MVA, cm²</th>
<th>Gradient, mm Hg</th>
<th>PAP</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&gt;1.8</td>
<td>2–4</td>
<td>Normal</td>
<td>Usually absent</td>
<td>S₂-OS &gt;120 ms; normal P₂</td>
<td>IE prophylaxis</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.2–1.6</td>
<td>4–9</td>
<td>Normal</td>
<td>Class II</td>
<td>S₂-OS 100–120 ms; normal P₂</td>
<td>IE prophylaxis; diuretics</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>1.0–1.2</td>
<td>10–15</td>
<td>Mild pulmonary HTN</td>
<td>Class II–III</td>
<td>S₂-OS 80–100 ms; P₁ increase</td>
<td>IE prophylaxis; BMV if applicable or surgery if more than mild Sx</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;1.0</td>
<td>&gt;15</td>
<td>Mild to severe pulmonary HTN</td>
<td>Class II–IV</td>
<td>S₂-OS &lt;80 ms; P₂ increase; RV lift Sx if R heart fails</td>
<td>IE prophylaxis; BMV or surgery</td>
</tr>
</tbody>
</table>

MVA indicates mitral valve area; PAP, pulmonary artery pressure; OS, opening snap; IE, infective endocarditis; HTN, hypertension; Sx, symptoms; and RV, right ventricular.

Medical Therapy

The medical therapies for patients with MS in sinus rhythm are relatively limited. In general, all patients with MS should undergo appropriate antibiotic prophylaxis against infective endocarditis for those procedures known to cause bacteremia. Diuretics are useful for treating mild symptoms.

AF commonly accompanies MS and is more related to age than to stenosis severity. When AF occurs acutely, it is often associated with a rapid ventricular response. Because increased heart rate primarily reduces time in diastole, the arrhythmia causes further impairment in left ventricular filling, which leads to abrupt left atrial hypertension and reduced cardiac output. Immediate rate control is imperative and can be effected by administration of β-blockers or rate-affecting calcium channel blockers. If these therapies are ineffective in controlling rate and the patient is unstable, immediate DC cardioversion is indicated.

The patient with MS in chronic AF is at risk of embolic stroke (at a rate of between 7% and 15% per year). Accordingly, all such patients require warfarin anticoagulation with a target international normalized ratio of 2.5 to 3.5. After a first embolic event, the recurrence rate is increased ~2-fold without anticoagulation. Chronic rate control for such patients is usually maintained with the use of digoxin, a β-blocker, a calcium channel blocker, or some combination of these agents. Adequacy of rate control should be monitored not only at rest but also during activity, because in many patients, apparently adequate rate control at rest belies tachycardia with even mild activity. Such patients are at risk for developing tachycardia-induced cardiomyopathy.

Mechanical Relief of Obstruction

Because MS is a mechanical obstruction to forward flow, the only definitive therapy is mechanical relief of this obstruction. Three procedures are effective in providing such therapy. These are BMV, open commissurotomy, and mitral valve replacement. Because clinical trials have found BMV to be superior to closed surgical commissurotomy, the latter procedure has been largely abandoned except in areas where it is less expensive to perform closed commissurotomy than BMV.

Timing of Mechanical Intervention

As with all valvular heart disease, no randomized trials have been performed to ascertain the best timing of intervention; rather, timing has been derived from the relatively scanty observational data that exist. As shown in Figure 3, the more

Figure 2. Echocardiogram from patient with MS.
advanced the patient's symptoms, the greater the survival advantage with mechanical relief of obstruction (surgical commissurotomy in this figure) compared with medical therapy. Thus, it seems reasonable to provide mechanical relief once more than mild symptoms are present. Furthermore, as shown in Figure 4, when pulmonary hypertension has developed, surgical risk is excessive (12% versus the usual 3% to 8% reported in most studies). Thus, it appears unwise to permit pulmonary hypertension to go uncorrected regardless of symptomatic status. Timing of intervention is typically a bit earlier in good candidates for BMV, a nonsurgical procedure with a very low morbidity and mortality in experienced hands compared with open heart surgery. On the other hand, if it appears that mitral valve replacement will be required, its higher risks usually delay surgery until a bit later in the course of the disease.

**Balloon Mitral Valvotomy**

During BMV, a large balloon is introduced across the mitral valve via either the transseptal or retrograde route. Inflation of the balloon fractures the rheumatic fusion of the valve leaflets at the commissures, dramatically improving leaflet excursion and orifice area. Successful BMV is usually defined as a postprocedure mitral valve area of \( >1.5 \text{ cm}^2 \) with no more than moderate mitral regurgitation. In fact, postprocedure mitral valve area is usually close to 2.0 \( \text{cm}^2 \) in many reported studies. Randomized trials comparing BMV to closed commissurotomy show it to be superior to closed commissurotomy, providing an often larger valve area and exhibiting excellent long-term durability. Sixty-five percent of patients are free of restenosis 10 years after the procedure. Recently, encouraging results have been reported with the use of a reusable metallic valvulotome. Reuse of the device is helpful in reducing the cost of the procedure.

Suitability for BVM is determined by valve morphology and the amount of mitral regurgitation present. The Wilkins score gives a rough guide to the suitability of the mitral valve’s morphology for BMV. This scoring system assigns a point value from 1 to 4 for each of (1) valve calcification, (2) leaflet mobility, (3) leaflet thickening, and (4) disease of the subvalvular apparatus. In general, patients with a score of <9 and less than moderate mitral regurgitation have the best outcomes, although many patients have benefited from BMV despite higher valve scores. Thus, in most patients with high scores, a surgical approach is advisable; however, in patients with serious comorbidities for whom surgery seems ill advised, BMV may still provide benefit.

Before BMV, a transesophageal echocardiogram is performed in all patients to look for the presence of clot (an obvious risk for embolization) in the left atrium or left atrial appendage. If thrombus is found, BMV is abandoned, and the patient is begun on warfarin therapy for several months, at which time a repeat transesophageal echocardiogram is performed. If the thrombus has disappeared, BMV can then be attempted.

**Open Commissurotomy**

Recent emphasis on mitral valve conservation may lead to increased use of this procedure, wherein the surgeon, under direct vision, may be able to provide relief of obstruction in patients thought not to be BMV candidates because of poor valve morphology. Exactly what percentage of patients would likely have a bad outcome with BMV yet a good outcome with open commissurotomy is unknown but probably is small. However, when the valve can be conserved, it avoids the risks inherent to prosthetic valves and also avoids the need for anticoagulation in patients in sinus rhythm.

**Mitral Valve Replacement**

In cases in which rheumatic involvement of the valve precludes conservation, mitral valve replacement must be performed. The operative risk is 3% to 8% in the absence of pulmonary hypertension and other comorbidities. The choice of prosthesis is based on patient age, the risk of anticoagulation, and patient and surgeon preference. Table 2 presents the utility of the different valve procedures for MS.

**Special Issues**

**Atrial Fibrillation**

AF occurs commonly in MS, affecting \( \approx 40\% \) of all patients. Rheumatic AF appears different in pathophysiology from this arrhythmia in nonrheumatic disease. In nonrheumatic AF, increased atrial size and pressure are usually invoked as major factors in initiating the arrhythmia. As such, maneuvers to decrease left atrial size might be effective in preventing or
TABLE 2. Mechanical Therapy for MS

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Advantage</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMV</td>
<td>Sx; MVA &lt;1.5 cm² with good valve score.</td>
<td>MVA &gt;1.5 cm²</td>
<td>Percutaneous</td>
<td>Reduced applicability with poor valve morphology</td>
</tr>
<tr>
<td></td>
<td>Pulmonary HTN, MVA &lt;1.5 cm² with good valve score.</td>
<td>More than moderate MR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sx or pulmonary HTN + high-risk surgery and any valve score.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open commissurotomy</td>
<td>Sx, MVA &lt;1.5 cm²; pulmonary HTN with MVA &lt;1.5 cm²</td>
<td>MVA &gt;1.5 cm²</td>
<td>Avoids prosthetic valve</td>
<td>Limited applicability</td>
</tr>
<tr>
<td>Mitral valve repair</td>
<td>Sx, MVA &lt;1.5 cm² or pulmonary HTN with MVA &lt;1.5 cm²</td>
<td>MVA &gt;1.5 cm²</td>
<td>Applicable when BMV and open commissurotomy fail</td>
<td>All the risks of a prosthesis</td>
</tr>
</tbody>
</table>

MVA indicates mitral valve area; HTN, hypertension; Sx, symptoms; LA, left atrial; and MR, mitral regurgitation.

Concomitant Valve Disease

As noted above, rheumatic fever may involve all of the cardiac valves. Most commonly, MS is accompanied by aortic regurgitation. Because the presence of MS reduces cardiac output (and thus aortic flow), the copresence of MS blunts the usual presentation of aortic regurgitation.40 For any given severity of aortic regurgitation, MS reduces expected cardiac dilatation, stroke volume, and the physical signs caused by those factors, leading the clinician to underestimate aortic regurgitation severity both clinically and during echocardiography. In such cases, quantitative echocardiography-Doppler studies and/or cardiac catheterization may be necessary to resolve the issue. In symptomatic patients for whom valve surgery is contemplated, double-valve replacement carries increased risk compared with single-valve replacement. Therefore, it is advantageous, when possible, to perform BMV first and then perform aortic valve replacement.41

Tricuspid regurgitation also frequently accompanies MS. In most cases, tricuspid regurgitation results from right ventricular dilatation secondary to the pulmonary hypertension that complicates MS. As such, mild to moderate tricuspid regurgitation usually improves after correction of the MS.42 However, if severe tricuspid regur- gitation exists or if there is anatomic deformity of the tricuspid valve, surgical intervention for tricuspid regurgitation is usually necessary. Correction of tricuspid regurgitation is usually afforded by ring annuloplasty at the time of mitral surgery.

Summary

MS is usually caused by rheumatic fever, a disease rare in developed countries today but that still persists in a large part of the world. When complicated by AF, rate control and anticoagulation are mandatory in the absence of pressing contraindications. Once more than mild symptoms exist or once asymptomatic pulmonary hypertension occurs, mechanical relief of MS is indicated. In most cases, such relief is provided by the durable commissurotomy created at BMV. In other cases, surgical correction is needed. After these interventions, prognosis is excellent.

References


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