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EDITORIAL COMMENT

New Concepts in an Old Disease

Exercise Intolerance in Moderate Mitral Stenosis*

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Rheumatic mitral stenosis (MS) is a relatively infrequent disorder in the United States and in most developed countries. Although immigration patterns are changing its epidemiology, most patients with MS in the United States are elderly women. The mechanisms are not well understood for the slowly progressive thickening, stiffening, and calcification of the valve leaflets that occur long after the initial rheumatic inflammation abates, but the pathophysiology of symptoms from MS has been classically viewed as straightforward: obstruction to efficient flow from left atrium to left ventricle (LV) (1).

In developed countries, end-stage MS with florid, class IV heart failure is thankfully rare. Instead, most patients with MS have varying degrees of exercise intolerance, manifested as dyspnea and fatigue with exertion. Because MS is thought to spare the LV, intervention with either percutaneous valvuloplasty (if valve morphology is suitable) or surgery is usually delayed until patient symptoms are severe and mitral valve area (MVA) is severely reduced. Management of patients with moderate MS can be challenging because symptoms are frequently out of proportion to MVA, and effective pharmacological interventions are lacking.

In this issue of *iJACC*, Laufer-Perl et al. (2) report the results of an elegant study that in several ways challenge conventional wisdom regarding the mechanisms and management of exercise intolerance in moderate MS. The study was an intergroup comparison of 20 patients (average age 65 years; 80% women) with moderate rheumatic MS and 20 control subjects without cardiac disease matched for age, sex, and LV ejection fraction. The study participants underwent semisupine cycle ergometry to the endpoint of exhaustion with simultaneous expired gas analysis and careful Doppler echocardiography. The investigators then repeated the examinations in a subset of participants following withdrawal of beta-adrenergic blocker medications.

The MS patients had reduced exercise capacity compared with control subjects, confirmed as peak oxygen consumption (VO_2) (2). This was associated with reduced peak heart rate, stroke volume, end-diastolic volume, ejection fraction, and tidal volume. There was evidence for abnormal LV function. Patients with the worst exercise intolerance had the greatest reduction in heart rate, tidal volume, and MVA. However, in multivariable analyses, only peak heart rate, tidal volume, and arteriovenous-oxygen difference (A-VO_2D) were independent predictors of exercise capacity, whereas mitral valve (MV) gradient and MVA were not. Even more surprising, beta-blockers were observed to worsen the heart rate and stroke volume responses, leading to a substantially lower peak VO_2 that trended toward statistical significance; this occurred despite a modest reduction in MV gradient at peak exercise.

How can these results be reconciled with the long-held notion that exercise intolerance in MS is due primarily or even solely to reduced LV filling, increased mitral gradient, and increased left atrial pressure due to shortened diastolic filling time as a result of high heart rate during exercise, and that this can be rectified by reducing heart rate to increase diastolic filling time? By the Fick equation for oxygen consumption, peak VO_2 is determined as: HR × stroke

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volume × arteriovenous oxygen difference (A VO_2Diff). In healthy human subjects, the increase in VO_2 during maximal exercise is achieved by a 150% increase in heart rate (HR), a 40% increase in stroke volume, and a 150% increase in A VO_2Diff (3). Thus, HR is the dominant determinant of peak VO_2 along with A VO_2diff, which is determined by peripheral vascular and skeletal muscle function. Stroke volume, however, is a relatively minor contributor to peak VO_2. Furthermore, the contribution of increasing stroke volume to VO_2 occurs primarily during early stages of exercise, when heart rates are low (3). At high levels of exercise, nearly all of the increase in VO_2 results from increasing HR (3).

In patients with MS, the classic work of Gorlin et al. showed that reduced exercise cardiac output is the primary determinant of their exercise intolerance. Subsequently, Rigolin et al. (4) showed that chronotropic incompetence was a significant contributor to the reduced exercise cardiac output and that peripheral factors, assessed as invasively measured A-VO_2D, also contributed to reduced exercise capacity, whereas neither resting MVA nor exercise pulmonary wedge pressure were significant determinants. The important contribution of heart rate response to exercise capacity in MS should not be surprising, because the ability to increase stroke volume is severely impaired due to fixed obstruction of the mitral valve leaflets, which prevents the normal exercise-related increase in diastolic mitral valve area (4,5).

In the present study, the MS patients already had abnormally low heart rate response to exercise, which was a significant, independent contributor to their exercise intolerance (2). Thus, further lowering of heart rate with beta-blockade was unlikely to provide benefit, and would have been expected to further worsen heart rate and cardiac output, impairing exercise capacity even further. These results are supported by 3 other studies of the effect of heart rate reduction on exercise capacity in MS (6,7). In a randomized, controlled, crossover trial, atenolol had no effect on any measure of exercise capacity, despite significantly reducing exercise heart rate, increasing filling time, and reducing mean gradient (6). In a randomized trial of metoprolol and ivabradine, both agents significantly reduced objectively measured exercise capacity, despite reduced mean MV gradient (7). Although symptoms improved by patient report, this is of uncertain significance because that was a subjective evaluation and there was no placebo control (7).

How, then, should clinicians view beta-blockade in moderate MS, given that all studies, now a total of 4 (2 reported since the 2014 American Heart Association/American College of Cardiology guidelines designated beta-blockade for symptomatic MS in sinus rhythm as a Class IIb recommendation, Level of Evidence: B [1]) have shown either no benefit or worsening of exercise capacity? The present study is helpful in this regard, as it demonstrates the potential utility of careful exercise testing combined with echo Doppler (2). The authors found some heterogeneity in the results regarding beta-blockade, as have prior studies. This suggests that when beta-blockade is considered, it would be prudent to perform exercise testing when possible before and after initiation to determine if the patient had a favorable or adverse response. This is a practical suggestion, because the equipment required for such testing is widely available.

Three other findings from the present study are enlightening (2). First, there was evidence of abnormal LV volume responses to exercise out of proportion to mitral valve dynamics, suggesting the possibility of intrinsic LV myocardial dysfunction. Second, the finding that exercise A-VO_2D was abnormally reduced and was an independent predictor of exercise capacity indicates that noncardiac abnormalities, such as skeletal muscle and or arterial dysfunction, contribute to exercise intolerance in MS, as indicated earlier by Rigolin et al. (4). Third, MS patients had abnormal tidal volume response, and this was also an independent predictor of exercise capacity. The skeletal muscle and pulmonary findings parallel those in heart failure (8). As the authors suggest, abnormalities in myocardial, skeletal muscle, pulmonary, and arterial function in MS could be related to ongoing systemic inflammation, which has been described by several investigators (9).

Balloon valvuloplasty can improve MVA with no immediate effect on exercise capacity (10). Exercise capacity improves later, due to delayed improvements in skeletal muscle and pulmonary function (10). This pattern of improvement in exercise capacity mirrors that seen following cardiac transplant, further supporting the relevance of extracardiac contributions.

These results suggest that future studies (and individual patient care) in moderate MS should include objective, detailed assessments during exercise. They also suggest that efforts to improve exercise intolerance in moderate MS should include focusing on the important contributions of chronotropic incompetence and peripheral skeletal muscle, arterial, and pulmonary dysfunction, rather than focusing solely on the valve gradient. Finally, the results suggest

that, as in other related cardiovascular disorders, including heart failure with preserved ejection fraction (11) and atrial fibrillation (12), improved patient outcomes could potentially be achieved by addressing the systemic, extracardiac mechanisms that contribute to exercise intolerance in moderate MS patients.

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