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Left Ventricular Dysfunction and Mitral Stenosis

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Rheumatic fever once dominated as the leading cause of valvular heart disease, and there has been a progressive decline in its prevalence over the last 50 years. Although any valves might be affected by rheumatic fever, the ones most often affected are the mitral and aortic valves. Mitral stenosis (MS) is the major valvular sequela of rheumatic fever observed in adults. Although there are numerous other causes of MS, including severe mitral annular calcification, carcinoid tumor, methylsergide therapy, Fabry's disease, Whipple's disease, systemic lupus erythematous, and mucopolysaccharidosis [1], more than 99% of MS is rheumatic in nature [2].

The prevalence of left ventricular (LV) dysfunction with MS is controversial. Much of the research performed on this topic is several decades old secondary to the declining prevalence of rheumatic heart disease. Although it is generally believed that LV contractility is normal in most cases of MS [3], some studies have suggested otherwise. Several studies have reported that the prevalence of a reduced LV ejection fraction in patients who have pure MS may be as high as 33% [4–7]. Most recently, Snyder and colleagues [8] reported an ejection fraction of 0.50 or less in 21 of 72 patients undergoing cardiac catheterization for MS. Choi and colleagues [9], using a radionucleotide technique, reported an ejection fraction of less than 0.45 in 18 of 36 patients who had MS.

Before the advent of surgical commisurotomy, the importance of determining the etiology of the LV dysfunction was a moot point because there was no effective therapy for either problem. With the advent of surgical procedures and later endovascular therapies, it has become clinically relevant to assess the effect of valvular obstruction versus myocardial insufficiency in MS [10]. Studies by Harvey and colleagues [11] and Fleming and Wood [12] were the first of many that have sought to determine the cause and prevalence of LV dysfunction in MS. This article focuses on the leading mechanistic theories and proposed treatment modalities for patients who have LV dysfunction and MS.

To appreciate the attempts to explain how this valvular disorder might induce LV dysfunction, one must have an understanding of the pathophysiology of MS, which is extensively reviewed elsewhere in this issue. The essential mechanisms to be noted are the pancardiac inflammation that occurs during acute rheumatic fever and the effects of potential chronic inflammation on the myocardium. During the acute phase, all three layers of the heart are involved (endocardium, myocardium, and pericardium) [3]. Although the most common long-term effect of this acute inflammation is valvular scarring and stenosis, chronic inflammation and scarring of the endocardium may occur long after the initial acute attack. The continuum between acute and chronic inflammation is represented histologically by initial fibroid necrosis, which is followed by the appearance of histiocytes and giant cells in a granulomatous stage [13]. This chronic inflammation with resultant fibrosis may be one feature of the so-called "myocardial factor" noted by Fleming and Wood [12].

In addition to the primary myocardial effects of rheumatic fever, one must also consider the long-term hemodynamic effects of MS. The effect of MS on circulatory pressures and blood flow can

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be summarized in four separate and distinct clinical mechanisms: (1) increased transmitral pressure gradient in diastole, (2) increased transmitral blood velocity, (3) reduction in total flow across the valve, and (4) left atrial hypertension leading to increased pulmonary pressures and subsequent right ventricular overload [14]. These effects may contribute independently or in summation to the development of LV dysfunction in some patients.

Leading theories of etiologies of left ventricular dysfunction

MS inherently reflects a mechanical obstruction to flow from the left atrium to the left ventricle. For many years, this mechanical obstruction was believed to be the leading etiology of reduced cardiac function in patients who had MS (Table 1). Baker and colleagues [15,16] emphasized this effect as they explored the success of commissurotomy with the first reports of this treatment. The basis of this belief stemmed from the relief of symptoms after surgical intervention as the determination of LV function was limited at the time. With advances in technology, including the advent of indicator-dilution volumetric techniques and angiography, investigators began to quantitate MS-associated impaired LV dysfunction. Using dye-dilution techniques, Levinson and colleagues [17] were the first to demonstrate a reduced end-diastolic volume, reduced ejection fraction, and a significant decrease in cardiac output in 12 patients who had MS. This mechanical obstruction hypothesis was the leading theory of clinical symptoms and of LV dysfunction into the 1950s [18].

Table 1
Proposed etiologies of the left ventricular dysfunction in mitral stenosis

1. Reduced filling of LV from mechanical obstruction from stenotic mitral valve
2. Chronic inflammation leading to abnormal wall motion from myocardial endofibrosis
3. Scarring of the subvalvular apparatus leading to wall motion abnormalities
4. Reduced LV compliance leading to profound diastolic function
5. Increased afterload leading to remodeling
6. Abnormal right-left septal interaction from pulmonary hypertension
7. Concomitant diseases such as systemic hypertension and coronary artery disease

In the 1950s, researchers began to raise the possibility that there may exist a factor specific to the left ventricle because some patients did not have relief of symptoms after surgical intervention. One of the initial proposed etiologies of LV dysfunction in MS was the effect of regional wall motion abnormalities. This theory developed with the advent of left heart catheterization, which permitted visual inspection of the LV cavity and assessment of motion by way of ventriculography. Holzer and colleagues [19] were among the first to attempt to angiographically quantify contraction abnormalities. In their study, they noted wall motion abnormalities in the basilar regions and suggested that this dysfunction could be residual from the initial rheumatic fever event [10]. Curry and colleagues [20] furthered this theory, noting additional wall motion abnormalities in the anterolateral wall of some patients who had MS. Abnormalities of the posterobasal and anterolateral walls were also found by Horwitz and colleagues [21] and Bolen and coworkers [22]. Hildner and colleagues [23] further qualitatively analyzed patients who had pure MS and reported LV enlargement and abnormal contraction in over half of their study population. This work spurred the search for the elusive myocardial factor because this was believed to be the cause of the reduced ejection and wall motion abnormalities present in these patients.

Grant [24] and then later Heller and Carleton [4] proposed an alternative theory for these wall motion abnormalities observed on ventriculography. Drawing from pathologic data first published in 1929 by Kirch [25], these investigators postulated that immobilization and atrophy of the posterobasilar wall might be related to thickening of the mitral apparatus, causing tethering and restriction of the adjacent myocardium with resultant segmental or regional dysfunction [10]. This implication of a malformed posterobasal area of the left ventricle as the probable origin of LV dysfunction was more evidence pointing to a myocardial versus a valvular etiology of LV dysfunction. This theory was further supported by work by Sunamori and colleagues [26] who found fibrosis in the myocardium at the base of papillary muscles removed at the time of mitral valve replacement (MVR).

From the concept of a restricted ventricle, either from tethering or from residual myocardial inflammation, the precept of reduced compliance

arose. Feigenbaum and coworkers [27] first attempted to assess mean compliance using the ratio of mean mitral valve flow to change in chamber pressure versus time. Of interest, there was no difference in this study between control patients and MS patients. Since this initial study, many others have affirmed that the combination of a rigid mitral apparatus [4,20], chamber atrophy [24], potential endomyocardial fibrosis [28], and a contribution from the right-sided loading of the heart [20] leads to reduced compliance.

To investigate the potential effect of each factor upon compliance in isolation, Liu and colleagues [7] conducted an elegant study using conductance catheter/micromanometer techniques coupled with transient inferior vena cava (IVC) occlusion to alter loading conditions. In their study, the investigators compared nine patients with MS with eight age-matched controls. In a subset of the MS patients, measurements were obtained acutely and within 3 months after percutaneous mitral balloon valvuloplasty. These investigators noted several conclusions. First, they noted that the finding of reduced diastolic compliance was reversed shortly after valvuloplasty. As endomyocardial fibrosis should not be acutely reversed by any procedure, these investigators rejected this hypothesis. Second, the theory of chamber atrophy from chronic underfilling was also refuted on the immediate effect of valvuloplasty on the pressure volume curves. Third, by measuring the end-diastolic pressure volume curves with complete unloading of the right ventricle by way of IVC occlusion, they rejected the effect of the right ventricle upon diastolic compliance. In addition, after balloon valvuloplasty, there was a substantial increase in left ventricular chamber compliance that essentially equaled that of the right ventricle. The conclusion of the study was that the etiology of reduced diastolic compliance seen in MS must be the immobility of the mitral apparatus. Liu and colleagues [7] likened this tethering effect to pericardial constriction and percutaneous mitral balloon valvotomy (PMBV) to release of this constriction by sheering of the mechanical constraint and subsequent return to normal diastolic function.

One precept of the mechanical obstruction hypothesis was that the pure underfilling of the left ventricle contributed to its impaired performance. Many investigators explored the relationship between LV end-diastolic volumes and impaired LV dysfunction. The results have been conflicting, with some investigators reporting smaller than normal LV end-diastolic volumes [6,20] and others noting normal or increased volumes [5,29–31]. Wisenbaugh and colleagues [32] reported similar end-diastolic volumes, end-diastolic pressures, and end-diastolic wall stress among patients who had MS and an ejection fraction less than 55%, patients who had MS and an ejection fraction greater than 55%, and control patients. McKay and coworkers [33] measured preload before and after percutaneous valvuloplasty and showed that end-diastolic volumes did not increase at all or increased very little after the procedure. Furthermore, Wisenbaugh and the procedure [32] noted a modest increase in preload measurements after valvuloplasty in patients who had MS and reduced ejection fraction ($<55\%$), without normalization of ejection fraction. Therefore, most agree that the underfilling hypothesis has been successfully refuted as an etiology of impaired LV dysfunction in pure MS.

Increased afterload has been examined also as a potential cause of LV dysfunction in MS. Gash and colleagues [6] proposed that the reduction in ejection fraction can be explained by high afterload that is not met by an increase in preload due to the reduction in mitral valve orifice seen in MS. They hypothesized that the higher afterload is a result of inadequate end-systolic wall thickness, which in turn increases wall stress at a normal LV systolic pressure. Kaku and colleagues [31] and Mohan and coworkers [5] independently found similar evidence for increased afterload in this patient population. Wisenbaugh and colleagues [32] investigated the effect of valvuloplasty on afterload, noting no significant decrease despite an apparent increase in preload. The conclusion from this study proposed that there was yet another unmeasured factor, perhaps endothelin, that results in higher peripheral vascular resistance and vasoconstriction in this patient population [29,32].

Further evidence for an altered neurohormonal axis can be demonstrated in patients who have MS. Ashino and colleagues [34] demonstrated neurohormonal activation by showing increased serum concentrations of various neurotransmitters and their metabolites and by examining microneurographically measured muscle sympathetic nerve activity. The stimulus for this activation is thought to be altered hemodynamics given that this increased sympathetic activity in MS is completely reversed 1 week after PMBV [1]. The well-known alterations in the renin-angiotensin-aldosterone system seen in other etiologies of heart

failure have not been fully explored in this patient population. This deficit is likely due to the recent ability to assess these changes in the setting of a decreasing patient population that has MS and LV dysfunction.

Long-standing MS is a well-known cause of pulmonary hypertension, which in turn can affect right ventricular function. An association often cited has been the presence of an impaired right ventricle with an impaired left ventricle. In many patients who have MS, a brief posterior or leftward motion of the interventricular septum is prominent in early diastole, just after the mitral valve opens [10]. The exaggerated displacement of the septum is due to unequal filling of the two ventricles [10,35]. Given the mechanical obstruction to LV filling and the lack of obstruction on the right side, early diastolic filling is more rapid in the right ventricle versus the left ventricle. This rapid inflow coupled with the diastolic suction component from the left side results in the leftward movement of the interventricular septum seen in MS. The effects on the septum from the pulmonary hypertension induced by MS have been implicated in impaired LV function. In fact, the septum may be hypertrophied, hypokinetic, or dyskinetic [36–38]. These septal abnormalities, per some investigators, may contribute to the decrease in LV systolic function seen in some patients with MS.

MS provides a milieu for diastolic dysfunction, which is a common cause of heart failure. In the presence of LV diastolic dysfunction, the symptoms of dyspnea and the degree of increase in left atrial pressure may be more than expected from the severity of the MS [1]. The deleterious effect of diastolic dysfunction in patients who have MS was shown by studies performed by Sabbah and colleagues [39] and Paulus and coworkers [40]. These investigators, by way of micromanometer recordings, demonstrated that negative intraventricular pressures are generated in early diastole in patients who have MS (Fig. 1). This diastolic suction effect provides less reliance on atrial contraction for LV filling. When diastolic dysfunction ensues, most commonly from hypertensive heart disease, this mechanism of filling is lost. In addition, one may see an increase in late diastolic pressure in these patients due to the concomitant presence of diastolic dysfunction. The combination of these two deleterious effects can contribute to a profound increase in symptoms. Hence, both systolic and diastolic function are important in patients who have MS.

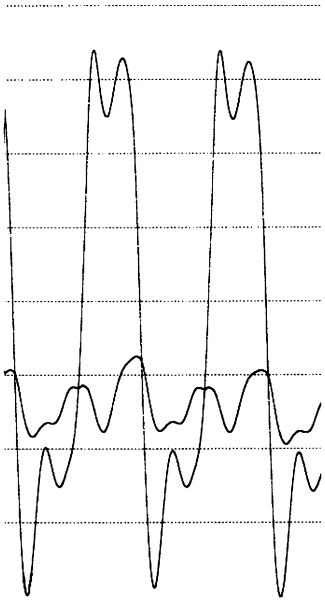

Fig. 1. LV and left atrial pressure waveforms in MS. Although these recordings were made with fluid-filled systems, micromanometer recordings have shown that LV pressure can be negative in early diastole in patients who have MS. The generation of negative pressure is due to the normal generation of a suction force in the left ventricle during early diastole accompanied by restricted inflow due to the MS. The end-diastolic pressure is elevated in this example. In the individual patient, the causes for the elevated LV end-diastolic pressure are variable but may include reduced chamber compliance due to the tethering effect of the mitral apparatus in MS.

In addition to hypertensive heart disease, coronary artery disease (CAD) is another common cause of impaired LV systolic and diastolic function in this patient population. The frequency of coronary disease in this patient population varies depending on which age group is surveyed. Mattina and colleagues [41] attempted to assess the prevalence of CAD in patients who had MS and the reliability of the symptoms of angina pectoris to predict coronary disease. In their retrospective study of 96 patients, they found angiographically significant coronary disease in 27 (28%) of their population. These patients were all over age 40 years. In addition, they determined that the presence of angina had a sensitivity of 37% and a specificity of 84% for CAD. They concluded that CAD in patients with MS who are older than 40 years of age is common and often clinically silent. In contrast, a more recent study by Guray and colleagues [42] noted

a different threshold for coronary angiography. In their study of 837 patients (35–77 years old), they found a prevalence of only 7.5% of angiographically significant (defined as greater than 50% narrowing) CAD. They noted that the presence of angina pectoris had a sensitivity of 33.3%, a specificity of 86.3%, a positive predictive value of 16.5%, and a negative predictive value of 94.1%. Guray and colleagues [42] concluded that routine coronary angiography is not necessarily indicated in patients with MS, particularly in patients who are younger than 40 years of age and have no coronary risk factors or angina pectoris. Overall, the prevalence of coronary disease without traditional risk factors is thought to be low in this population. Therefore, angiography to determine the cause of LV dysfunction in patients who have MS should likely be limited to patients who have traditional CAD risk factors.

Diagnosis of left ventricular dysfunction in mitral stenosis

Echocardiography and the determination of ejection fraction is the main current method to diagnose LV dysfunction in MS (Fig. 2). Although ejection fractions derived from echocardiography are often used to drive clinical practice, they tend to be subjective and variable [43]. Much of this is due to the load-dependent variables measured and the high prevalence of atrial fibrillation seen in this patient population. This subjectivity has undoubtedly led to the varying rates reported of LV dysfunction with MS. With the development of Doppler tissue imaging (DTI) and strain rate imaging (SRI), recent studies have begun to report indices of subclinical LV dysfunction in this patient population that are not load dependent. Ozer and colleagues [44], on the basis that LV long-axis function evaluated by M-mode or tissue Doppler echocardiography is a practical index of LV function [45,46], reported that these indices are reduced in patients who have MS. Of interest, these investigators explored these markers of LV function in patients who were thought to have normal LV ejection fraction as assessed by fractional shortening. Similarly, using DTI, Ozdemir and colleagues [47] showed that in patients who have pure MS, there was a reduction in LV systolic and diastolic myocardial velocities. Thus, these investigators demonstrated LV dysfunction in patients who had proposed normal ejection fractions by standard echocardiography.

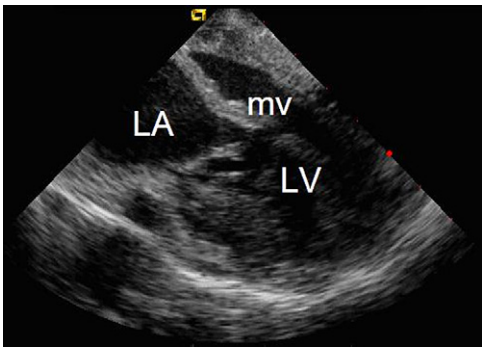

Fig. 2. An intracardiac ultrasound from a patient who had MS. Note the thickening of the anterior leaflet, the small chamber size, and the normal LV wall thickness. During systole, there was normal chamber contraction and normal wall thickening. Often, LV systolic function is normal and, even when the ejection fraction is somewhat reduced in MS, it does not appear to impact on surgical mortality. LA, left atrium; MV, mitral valve.

Working on the basis that DTI can be difficult to use clinically, Dogan and coworkers [48] proposed another method to assess LV function in MS patients, namely, strain rate and strain rate imaging (SRI). This new technique, which is derived from DTI, allows the determination of velocity gradients between two myocardial points [49]. One attractive aspect of using this method is that SRI is not affected by the rotation and translation of the whole heart, contraction of adjacent segments, or basoapical velocity gradients that complicate segmental analysis of diastolic function [48,50]. Dogan and coworkers [48] showed that there was impaired long-axis function in patients who had mild to moderate MS and normal global systolic function. This recent study is of interest in its use of strain rate and SRI. The determination of global long-axis function by way of these methods was recently shown to be able to predict contractile reserve in asymptomatic patients who had severe mitral regurgitation [51]. If the use of these new techniques is widely adopted, then the prevalence of LV dysfunction in MS may dramatically rise.

The use of serum markers, specifically B-type natriuretic peptide (BNP), has become commonplace in the diagnosis of patients who have heart failure. It is unfortunate that little information exists regarding the use of BNP in patients who have valvular heart disease. The use of BNP in patients who have MS remains controversial. In various studies, BNP levels have clearly been

shown to be elevated in patients who have MS [52,53]; however, there has been a lack of correlation between the severity of MS and BNP levels. Yoshimura and colleagues [52] found higher levels of BNP in patients who had MS compared with controls, but also found no correlation with level of BNP and wedge pressure. Most recently, two separate studies [54,55] have investigated the precursor to BNP (ie, N-terminal [NT]-proBNP). Both studies reported that NT-proBNP correlates positively with MS severity. In addition, Arat-Ozkan and colleagues [54] correlated NT pro-BNP with functional class and proposed this method as a manner to follow patients who have MS. It is unfortunate that although NT-proBNP correlated well with left atrial and right ventricular dimensions, New York Heart Association (NYHA) class, and mitral valve area, there was no investigation as per the use of NT-proBNP in patients who had MS and a reduced ejection fraction. Although there have been recent data on the use of BNP as a useful clinical marker in determining optimal surgical timing in valvular heart disease patients [56], data investigating or guiding the use of BNP in patients who have MS and LV dysfunction are nonexistent.

Other serum markers can also be elevated in rheumatic MS, including C-reactive protein [57], circulating adhesion molecules [58], and even tumor markers such as CA-125 [59]. The only marker that has been correlated with heart failure has been CA-125. This finding echoes other reports of increased tumor markers occasionally seen in heart failure patients. The proposed mechanism is venous congestion and subsequent activation of the peritoneal mesothelium. Although interesting, there have been no studies demonstrating a clear biomarker that will successfully predict the presence of LV dysfunction in MS.

Treatment of left ventricular dysfunction in mitral stenosis

Mitral valve replacement

Mitral valve replacement (MVR) is currently recommended (Class I) for patients who have moderate to severe MS with NYHA class III or IV symptoms who are not considered candidates for mitral balloon valvulotomy [60]. It is a class IIa indication in for patients who have NYHA class I and II symptoms with severe pulmonary hypertension who are not candidates for balloon valvulotomy. With respect to ejection fraction, no studies have provided clear evidence of improved ejection performance after surgical therapy for MS [61–63].

Little data exists regarding the outcomes in patients who have reduced ejection fraction with MVR. Snyder and colleagues [8] investigated the influence of preoperative ejection fraction in an MS population undergoing surgical commissurotomy or MVR. In their study, they found that preoperative ejection fraction did not predict perioperative mortality or short-term symptomatic response.

The issue of preservation of chordae with MVR was addressed by Chowdhury and colleagues [64]. They reviewed patients who had rheumatic MS and underwent MVR with complete excision of subvalvular apparatus, preservation of the posterior chordopapillary apparatus, or total chordal preservation (Fig. 3). Total or posterior chordopapillary preservation was associated with lower incidence of low cardiac output and better long-term survival. In the group with complete chordal excision, the LV ejection fraction was significantly decreased postoperatively and continued to decline over time and did not improve by 4 years. It is unfortunate that the patient population in this study was tainted by mixed mitral valve disease, which limits the extraction of this study given the known benefit of chordal preservation in patients who have mitral regurgitation. In addition, this study did not strictly include patients who had a reduced

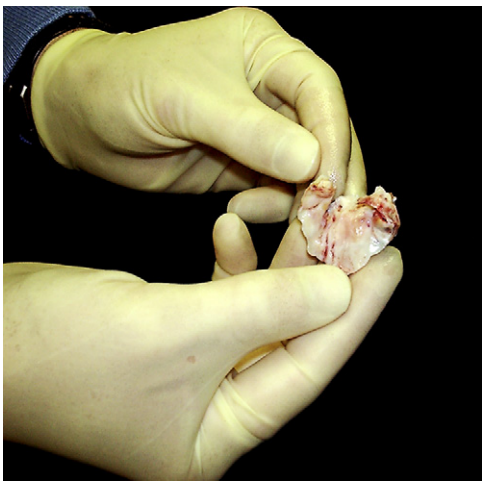

Fig. 3. A surgically excised mitral valve in a patient who has MS demonstrates the fibrosis and thickening of a leaflet and a portion of the subvalvular apparatus.

ejection fraction, which further limits the generalizability of this data.

The best study that addressed patients who had a reduced ejection fraction and MS undergoing MVR was performed by Mangoni and coworkers [65]. These investigators evaluated 16 patients who had MS without significant mitral regurgitation with an LV ejection fraction less than 50% (mean, 0.45) and compared them with patients who had MS and an ejection fraction greater than 60% (mean, 0.66). All patients underwent MVR and were followed closely for morbidity and mortality. In patients who had a reduced ejection fraction, there was a higher incidence of in-hospital heart failure and an increase in heart failure–related deaths. There was no difference, however, in overall mortality, rate of cardiac admission, or mean Specific Activity Scale score. The investigators concluded that moderate depression of LV ejection fraction should not be a contraindication to MVR for MS.

Percutaneous mitral balloon valvotomy

PMBV has provided an arena in which to study the effect of relieving the ventricular inflow obstruction inherent to this disease. Given that one leading theory of reduced LV function is impaired inflow, PMBV should affect LV ejection fraction by removal of the obstruction. It is unfortunate that this has been yet another topic of debate.

Although there have been no studies strictly including patients who have LV dysfunction, there have been numerous reports on the effects of PMBV on LV end-diastolic volume, LV end-diastolic pressure, and ejection fraction. Several studies have demonstrated that PMBV improves diastolic filling and increases end-diastolic volume immediately [66–69]. Other investigators have shown the contrary, with no response in these indices with PMBV [32,70–72]. In the studies with an improvement in filling indices, the ejection fraction was also shown to increase [66,67,69]. To complicate the matter further, in the studies by Fawzy and colleagues [66] and Yasuda and colleagues [69], LV end-diastolic volumes and ejection fraction continued to improve at follow-up after PMBV. Fawzy and colleagues [66] also noted an increased systemic vascular resistance at baseline, corroborating the theory of increased afterload in these patients. Most important, this increased peripheral resistance was noted to be markedly decreased when measured 12 months after PMBV. Although no studies have specifically addressed patients who have reduced ejection fraction, extrapolation from the aforementioned studies suggests a neutral or a positive effect of PMBV on indices of LV function.

Medical therapy

There are limited data regarding the medical therapy of patients who have MS and LV dysfunction. Although β-blockade is common in patients who have MS, valvular heart disease is often an exclusion criterion for heart failure trials, leading to a large void in the optimal treatment of these patients. Angiotensin-converting enzyme (ACE) inhibition has been classically seen as contraindicated given the fear of hypotension in the setting of a fixed obstruction. Sebastian and colleagues [73] investigated the effect of ACE inhibition in three patients who had severe MS in whom surgery was delayed. These investigators reported an initial improvement in symptoms and, more important, ACE inhibition did not cause an excessive fall in blood pressure or impairment of renal function. The largest trial to date using ACE inhibitors in patients who had MS came from Chockalingam and coworkers [74] who studied 109 patients who had MS and NYHA class III and IV symptoms. The patient population in this study included mixed mitral valve disease and some patients concomitant aortic valve disease. The findings were that irrespective of valve pathology, the use of an ACE inhibitor (enalapril) improved functional status and exercise capacity. It was not surprising that the greatest effects were in patients who had concomitant regurgitant valvular heart disease. It is unfortunate that no measure of ejection fraction was made for this study, but extrapolation from thousands of patients in heart failure studies suggests that patients who have MS and reduced ejection fraction would also benefit from ACE inhibition. At the current time, however, no specific data for this population exist as per the optimal medical regimen.

Summary

A reduced ejection fraction in the setting of MS is relatively commonplace, with a prevalence of approximately 30%. The etiologies of the impairment have been attributed to impaired diastolic filling, impaired myocardial contractility, excessive LV afterload, rigidity and fixation of the posterobasal LV myocardium from scarring or concomitant inflammation, effects from the right

ventricle, or a combination of these forces [65]. Although there is much debate, most likely the etiology of impaired LV function in patients with MS is patient specific and multifactorial in nature. The diagnosis of impaired LV function can be difficult with current methodologies given the subjectivity and load dependence of echocardiography, although new methods are being developed. The treatment of MS with LV dysfunction appears to be moot, in that all invasive treatments except those involving chordal excision appear to be beneficial. Medical therapy of these conditions is currently limited. Although standard of care involves β-blockade for prolongation of diastolic filling time, which also provides benefit in LV dysfunction, there are some data regarding ACE inhibition. Regardless, a reduced ejection fraction does not appear to alter long-term outcomes, either surgical or percutaneous.

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