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Mechanisms of Effort Intolerance in Patients With Rheumatic Mitral Stenosis

Combined Echocardiography and Cardiopulmonary Stress Protocol

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ABSTRACT

OBJECTIVES This study sought to evaluate mechanisms of effort intolerance in patients with rheumatic mitral stenosis (MS).

BACKGROUND Combined stress echocardiography and cardiopulmonary testing allows assessment of cardiac function, hemodynamics, and oxygen extraction (A-Vo_2 difference).

METHODS Using semirecumbent bicycle exercise, 20 patients with rheumatic MS (valve area 1.36 ± 0.4 cm^2) were compared to 20 control subjects at 4 pre-defined activity stages (rest, unloaded, anaerobic threshold, and peak). Various echocardiographic parameters (left ventricular volumes, ejection fraction, stroke volume, mitral valve gradient, mitral valve area, tissue s′ and e′) and ventilatory parameters (peak oxygen consumption [Vo_2] and A-Vo_2 difference) were measured during 8 to 12 min of graded exercise.

RESULTS Comparing patients with MS to control subjects, significant differences (both between groups and for group by time interaction) were seen in multiple parameters (heart rate, stroke volume, end-diastolic volume, ejection fraction, s′, e′, Vo_2, and tidal volume). Exercise responses were all attenuated compared to control subjects. Comparing patients with MS and poor exercise tolerance (<80% of expected) to other subjects with MS, we found attenuated increases in tidal volume ($p = 0.0003$), heart rate ($p = 0.0009$), and mitral area ($p = 0.04$) in the poor exercise tolerance group. These patients also displayed different end-diastolic volume behavior over time (group by time interaction $p = 0.05$). In multivariable analysis, peak heart rate response ($p = 0.01$), tidal volume response ($p = 0.0001$), and peak A-Vo_2 difference ($p = 0.03$) were the only independent predictors of exercise capacity in patients with MS; systolic pulmonary pressure, mitral valve gradient, and mitral valve area were not.

CONCLUSIONS In patients with rheumatic MS, exercise intolerance is predominantly the result of restrictive lung function, chronotropic incompetence, limited stroke volume reserve, and peripheral factors, and not simply impaired valvular function. Combined stress echocardiography and cardiopulmonary testing can be helpful in determining mechanisms of exercise intolerance in patients with MS. (J Am Coll Cardiol Img 2016;■:■–■) © 2016 by the American College of Cardiology Foundation.

Multiple mechanisms are held responsible for the limited exercise capacity of patients with rheumatic mitral stenosis (MS). Studies of exercise limitation in MS have predominantly used exercise tests combined with catheterization (1) or the equilibrium cardiac output (CO) rebreathing technique (2) to calculate CO and peripheral muscle oxygen extraction. The studies were limited by: 1) the invasive nature of the catheterization techniques, resulting in selection bias in those studies;

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ABBREVIATIONS AND ACRONYMS

AT = anaerobic threshold

A-Vo_2 difference = arterial-venous oxygen content difference

CO = cardiac output

CPET = cardiopulmonary exercise (stress) test

EF = ejection fraction

HR = heart rate

LV = left ventricle

MS = mitral stenosis

NYHA = New York Heart Association

RER = respiratory exchange ratio

SE = stress echocardiography

SPAP = systolic pulmonary artery pressure

SV = stroke volume

and 2) insufficient anatomic data provided with both techniques (3). Therefore, we created a combined cardiopulmonary exercise (stress) test (CPET) and stress echocardiography (SE) protocol that allows assessment of cardiac and peripheral responses to exercise at 4 pre-defined levels (rest, unloaded cycling, anaerobic threshold [AT], and peak). Our aims were: 1) to test whether cardiovascular response to exercise differs between patients with MS and normal subjects; 2) to look for differences in cardiovascular response to exercise between patients with MS having poor exercise tolerance and those with preserved exercise tolerance; and 3) to assess the independent factors associated with limited exercise capacity in patients with MS.

METHODS

STUDY POPULATION. Between January 2013 and July 2015, we performed 173 combined CPET and SE examinations. The study included all consecutive patients who had rheumatic MS (N = 20). There were no selection criteria for the MS group, but because cardiopulmonary stress or SE testing is rarely performed in patients with very severe MS (1) (valve area <1 cm^2) or in asymptomatic or severely symptomatic (New York Heart Association [NYHA] functional class IV) patients, our group consisted mostly of patients in the moderate-to-severe (1) range (valve area 1.0 to 1.5 cm^2) with milder symptoms (NYHA functional class II or III). Control subjects were selected from 37 patients with no cardiac disease who were referred for evaluation of dyspnea; 20 were selected after matching for age, gender, and ejection fraction (EF). Nine of these patients were determined to have dyspnea on the basis of peripheral factors; the other 11 had normal exercise capacity. Subanalysis was performed in the MS group, comparing the 10 patients who had reduced exercise capacity (<80% of predicted) with the 10 patients who had preserved exercise capacity (>80% of predicted).

A second CPET was performed in 13 patients with MS without echocardiography and without change in medical therapy (including β-blocker if present): 6 of 7 patients who underwent intervention and 7 others who were treated conservatively. The intervention group included 6 patients who had mitral valve replacement (1 of whom refused repeat CPET) and 1 who had balloon valvuloplasty.

In a third analysis, 7 patients with MS underwent repeat CPET combined with SE after withdrawal of β-blocker therapy.

These data were collected in the course of routine clinical care. Observers who performed and analyzed the exercise gas exchange data and the echocardiographic images were blinded to patient group and other characteristics. This retrospective study was approved by our Institutional Review Board at Tel Aviv Medical Center.

EXERCISE PROTOCOL. Exercise was performed as previously described (4). A symptom-limited graded ramp bicycle exercise test was performed in the semisupine position on a tilting dedicated microprocessor controlled eddy current brake SE cycle ergometer (Ergoselect 1000 L, CareFusion, San Diego, California) We estimated the expected peak Vo_2 on the basis of the patient's age, height, and weight after considering the patient's history. We then calculated the work rate increment necessary to reach the patient's estimated peak Vo_2 in 8 to 12 min. The protocol included 3 min of unloaded pedaling, a symptom-limited ramp graded exercise, and 2 min of recovery. Breath-by-breath minute ventilation, carbon dioxide production (Vco_2), and oxygen consumption (Vo_2) were measured using a Medical Graphics metabolic cart (ZAN, nSpire Health Inc., Oberthulba, Germany). Peak Vo_2 was the highest averaged 30-s Vo_2 during exercise. AT was determined manually using the modified V-slope method. The respiratory exchange ratio (RER) was defined as the ratio between Vco_2 and Vo_2 obtained from ventilatory expired gas analysis (2). In 7 patients taking β-blockers during the first exercise test, β-blockers were subsequently withdrawn before a second examination. In patients on β-blocker therapy, chronotropic incompetence on stress testing was determined when <62% of heart rate (HR) reserve was used (5).

EXERCISE ECHOCARDIOGRAPHY TESTING. Echocardiographic images were obtained concurrently with breath-by-breath gas exchange measurements in a continuous manner as previously described (3). Each cycle of imaging included left ventricular (LV) end-diastolic and end-systolic volumes, stroke volume (SV), peak E- and A-wave velocities, deceleration time, and septal e′ and lasted between 30 and 60 s. LV end-diastolic volume, end-systolic volume, and EF were calculated according to the single plane ellipsoid apical 4-chamber area-length method. Left atrial volume was calculated according to the biplane area-length method. SV was calculated by multiplying the LV outflow tract area at rest by the LV outflow tract velocity-time integral measured by pulsed-wave Doppler during each activity level.

All echocardiographic measurements were done using manual tracing (4). We then analyzed the echocardiographic data retrospectively at 4 different stages. Rest stage images were taken before cycling. Unloaded stage images were taken during unloaded exercise. AT and the HR at the AT were determined manually and retrospectively using the gas exchange measurements and the modified V-slope method. On the basis of the HR at the AT echocardiogram, data were analyzed from the images captured immediately after reaching the HR at the AT. Peak exercise images were defined as those captured immediately after reaching RER >1.05 (5). A-Vo_2 difference was calculated using the Fick equation as follows: Vo_2/echocardiography-calculated CO at each activity level (5). Mitral valve area at rest and during exercise was calculated by applying the continuity equation as the ratio of SV to the mitral valve velocity-time integral, according to previously published recommendation (6).

STATISTICAL ANALYSIS. Descriptive results are expressed as mean ± SD for continuous variables and as percentages for categorical variables. For the analysis of differences in echocardiographic and exercise variables, paired Student *t* test was used for comparisons between MS and matched control groups. For comparisons between the reduced and preserved exercise capacity groups, we used analysis of variance for continuous, normally distributed variables; Wilcoxon test for other continuous variables; and Fisher exact test or chi-square test for categorical variables. To analyze the differences in the various stages of effort, we used the repeated measures linear model analysis to define the within-group effect for each parameter over time, the between group differences over time, and the group by time interactions. To analyze the associates of exercise tolerance in patients with MS, the primary endpoint was peak Vo_2. Univariate analysis to assess the association of rest and effort (at each stage) parameter and peak Vo_2 was performed in the first step. In the second step we used stepwise multivariate linear regression models (with peak Vo_2 as the dependent variable, and the echocardiographic and cardiopulmonary stress variables as independent variables) for each effort stage individually. The entry criterion was a univariate p value <0.1. To detect colinearity, we used correlation factor analyses to determine whether any pairs of predictor variables were correlated (correlation coefficients >0.9). If any such pairs were found, the variable with the lowest univariate p value was chosen for inclusion in the analysis. The incremental value of stress parameters (for each effort stage individually) on rest clinical and echocardiographic parameters was tested by nested models with *F* tests. All computations were performed using JMP statistical software for Windows version 9.0 (SAS Institute Inc., Cary, North Carolina).

INTEROBSERVER AND INTRAOBSERVER VARIABILITY. Interobserver variability for peak velocity, mean gradient, and SV at peak exercise was determined by a second independent blinded observer who measured the echocardiographic variables in 10 randomly selected patients. Intraobserver variability was determined by having the first observer remeasure the same parameters in these same 10 patients at least 1 month after the initial measurements. Interobserver and intraobserver variability were assessed using the Bland-Altman method and the within-subject coefficient of variation. The within-subject coefficient of variation (calculated as the ratio of the standard deviation of the measurement difference to the mean value of all measurements) provides a scale-free, unit-less estimate of variation expressed as a percentage.

RESULTS

ECHOCARDIOGRAPHIC AND STRESS CORRELATES OF EXERCISE CAPACITY. Patients with MS had a mean valve area of 1.36 ± 0.4 cm^2 and a mean gradient of 5.3 ± 3.0 mm Hg. None of our patients had significant (greater than mild) involvement of other valves. Mitral regurgitation was trivial or none in 10 patients, mild in 8, and moderate in 2. Various clinical and exercise characteristics of the MS and control subjects are given in **Table 1**. Per patient data are given in Online Table 1. Echocardiographic and combined CPET-SE parameters of the MS and control groups in each of the exercise phases are given in Online Table 2 and in **Figure 1**.

Various clinical and exercise characteristics of the MS subgroups (preserved vs. reduced exercise capacity) are given in **Table 2**. Echocardiographic and combined CPET-SE parameters of the MS subgroups in each of the exercise phases are given in **Table 3** and **Figure 2**. Patients with reduced exercise capacity had attenuated changes in end-diastolic volume, HR, and tidal volume, but no difference in transmitral gradient compared to patients with MS and preserved function. Systolic pulmonary artery pressure (SPAP) increased during exercise in both MS subgroups. However, in those with preserved exercise capacity it

TABLE 1 Participant Characteristics

	Patients With MS (n = 20)	Control Subjects (n = 20)	p Value
Age, yrs	64.5 ± 10 (37-79)	62.5 ± 18 (33-84)	0.8
NYHA functional class	I: 0, II: 10 III: 10 IV: 0	I: 20, II: 0 III: 0 IV: 0	<0.0001
Female	16 (80)	16 (80)	0.9
Ejection fraction, %	64.9 ± 9 (53-78)	66.1 ± 8 (56-80)	0.8
Body surface area	1.73 ± 0.17 (1.45-2.1)	1.77 ± 0.2 (1.48-2.16)	0.4
β-Blockers	15 (75)	3 (15)	<0.0001
Diastolic dimension, mm	45.0 ± 5 (38-54)	46.3 ± 4 (40-57)	0.4
Systolic dimension, mm	28.7 ± 5 (22-44)	27.7 ± 4 (20-35)	0.5
End-diastolic volume, cc	106 ± 23 (73-167)	115 ± 32 (66-213)	0.2
End-diastolic volume index, cc/m^2	62 ± 15 (43-88)	65 ± 19 (38-84)	0.3
End-systolic volume, cc	37 ± 12 (20-66)	40 ± 17 (13-83)	0.5
End-systolic volume index, cc/m^2	21 ± 7 (11-35)	22 ± 9 (9-37)	0.8
RA area	18.8 ± 7 (13-43)	13.9 ± 4 (8-24)	0.01
LAVI, cc/m^2	68.1 ± 43 (35.2-217)	31.8 ± 15 (15.6-80.6)	0.0001
Stroke volume, cc/beat	66.1 ± 18 (42-100)	75.7 ± 17 (46-117)	0.05
Cardiac index, l/min/m^2	2.9 ± 1.0 (1.6-5.5)	3.3 ± 0.8 (2.5-5.3)	0.1
E', cm/s	4.6 ± 1 (2-7.4)	7.0 ± 3 (3-12)	0.001
E/e' ratio	34.3 ± 19 (16-72)	11.0 ± 5 (5-18)	<0.0001
S', cm/s	4.7 ± 1.2 (2.3-7)	6.1 ± 1.2 (4-9)	0.002
Right ventricular systolic pressure, mm Hg	36.6 ± 16 (18-84)	27.5 ± 4 (20-37)	0.03
FVC, l	2.1 ± 0.7 (1.05-3.9)	2.7 ± 1.2 (1.43-5.23)	0.04
FVC, % predicted	80.0 ± 17 (50-103)	90.3 ± 14 (74-121)	0.04
FEV_1, l/s	1.7 ± 0.6 (0.95-3.4)	2.4 ± 1.2 (1.24-5.2)	0.03
FEV, % predicted	79.6 ± 16 (55-104)	94.2 ± 16 (73-118)	0.003
VE/V_{CO_2} ratio @ AT	36.3 ± 8 (25-43)	29.1 ± 6 (21-37)	0.003
Workload, W	61 ± 31 (15-118)	122 ± 69 (46-304)	0.001
HR @ peak	121 ± 29 (60-173)	140 ± 27 (103-184)	0.03
HR, % predicted	75 ± 17 (38-109)	85 ± 13 (69-119)	0.03
Chronotropic incompetence for β-blocker	6 (30)	1 (5)	0.03
O_2 pulse max, ml/beat	7.3 ± 1 (4-10)	10.2 ± 3 (6-19)	0.001
V_{O_2}max, l/min	0.9 ± 0.2 (0.37-1.4)	1.5 ± 0.7 (0.75-3.3)	0.001
V_{O_2}max, % predicted	61.3 ± 15 (34-92)	85.1 ± 14 (64-115)	<0.0001
V_{O_2}/kg max, ml/min/kg	13.0 ± 4 (6.7-21)	20.9 ± 8 (13.1-43)	0.0007
V_{O_2}/kg, % predicted	73.2 ± 22 (33-115)	93.4 ± 9 (72-126)	0.001
Peak VT	1054 ± 314 (633-1581)	1637 ± 831 (767-4181)	0.005
Breathing reserve, l/min	37.6 ± 19 (10-92)	45.3 ± 29 (15-102)	0.2
Peak A-VO_2 difference	0.11 ± 0.02 (0.08-0.16)	0.10 ± 0.02 (0.07-0.15)	0.1
RER ratio	1.08 ± 0.1 (0.97-1.34)	1.11 ± 0.1 (1.01-1.38)	0.3

Values are mean ± SD (range) or n (%) unless otherwise indicated.

AT = anaerobic threshold; A-V difference = arterial-venous difference; FEV = forced expiratory volume; FEV_1 = forced expiratory volume first second; FVC = forced vital capacity; HR = heart rate; LAVI = left atrial volume index; MS = mitral stenosis; NYHA = New York Heart Association; O_2 pulse = oxygen consumption per cardiac cycle; RA = right atrium; RER = respiratory exchange ratio; VE = minute ventilation; V_{CO_2} = carbon dioxide output; V_{O_2} = oxygen consumption; VT = tidal volume.

increased steadily throughout exercise, whereas in patients with reduced exercise capacity it started a bit higher, increased in the first stage of exercise, and then showed little change between AT and peak exercise ($p = 0.03$ for the time · group interaction).

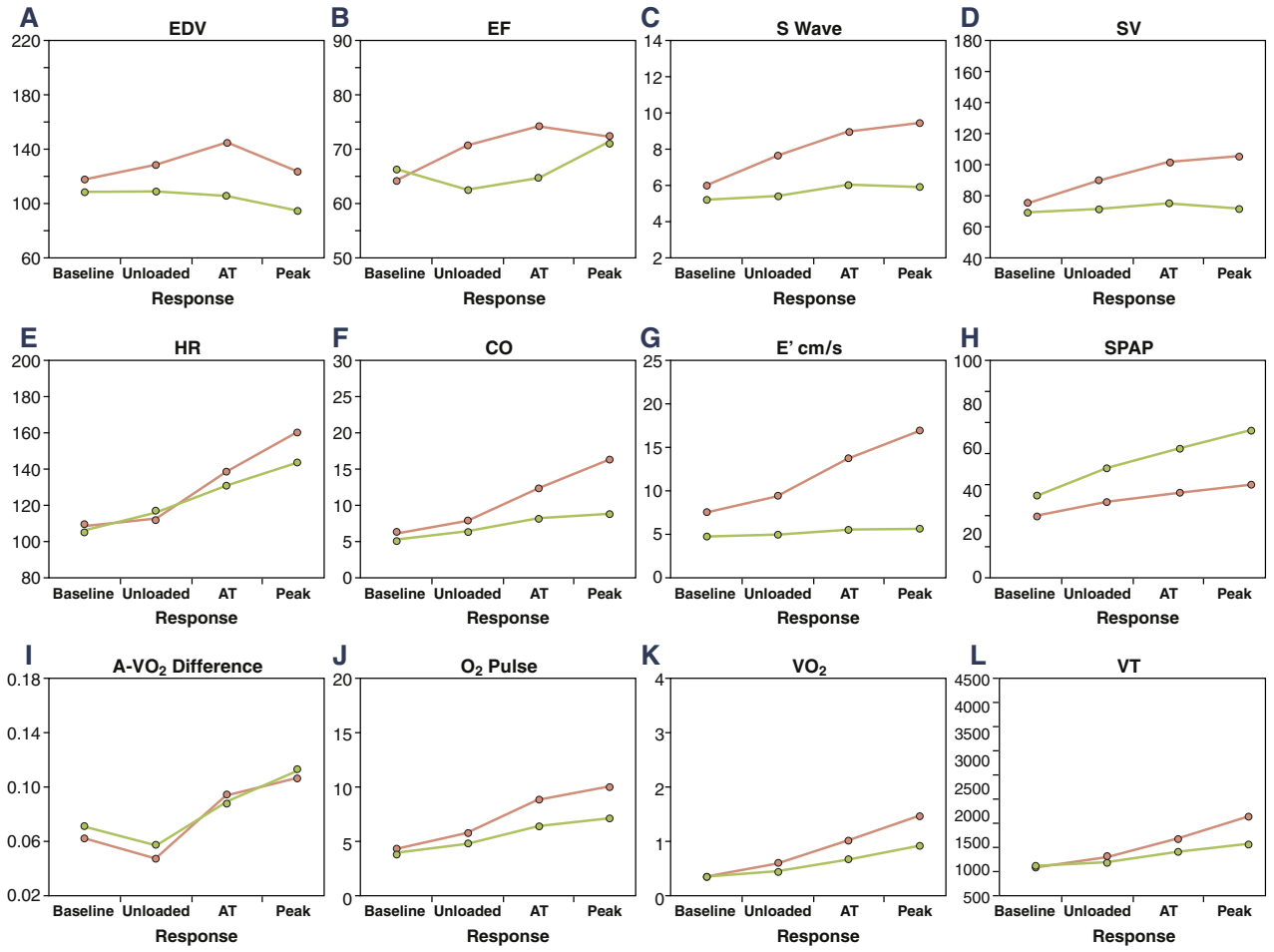
UNIVARIATE AND MULTIVARIABLE ANALYSIS. The results of univariate analysis to test associations between rest and stress parameters and peak V_{O_2} are given in Table 2. Stepwise multivariable analyses to explore the independent determinants of peak V_{O_2} at all exercise stages are given in Table 4. The best model to determine peak V_{O_2} used parameters measured at peak exercise ($p < 0.005$ for nested models compared to rest clinical and echocardiographic parameters), but even models based on early stages of exercise improved the prediction compared to models using rest parameters ($p < 0.05$ for both). The independent determinants of exercise capacity at peak exercise were HR, tidal volume, and A-V_{O_2} difference.

Peripheral oxygen extraction and effort capacity. There was no difference between MS subgroups in exercise response of average A-V_{O_2} difference (Table 3 and Figure 2). Nevertheless, low peak A-V_{O_2} difference was a strong univariate correlate of reduced exercise capacity and an independent predictor of low peak V_{O_2} (Tables 2 and 4).

Chronotropic incompetence. Peak HR and percent of predicted HR were decreased in the MS group compared to the control group (Table 1). Although the use of β-blockers was more prevalent in the MS group (75% vs. 15%; $p < 0.0001$), we were able to show that chronotropic incompetence was more common in patients with MS (30% vs. 5%; $p = 0.03$) by using criteria accounting for the presence of β-blocker therapy (7). Furthermore, chronotropic incompetence was more common in the patients with MS having reduced exercise capacity (50% vs. 10%; $p = 0.04$) and contributed significantly to poor exercise capacity ($p = 0.02$). Results of the second CPET (comparing post-intervention with conservative therapy subgroups), performed 9.5 ± 6.9 months (range 0.7 to 15.0 months) post-intervention, are given in Table 5. On the initial (baseline) CPET, peak HR, peak O_2 pulse, peak O_2, and peak RER were similar between patients ultimately treated conservatively or with intervention. On subsequent CPET, peak O_2 pulse (a surrogate for SV and A-VO_2 difference) increased significantly only in the interventional group, with a trend for increase in peak O_2 as well. Mitral intervention (compared to conservative treatment) was associated with improved peak O_2 pulse ($p = 0.05$) and peak O_2 ($p = 0.055$). However, RER and peak HR did not change in either group, and there were no significant associations between mitral intervention and changes in RER ($p = 0.7$) or peak HR ($p = 0.4$).

Use of β-blockers in MS. Our data show profound chronotropic incompetence and abnormal SV

FIGURE 1 **Echocardiographic Parameters at All Activity Stages in the MS and Control Groups**



Baseline, unloaded, anaerobic threshold (AT), and maximal cardiopulmonary exercise (stress) test and stress echocardiography test for **(A)** EDV, **(B)** EF, **(C)** S-wave, **(D)** SV, **(E)** HR, **(F)** CO, **(G)** E', **(H)** SPAP, **(I)** A-Vo_2 difference, **(J)** O_2 pulse, **(K)** Vo_2, and **(L)** VT in the patients with MS **(green)** and control subjects **(pink)**. CO = cardiac output; EDV = end-diastolic volume; EF = ejection fraction; HR = heart rate; MS = mitral stenosis; SPAP = systolic pulmonary artery pressure; SV = stroke volume; VT = tidal volume.

reserve, particularly in the reduced exercise capacity group. Because β-blockers can impair chronotropic response, SV, and CO reserve, we compared the CPET-SE results in the 7 patients with MS who performed the testing twice, off and on β-blockers. In these patients, peak HR (115 ± 20 beats/min vs. 93 ± 14 beats/min; p = 0.03) and peak exercise mean transmitral gradient (14.0 ± 6 mm Hg vs. 12.0 ± 4.0 mm Hg; p = 0.2) were lower with β-blockers. Peak SV tended to decrease (75.8 ± 29.0 cc vs. 68.6 ± 7.0 cc; p = 0.5). This in combination with a reduced HR response resulted in a significant decrease in peak CO (8.8 ± 1.6 vs. 6.3 ± 0.88; p = 0.05) and a trend for reduced exercise capacity (0.99 ± 0.4 l/min vs. 0.76 ± 0.1 l/min; p = 0.2). Surprisingly, the use of β-blockers did not decrease the peak systolic pulmonary pressure (80.7 ± 25.0 mm Hg vs. 81.4 ± 13.0 mm Hg; p = 0.6).

Mitral valve gradient, area, and systolic pulmonary pressure. No correlation was found between peak Vo_2 and transmitral gradient during exercise. Similarly, there was no correlation between mitral valve area and peak Vo_2.

INTEROBSERVER AND INTRAOBSERVER VARIABILITY. Comparison of intraobserver parameters showed good agreement between measurements of peak velocity (mean difference 0.8 ± 4.5 cm/s; r = 0.97;

TABLE 2 Characteristics of Patients With MS Stratified by Exercise Capacity and Univariate Analyses to Explore the Contribution of Different Exercise Parameters on Maximal Exercise Capacity (Vo_2max)

	MS Reduced Exercise Capacity (n = 10)	MS Preserved Exercise Capacity (n = 10)	p Value for Univariate	p Value for Student *t* Test
Age, yrs	68.5 ± 9 (51–79)	60.5 ± 9 (37–73)	0.07	0.07
NYHA functional class	I: 0 II: 3 III: 7, IV: 0	I: 0 II: 7 III: 3, IV: 0	0.1	
Female	8 (80)	8 (80)	0.3	1.0
Atrial fibrillation	2 (20)	4 (40)	0.7	0.3
Height, m	157 ± 7 (150–169)	166 ± 7 (158–178)	0.001	0.006
Weight, kg	68.9 ± 15.0 (50–91)	69.5 ± 12.0 (58–98)	0.3	0.9
β-blockers	8 (80)	7 (70)	0.8	0.6
Ejection fraction, %	65.4 ± 9.0 (53–78)	67.5 ± 9.0 (55–78)	0.6	0.6
End-diastolic volume index, cc/m^2	68.9 ± 13.0 (51–88)	54.9 ± 12.0 (43–81)	0.05	0.02
End-systolic volume index, cc/m^2	23.7 ± 7.5 (13–35)	19.1 ± 5.2 (11–27)	0.3	0.1
LAVI, cc/m^2	64.3 ± 27.0 (35.8–120.0)	71.8 ± 55.0 (35.2–217.0)	0.5	0.7
Stroke volume, cc/beat	63 ± 16 (42–96)	68 ± 20 (46–100)	0.9	0.5
Cardiac index, l/min/m^2	2.8 ± 0.8 (1.6–4.0)	3.0 ± 1.2 (1.6–5.5)	0.9	0.7
E', cm/s	4.5 ± 1.3 (2.0–7.4)	4.8 ± 1.4 (3.2–7.0)	0.3	0.7
E/e', ratio	34.9 ± 23.0 (19–72)	33.6 ± 12.0 (16–54)	0.6	0.9
S', cm/s	4.3 ± 1.3 (2.3–7.0)	5.3 ± 0.9 (4.1–6.3)	0.1	0.09
Mean mitral gradient	5.5 ± 2.7 (2–12)	5.0 ± 3.9 (2–15)	0.3	0.8
Mitral valve area continuity	1.3 ± 0.5 (0.8–2.1)	1.4 ± 0.4 (1.0–2.4)	0.4	0.3
SPAP, mm Hg	46 ± 17 (30–84)	36 ± 13 (18–62)	0.02	0.07
Wilkins score	10.2 ± 2.8 (7–15)	7.5 ± 1.9 (5–10)	0.007	0.004
FVC, l	1.6 ± 0.4 (1.05–2.3)	2.5 ± 0.7 (1.5–3.9)	0.0001	0.003
FVC, % predicted	72 ± 15 (50–96)	88 ± 15 (54–103)	0.01	0.03
FEV_1, l/s	1.3 ± 0.3 (0.95–1.8)	2.1 ± 0.6 (1.3–3.4)	<0.0001	0.002
FEV, % predicted	71 ± 13 (56–96)	88 ± 14 (55–104)	0.003	0.01
End-diastolic volume index @ peak	61.6 ± 14.0 (46.6–90.1)	56.1 ± 19.0 (35.2–89.3)	0.1	0.5
End-systolic volume index @ peak	21.8 ± 11.0 (12.9–46.3)	15.8 ± 7.0 (7.9–29.4)	0.04	0.1
Ejection Fraction (%) @peak	65.9 ± 9.0 (49–76)	73.5 ± 9.0 (55–85)	0.08	0.1
Tissue Doppler S', cm/sec @peak	4.9 ± 2 (2–8)	6.1 ± 2.0 (3.9–8.0)	0.2	0.1
Tissue Doppler e', cm/sec @peak	5.3 ± 2.2 (3–9)	5.9 ± 1.5 (4.0–7.1)	0.09	0.7
Stroke Volume, ml @peak	59 ± 16 (40.8–96.0)	72 ± 20 (50.5–119.3)	0.1	0.1
Cardiac output, l/min @peak	6.1 ± 1.8 (2.4–9.8)	9.7 ± 1.8 (7.3–12.9)	0.0001	0.0003
VT @ peak	807 ± 160 (633–1,076)	1,302 ± 216 (928–1,581)	<0.0001	<0.0001
A-Vo_2 difference @ peak, l/l	0.11 ± 0.02 (0.07–0.14)	0.11 ± 0.02 (0.08–0.14)	0.05	0.9
Mean mitral gradient @ peak	10.6 ± 6.0 (3–22)	14.4 ± 6.0 (6.0–22.5)	0.2	0.1
Mitral valve area continuity @ peak	1.3 ± 0.4 (0.8–2.0)	1.6 ± 0.8 (0.8–3.4)	0.7	0.3
HR @ peak	105 ± 24 (60–134)	138 ± 25 (105–173)	0.0004	0.007
HR, % predicted	65.9 ± 15.0 (38–86)	84.4 ± 15.0 (64–109)	0.0007	0.01
O_2 pulse max, ml/beat	6.6 ± 1.6 (4–8)	8.0 ± 1.2 (6–10)	0.004	0.04
Vo_2max, l/min	0.7 ± 0.17 (0.37–0.9)	1.09 ± 0.2 (0.89–1.4)	NA	0.0001
Vo_2max, % predicted	54 ± 16 (34–78)	68 ± 11 (52–92)	0.0004	0.04
Vo_2/kg max, ml/min/kg	10.3 ± 3.5 (6.7–17.5)	15.7 ± 3.0 (13.4–21.5)	<0.0001	0.002
Vo_2/kg, % predicted	64 ± 25 (33–90)	82 ± 17 (62–115)	0.02	0.04
SPAP peak	77 ± 19 (51–103)	72 ± 22 (53–110)	0.5	0.8
Breathing reserve peak	27 ± 11 (10–48)	48 ± 20 (18.6–92.0)	0.03	0.01
Chronotropic incompetence (corrected for β-blocker)	5 (50)	1 (10)	0.02	0.04
RER ratio	1.05 ± 0.16 (0.97–1.34)	1.1 ± 0.09 (0.98–1.27)	0.09	0.3

Values are mean ± SD (range) or n (%) unless otherwise indicated.

A-VO_2 difference = arterial-venous difference; O_2 pulse = oxygen consumption per cardiac cycle; other abbreviations as in Table 1.

p = 0.86), mean gradient (mean difference -0.5 ± 0.4 mm Hg; r = 0.97; p = 0.3), and SV (mean difference 0.7 ± 1.4 cc; r = 0.96; p = 0.6). The Bland-Altman plot showed a random scatter of points around 0, indicating no systematic bias or measurement error proportional to the measurement value. Measurement variability (within-subject coefficient of variation) for intraobserver differences

TABLE 3 LV Dimensions, Function, and Hemodynamics Throughout Exercise Stages Among Patients With MS and Preserved or Reduced Exercise Capacity

		Baseline	Unloaded Effort	Anaerobic Threshold	Maximal Effort	Between Groups	Time · Group Interaction
End-diastolic volume, ml	MS preserved exercise capacity	107 ± 22	121 ± 31	119 ± 33	99 ± 33	0.8	0.05
	MS reduced exercise capacity	118 ± 22	107 ± 29	106 ± 38	102 ± 27		
End-systolic volume, ml	MS preserved exercise capacity	41 ± 9	40 ± 12	39 ± 15	32 ± 13	0.1	0.9
	MS reduced exercise capacity	36 ± 13	33 ± 14	32 ± 18	29 ± 18		
EF, %	MS preserved exercise capacity	67.5 ± 9.0	6.1 ± 5.0	66.7 ± 10.0	73.5 ± 9.0	0.2	0.5
	MS reduced exercise capacity	65.4 ± 9.0	62.7 ± 8.0	63.2 ± 7.0	65.9 ± 9.0		
S', cm/s	MS preserved exercise capacity	5.3 ± 0.9	6.2 ± 0.9	6.1 ± 1.3	6.1 ± 2.0	0.05	0.6
	MS reduced exercise capacity	4.3 ± 1.3	4.6 ± 1.6	4.9 ± 0.9	4.9 ± 2.0		
Stroke volume, ml	MS preserved exercise capacity	68 ± 20	71 ± 19	82 ± 18	72 ± 20	0.1	0.4
	MS reduced exercise capacity	63 ± 16	65 ± 11	62 ± 15	59 ± 16		
VT	MS preserved exercise capacity	667 ± 158	809 ± 150	1,093 ± 241	1,302 ± 216	0.0001	0.0003
	MS reduced exercise capacity	524 ± 64	589 ± 88	706 ± 193	807 ± 160		
Heart rate, beats/min	MS preserved exercise capacity	76 ± 14	87 ± 15	112 ± 20	138 ± 25	0.1	0.0009
	MS reduced exercise capacity	76 ± 14	89 ± 18	99 ± 23	104 ± 24		
Cardiac output, l/min	MS preserved exercise capacity	5.3 ± 2.0	6.1 ± 1.7	9.3 ± 2.4	9.7 ± 1.8	0.007	0.05
	MS reduced exercise capacity	4.8 ± 1.3	5.9 ± 1.2	6.3 ± 1.3	6.1 ± 1.8		
Mean mitral gradient	MS preserved exercise capacity	5.0 ± 3.9	7.9 ± 3.5	10.3 ± 4.2	14.4 ± 5.9	0.8	0.4
	MS reduced exercise capacity	5.5 ± 2.7	9.7 ± 3.4	10.3 ± 2.7	10.6 ± 5.7		
Mitral valve area	MS preserved exercise capacity	1.4 ± 0.4	1.7 ± 0.8	2.1 ± 0.9	1.6 ± 9.3	0.09	0.04
	MS reduced exercise capacity	1.3 ± 0.5	1.3 ± 0.4	1.3 ± 0.3	1.3 ± 0.4		
SPAP	MS preserved exercise capacity	31 ± 13	48 ± 13	60 ± 17	70 ± 19	0.7	0.03
	MS reduced exercise capacity	42 ± 16	52 ± 19	58 ± 15	65 ± 21		
A-Vo_2 difference, l/l	MS preserved exercise capacity	0.07 ± 0.02	0.06 ± 0.02	0.08 ± 0.02	0.11 ± 0.02	0.2	0.8
	MS reduced exercise capacity	0.07 ± 0.01	0.07 ± 0.01	0.1 ± 0.02	0.12 ± 0.03		

Values are mean ± SD.
EF = ejection fraction; LV = left ventricle; other abbreviations as in Tables 1 and 2.

was peak velocity 1.8%, mean gradient 2.4%, and SV 2.3%.

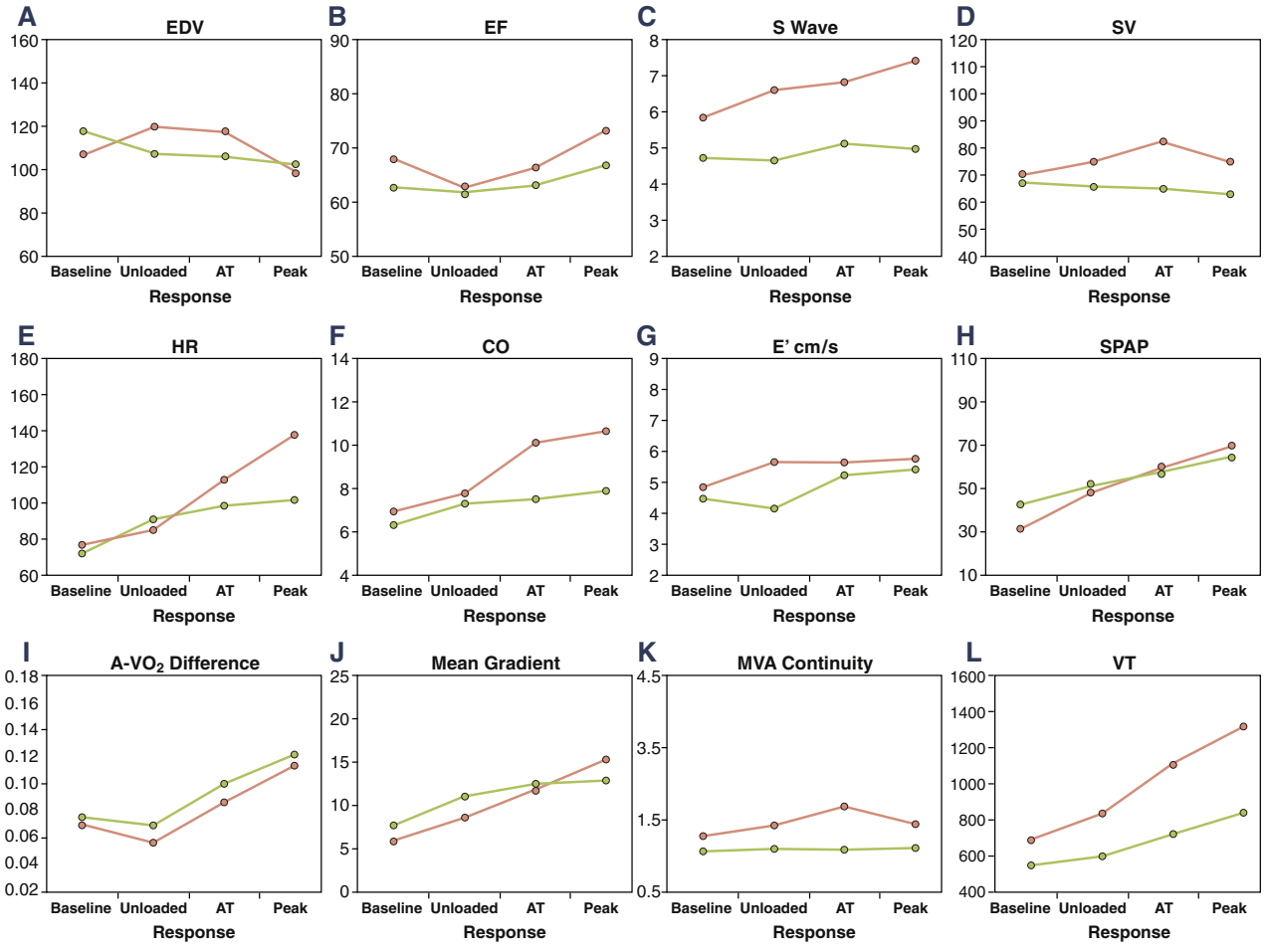
Comparison of interobserver parameters showed good agreement between measurements: peak velocity (mean difference -1.3 ± 3.1 cm/s; r = 0.98; p = 0.7), mean gradient (mean difference -0.3 ± 0.5 mm Hg; r = 0.93; p = 0.8), and SV (mean difference -1.7 ± 3.0 cc; r = 0.88; p = 0.7). The Bland-Altman plot showed a random scatter of points around 0, indicating no systematic bias or measurement error proportional to the measurement value. Measurement variability (within-subject coefficient of variation) for interobserver differences was peak velocity 1.3%, mean gradient 3.8%, and SV 4.8%.

DISCUSSION

Our major findings are that: 1) the combined CPET-SE protocol allows for detailed noninvasive evaluation of exercise physiology in patients with MS; 2) patients with MS have reduced exercise systolic reserve, relaxation, SV, HR, and ventilation compared to control subjects; 3) transmitral gradient and mitral valve area showed absence of any correlation with peak Vo_2 during exercise; and 4) chronotropic incompetence, limited SV reserve, peripheral factors (low peak A-Vo_2 difference), and limited tidal volume response each contribute to the reduced exercise capacity found in MS. The study provides several novel insights. First, patients with MS have abnormal SV reserve. Second, patients with MS have ventilatory abnormalities similar to those reported in heart failure patients (8). In addition, this study provides strong confirmation of an important evolving theme in heart failure physiology, that is, the contribution of chronotropic incompetence and peripheral, presumed skeletal muscle, abnormalities to exercise intolerance.

DETERMINANTS OF EFFORT INTOLERANCE. Chronotropic incompetence. In patients with MS, peak exercise HR was reduced, as was percent of HR reserve utilized. These factors likely contributed to the limited exercise capacity of these patients. This phenomenon has also been observed in patients with heart failure, both with preserved EF (9) and reduced EF (10). Even though β-blocker therapy was left unchanged, we were able to show that chronotropic incompetence was common in patients with MS, even when using

FIGURE 2 Echocardiographic Parameters at All Activity Stages in Patients With MS Having Preserved Exercise Capacity and Those With Reduced Exercise Capacity



Baseline, unloaded, anaerobic threshold (AT), and maximal cardiopulmonary exercise (stress) test and stress echocardiography test for **(A)** EDV, **(B)** EF, **(C)** S-wave, **(D)** SV, **(E)** HR, **(F)** CO, **(G)** E', **(H)** SPAP, **(I)** A-Vo_2 difference, **(J)** mean gradient, **(K)** MVA, and **(L)** VT in patients with mitral stenosis (MS) and preserved exercise capacity **(pink)** and patients with MS and reduced exercise capacity **(green)**. MVA = mitral valve area; other abbreviations as in Figure 1.

the criteria used in the presence of β-blocker therapy (7). Importantly, chronotropic incompetence was mostly seen in patients with MS and reduced exercise capacity, and it was a strong independent predictor of peak Vo_2. Furthermore, in exploratory analyses using CPET after mitral intervention, we found that improved exercise capacity (peak O_2) was related to improvement in SV and A-VO_2 difference (peak O_2 pulse) but not to improved chronotropic response (peak HR) or motivation (RER). Thus, chronotropic incompetence does not merely reflect the consequences of reduced motivation, or exercise capacity but seems to play an independent role in the pathogenesis of reduced exercise capacity in patients with rheumatic MS.

Use of β-blockers in patients with rheumatic MS. Our results showed that β-blockers decreased peak HR and tended to decrease the transmitral gradient at the end of exercise as expected. However, they tended to decrease SV, although normally the decrease in HR would be expected to produce supranormal SV by increasing the time for filling. The combined effect was a significant decrease in CO and a trend toward decreased peak Vo_2. These preliminary results are similar to those in previous reports (11,12) and suggest that the beneficial effect of decreasing transmitral gradient may be outweighed by the unfavorable decrease in CO and exercise capacity. It should be noted that the effects of β-blockers varied in individual patients. Some had a significant

decrease in transmitral gradient with no change (or even an increase) in exercise capacity, whereas others had no change in transmitral gradient but a significant decrease in CO and exercise capacity. We believe that our new noninvasive protocol may be useful in evaluating patients with MS to define the specific mechanisms limiting exercise capacity. This might improve patient selection for targeted therapies.

Abnormal SV. In the patients with MS and reduced exercise tolerance, no significant change or even a decrease in SV was observed. The reduced SV response in these patients may have resulted from the inability to utilize the Frank-Starling mechanism and a blunted increase in EF. Although our data cannot determine whether this results from subtle abnormalities in valve function or intrinsic LV dysfunction, it may be the result, at least in part, of concomitant LV reserve dysfunction.

Peripheral factors. Low peak A-Vo_2 difference was an independent predictor of reduced exercise capacity in our patients with MS, suggesting an important contribution of skeletal muscle abnormalities to exercise intolerance. Several reports have suggested that rheumatic MS is associated with systemic inflammation and increased levels of inflammatory cytokines (13). Similar pathophysiology has been implicated in inflammatory myopathies and heart failure associated skeletal muscle disease. Interestingly, balloon valvuloplasty was found to reduce levels of inflammatory cytokines (14), suggesting that symptomatic improvement after the procedure may result, at least in part, from changes in inflammatory mediators and possible improved skeletal muscular performance.

Ventilatory abnormalities. It has long been known that MS is associated with changes in pulmonary circulation and in the composition of lung tissue, including accumulation of water, proteins, and proteoglycans in the interstitium (15). These changes are important contributors to the clinical manifestations of MS. We found that baseline respiratory parameters were decreased in patients with MS compared to control subjects, and in the subgroup of patients with MS and reduced exercise capacity compared to patients with MS and preserved exercise capacity. During exercise, the inability to increase tidal volume during exercise was especially notable in the patients with MS and decreased exercise tolerance.

Mitral valve gradient and systolic pulmonary pressure. SE is an established tool in the evaluation of patients with MS, with a discrepancy noted between findings on resting echocardiography and symptoms.

TABLE 4 Multivariate Analyses to Explore the Contribution of Different Parameters on Maximal Exercise Capacity (Vo_2max)

	Vo_2 by Rest p Value	Vo_2 by Unloaded p Value	Vo_2 by AT Value	Vo_2 by Max p Value
Age, yrs	0.6	0.5	0.1	0.4
Height	0.3	0.1	0.3	0.4
EDV index, cc/m^2	0.1	0.1	0.5	0.5
ESV index, cc/m^2	0.3	0.3	0.6	0.6
SPAP	0.3	0.001	0.1	0.3
FEV_1	0.0003	0.1	0.1	0.4
S'	0.7	0.5	0.1	0.3
E'	0.5	0.5	0.008	0.3
Stroke volume	0.1	0.3	0.5	0.1
Heart rate	0.1	0.3	0.4	0.01
VT	0.2	0.09	0.0008	0.0001
VE	0.6	0.5	0.5	0.5
RVESA	0.1	0.4	0.5	0.6
EF	0.6	0.6	0.6	0.1
Mean mitral gradient	0.5	0.5	0.1	0.3
Mitral valve area	0.1	0.2	0.1	0.3
A-Vo_2 difference stress	0.3	0.3	0.4	0.03
p Value	0.01	0.0001	0.0001	<0.0001
R^2	0.61	0.86	0.88	0.95

AT = anaerobic threshold; EDV = end-diastolic volume; ESV = end-systolic volume; R^2 = coefficient of determination of the entire model; RVESA = right ventricular end systolic area; other abbreviations as in Tables 1, 2, and 3.

Traditionally SE focuses on the transmitral gradient and pulmonary artery pressure immediately after peak exercise because they are considered indicators of the overall hemodynamic burden of MS (16).

TABLE 5 CPET Examination Performed After Mitral Intervention or After Conservative Therapy

	Intervention	Conservative	p Value
Peak HR			
Baseline	126 ± 15	121 ± 42	0.8*
Post-intervention	110 ± 19	119 ± 29	0.6*
p Value paired Student paired *t* test	0.4†	0.8†	0.4‡
Peak O_2 pulse			
Baseline	6.6 ± 2.2	8.0 ± 1.0	0.2*
Post-intervention	8.2 ± 1.9	7.7 ± 1.8	0.7*
p Value paired Student paired *t* test	0.05†	0.6†	0.05‡
Peak Vo_2			
Baseline	0.83 ± 0.2	0.99 ± 0.3	0.3*
Post-intervention	0.94 ± 0.3	0.91 ± 0.3	0.8*
p Value paired Student paired *t* test	0.1†	0.2†	0.06‡
Peak RER			
Baseline	1.08 ± 0.1	1.08 ± 0.1	0.9*
Post-intervention	1.10 ± 0.1	1.10 ± 0.1	0.9*
p Value paired Student paired *t* test	0.4†	0.3†	0.7‡

Values are mean ± SD unless otherwise indicated. *Student *t* test. †Paired Student *t* test. ‡Univariate analysis to assess impact of intervention vs. conservative therapy on changes in time in heart rate, respiratory exchange ratio, peak O_2 pulse, and peak Vo_2.

CPET = cardiopulmonary exercise (stress) test; other abbreviations as in Table 1.

Surprisingly, we found no correlation between exercise capacity and transmitral gradient and little correlation between exercise capacity and SPAP (significant only in early exercise but not at peak). Brochet et al. (17) recently measured transmitral gradient and SPAP during various stages of exercise (although without measuring gas exchange). Their results resemble ours in that symptomatic patients with MS exhibited a rapid increase in mean transmitral gradient and SPAP at low levels of exercise compared with asymptomatic patients. In our study, as exercise continued, mean transmitral gradient leveled off and SPAP showed a blunted increase in the patients with MS and reduced exercise capacity compared to the patients in the preserved exercise capacity subgroup. Because SV and duration of diastole are important drivers of mean transmitral gradient and SPAP, it may be that the attenuated increase in SV and HR at later stages of exercise in patients with reduced exercise capacity attenuated the increase in transmitral gradient and SPAP. These observations suggest that the pattern of transmitral gradient and SPAP progression, rather than just peak values, play an important role in the exercise capacity of patients with MS. Our results are somewhat different from previous invasive studies, but this may be due to our use of semisupine exercise as opposed to the supine exercise used in catheterization-based studies (18). Pre-load is already maximized at supine exercise and LA pressures are exaggerated, so there is little chance to observe a significant Frank-Starling response in supine patients.

We believe that focusing on SPAP measured at peak exercise, as suggested by previous guidelines (19), may not be as useful as its rate of rise and the measurements made at a low level of exercise.

Combined cardiopulmonary exercise and SE protocol. Most previous studies of the determinants of exercise capacity in patients with MS measured CO invasively (20) or used the equilibrium carbon oxide rebreathing technique (21). Studies using catheterization are limited by their invasive nature and associated selection bias. Furthermore, patients are rarely able to perform maximal exercise during right heart catheterization. The carbon oxide rebreathing technique is limited by insufficient anatomic and hemodynamic data and cannot discriminate different causes of low CO.

Several studies attempted to assess exercise capacity in patients with MS using SE or dobutamine echocardiography (22). However, our protocol differs from these studies in several important aspects. First, we did not simply compare rest and immediate post-exercise images. Instead, we calculated the work rate increment necessary to reach the patient's estimated peak work in 8 to 12 min. This allowed enough time to acquire echocardiographic images, including comprehensive hemodynamic data, at multiple time points during exercise testing, even in the sickest patients. Second, we analyzed echocardiographic images at individual stages of effort instead of pre-selected power outputs. Third, we used semisupine exercise, which is far more physiological than the supine exercise performed in most previous studies.

CLINICAL IMPLICATIONS. Cardiopulmonary stress or SE testing is rarely performed in patients with very severe MS or in severely symptomatic (NYHA functional class IV) patients. Thus, our group consisted mostly of patients with MS in the moderate-to-severe range (1) and milder symptoms (NYHA functional class II or III). Our data suggest that the combined tests are extremely useful in patients with this intermediate range of MS, particularly when symptoms are out of proportion to resting hemodynamics (1). The most physiological form of exercise is upright treadmill, but that test makes continuous echocardiographic imaging impossible. In contrast, such imaging is readily performed in the semisupine position. The heterogeneity of the MS population poses a major challenge to development of optimal individualized therapy. A potential solution is to identify the particular factors contributing to a reduction in exercise capacity and peak Vo_2. In our study, combining CPET with echocardiography and noninvasive hemodynamic measurements permitted us to evaluate each component of Vo_2 and to subclassify patients on the basis of the dominant mechanism limiting exercise capacity (mitral, ventilatory, chronotropic, SV, peripheral, or other). This approach may improve patient selection for targeted therapeutics. For example, patients with MS could be classified into those with primarily impaired peripheral O_2 extraction, chronotropic incompetence, extreme anatomic damage to the mitral valve, or impaired SV response and be treated accordingly. Importantly, nearly all cardiovascular centers have the equipment needed for this testing, and the tests are noninvasive and inexpensive.

STUDY LIMITATIONS. The control group was heterogeneous, combining subjects with normal and abnormal exercise capacity. A-Vo_2 difference was not measured but was calculated (as Vo_2/CO) using the Fick equation. However, our results are similar to those reported previously in studies that measured A-Vo_2 difference invasively (23). We cannot exclude that the continued effects of β-blocker may have influenced the blunted HR response. However, the results were

unchanged when adjustments were made for long-term β-blocker use, with rates of chronotropic incompetence similar in patients who performed the tests with and without β-blockers. Although individual etiologies for effort intolerance and the effects of β-blockers on exercise capacity in patients with MS implied by our work are intriguing, they should be considered hypothesis generating. Further investigations via adequately powered prospective studies are needed before they can be applied to patient management. Until then, we caution against the use of the echocardiographic Doppler exercise findings in individual patient management.

CONCLUSIONS

In patients with rheumatic MS, exercise intolerance is predominantly due to chronotropic incompetence, limited stroke volume reserve, and peripheral factors, and not simply due to impaired valvular function. Combined testing can be helpful in determining mechanisms of exercise intolerance in these patients. Most important, the beneficial effect of reduced trans-mitral gradient associated with chronotropic incompetence may be outweighed by an unfavorable decrease in cardiac output and exercise capacity in some patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The heterogeneity of the rheumatic population poses a challenge to development of optimal individualized therapy in patients with MS. This is particularly true for patients with MS in the moderate-to-severe range, especially when symptoms are out of proportion to resting hemodynamics. A potential solution is to identify subjects in whom the reduction in effort capacity is attributable to any one of the components of peak V_{O_2}. In this study, combined CPET with echocardiography permitted us to evaluate each component of V_{O_2} to classify patients with rheumatic MS on the basis of the dominant mechanism limiting exercise capacity. This approach may improve selection for targeted therapeutics. For example, patients with MS could be classified into those with primarily impaired peripheral O_2 extraction, chronotropic incompetence, impaired SV response, severe mitral deformation, or pulmonary restriction and be treated accordingly. Furthermore, our study highlights the significant role of impaired peripheral oxygen extraction and chronotropic incompetence in contributing to exercise intolerance in patients with rheumatic MS.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine the effect of targeting different aspects of the limits to peak V_{O_2} in patients with MS. Although individual etiologies for effort intolerance implied by the combined tests are thought provoking, they need to be tested in adequately powered, prospective, randomized, controlled, and blinded fashion before they can be suggested for use in individual rheumatic MS patient management.

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APPENDIX For supplemental tables, please see the online version of this article.