ORIGINAL RESEARCH

Impact of Mitral Regurgitation Severity and Cause on Effort Tolerance–Integrated Stress Myocardial Perfusion Imaging and Echocardiographic Assessment of Patients With Known or Suspected Coronary Artery Disease Undergoing Exercise Treadmill Testing

Polydoros N. Kampaktsis, MD; Benjamin J. Albert, BSc; Jiwon Kim, MD; Lola X. Xie, MD; Lillian R. Brouwer, BA; Nathan H. Tehrani, MD; Michael Villanueva; Daniel Y. Choi, MD; Massimiliano Szulc, PhD; Mark B. Ratcliffe, MD; Robert A. Levine, MD; Richard B. Devereux, MD; Jonathan W. Weinsaft, MD

***Background*—**Mitral regurgitation (MR) has the potential to impede exercise capacity; it is uncertain whether this is because of regurgitation itself or the underlying cause of valvular insufficiency.

***Methods and Results*—**The population comprised 3267 patients who underwent exercise treadmill myocardial perfusion imaging and transthoracic echocardiography within 6±8 days. MR was present in 28%, including 176 patients (5%) with moderate or greater MR. Left ventricular systolic function significantly decreased and chamber size increased in relation to MR, paralleling increments in stress and rest myocardial perfusion deficits (all $P<0.001$). Exercise tolerance (metabolic equivalents of task) decreased stepwise in relation to graded MR severity ($P<0.05$). Workload was significantly lower with mild versus no MR (mean±SD, 9.8±3.0 versus 10.1±3.0; $P=0.02$); magnitude of workload reduction significantly increased among patients with advanced versus those with mild MR (mean±SD, 8.6±3.0 versus 9.8±3.0; $P<0.001$). MR-associated exercise impairment was accompanied by lower heart rate and blood pressure augmentation and greater dyspnea (all $P<0.05$). Both functional and nonfunctional MR subgroups demonstrated significantly decreased effort tolerance in relation to MR severity ($P\leq0.01$); impairment was greater with functional MR ($P=0.04$) corresponding to more advanced left ventricular dysfunction and dilation (both $P<0.001$). Functional MR predicted reduced metabolic equivalent of task–based effort (B=−0.39 [95% CI, −0.62 to −0.17]; $P=0.001$) independent of MR severity. Among the overall cohort, advanced (moderate or greater) MR was associated with reduced effort tolerance (B=−1.36 [95% CI, −1.80 to −0.93]; $P<0.001$) and remained significant ($P=0.01$) after controlling for age, clinical indexes, stress perfusion defects, and left ventricular dysfunction.

***Conclusions*—**MR impairs exercise tolerance independent of left ventricular ischemia, dysfunction, and clinical indexes. Magnitude of exercise impairment parallels severity of MR. **(*J Am Heart Assoc*. 2019;8:e010974. DOI: 10.1161/JAHA.118.010974.)**

Key Words: coronary artery disease • exercise stress test • mitral regurgitation

Mitral regurgitation (MR) has the potential to impede effort tolerance, but it is unclear whether this link is attributable to regurgitation itself or attributable to underlying causality of valvular incompetence. Direct effects of MR include increased left atrial preload, which can increase pulmonary arterial pressure and augment left ventricular (LV) dilation and dysfunction. It is also known that MR itself can result from LV ischemia and infarction,[1–4] each of which can alter LV performance and thus impede effort. Prior studies have shown exercise capacity to decrease in proportion to MR severity.[5–8] However, data have been largely accrued from small cohorts, prohibiting comprehensive analyses to test

From the Department of Medicine (P.N.K., J.K., L.R.B., N.H.T., M.V., D.Y.C., M.S., R.B.D., J.W.W.), and Department of Medicine and Radiology (J.K., J.W.W.), Weill Cornell Medical College, New York, NY; Department of Biomedical Engineering, Cornell University, Ithaca, NY (B.J.A.); Memorial Sloan Kettering Cancer Center, New York, NY (L.X.X., J.W.W.); Veterans Affairs Medical Center, University of California, San Francisco, CA (M.B.R.); and Massachusetts General Hospital, Harvard Medical School, Boston, MA (R.A.L.).

Correspondence to: Jonathan W. Weinsaft, MD, Department of Medicine and Radiology, Nuclear Cardiology Program, Weill Cornell Medicine, 525 E 68th St, New York, NY 10021. E-mail: jww2001@med.cornell.edu

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Clinical Perspective

What Is New?

- This is the first study to elucidate impact of mitral regurgitation (MR) on effort tolerance while controlling for variables that can impact both MR itself as well as exercise capacity, including left ventricular dysfunction and ischemia.
- Differences in effort tolerance among patients with and without functional MR were associated with underlying differences in left ventricular remodeling.
- Advanced (moderate or greater) MR was strongly linked to impaired effort tolerance during exercise treadmill testing, and remained associated with decreased effort after controlling for age, clinical indexes, stress perfusion defects, and impaired left ventricular function.

What Are the Clinical Implications?

- MR itself should be considered as a causal factor in patients with clinically reported decreased effort tolerance, irrespective of coronary artery disease or left ventricular dysfunction.
- Further studies are warranted to assess underlying mechanisms responsible for MR-associated impaired effort tolerance, as well as to test efficacy of targeted interventions (including revascularization of ischemic but viable segments within the mitral valve apparatus) as a strategy to reduce valvular regurgitation and improve clinical effort tolerance in patients with MR.

whether links between MR and impaired effort are independent of LV systolic dysfunction and ischemia.

Radionuclide myocardial perfusion imaging (MPI) is widely used as the primary noninvasive test to assess LV ischemia. MPI is often performed adjunctively with exercise treadmill testing, enabling near simultaneous assessment of effort tolerance as well as imaging-evidenced ischemia and LV function. Prior work by our group has shown presence and severity of MR to vary in proportion to perfusion deficits underlying the mitral valve.[9] However, in that cross-sectional analysis of the relation of perfusion to MR, nearly three fourths of patients with MR underwent pharmacologic stress testing, prohibiting assessment of exercise capacity. Moreover, prior studies have typically examined MR-associated effort intolerance within uniform cohorts of patients with functional or degenerative MR[5–8,10–13]; the relative difference in effort tolerance between the 2 conditions is unknown.

This study examined exercise in relation to MR among 3267 patients with known or suspected coronary artery disease (CAD) undergoing exercise MPI and transthoracic echocardiography (echo). Goals were as follows: (1) to test the impact of MR on effort when controlling for clinical indexes and LV causal factors for MR itself (ischemia, dysfunction); and (2) to compare effort tolerance between patients with functional and degenerative MR, together with LV remodeling, as a potential explanatory factor for differential effort tolerance in relation to MR cause.

Methods

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure, on request (contingent on approval of the Weill Cornell Institutional Review Board and assurance of data deidentification).

Study Population

The population comprised consecutive patients without prior mitral surgery who underwent exercise radionuclide MPI and echo within a 1-month interval: Patients with prosthetic mitral valves or annuloplasty rings were excluded so as to test the impact of cause and severity of native mitral valve pathologic features on effort tolerance. To directly test the impact of MR on effort, patients with concomitant left-sided valve disease (moderate or greater aortic stenosis/regurgitation or mitral stenosis) were also excluded. Testing was performed for clinical purposes at Weill Cornell Medicine; the Weill Cornell Medicine Institutional Review Board provided approval for this study protocol, including waiver of informed consent for use of preexisting imaging and clinical data, as analyzed for research purposes.

Testing Protocol

Exercise

Symptom-limited exercise treadmill testing was performed using a Bruce protocol: serial 12-lead ECG(electrocardiogram)s and blood pressure measurements were obtained (together with assessment of clinical symptoms) at baseline and at each exercise stage. Exercise was continued until a minimum target heart rate response (≥85% predicted maximum heart rate [220−age]) was achieved, after which examinations were terminated as prompted by symptoms (eg, fatigue and chest pain). For patients who tolerated the Bruce protocol but were unable to reach target heart rate, effort tolerance was calculated on the basis of peak stage achieved. For patients able to ambulate minimally but unable to tolerate workload increments, stage 1 was held before termination and exercise was categorized as Bruce stage 1 (4 metabolic equivalents of task [METs]) for study purposes.

Single-photon emission computed tomography

MPI was performed in accordance with a previously described protocol.[9,14,15] In brief, thallium-201 (≈3 mCi) or technetium-99m sestamibi (≈10 mCi) was injected intravenously; baseline (rest) perfusion images were acquired ≈10 minutes after

thallium-201 and 60 minutes after technetium-99m sestamibi injection. Technetium-99m sestamibi (≈30 mCi) was intravenously administered at peak stress (minimum heart rate, 220−age), and poststress images were acquired ≈30 minutes thereafter. A dual-headed scintillation camera system with a low-energy high-resolution collimator was used for image acquisition. Attenuation correction imaging and/or prone reposition imaging was used to differentiate between pathologic perfusion deficits and attenuation artifact.

Echocardiography

Noncontrast echoes were performed by experienced sonographers using commercial equipment. Images were acquired in standard parasternal as well as apical 2-, 3-, and 4-chamber orientations, in accordance with consensus (American Society of Echocardiography) guidelines.[16] MR was assessed using standard 2-dimensional color Doppler and spectral Doppler techniques.[17]

Image Analysis

Exercise single-photon emission computed tomography

MPI was interpreted by experienced readers, for whom high reproducibility has been previously reported.[14] Perfusion defect severity on a per-segment basis was graded using a standard 17-segment, 5-point, per-segment scoring system (0 indicates normal; 1, equivocal or mildly reduced; 2, moderately reduced; 3, severely reduced; and 4, absence of detectable radioisotope uptake).[18] Summed stress and rest scores were calculated by adding per-segment defect severity for all segments. Visual interpretation was confirmed by review of polar plots with comparison of segmental radiotracer intensity to computer-generated, sex-matched data sets. Summed stress and rest scores for myocardial segments subtending the anterolateral and posteromedial papillary muscles were calculated, as shown in Figure 1, in accordance with prior methods used by our group.[9,15]

Echocardiography

Echoes were interpreted by dedicated readers in a high-volume laboratory, for which experience on MR assessment in prior population-based studies has been reported.[9,19,20] MR was initially graded in accordance with consensus guidelines based on a 4-point scale, primarily determined on the basis of distance reached from the mitral orifice by the regurgitant jet (mild [1+] to ≤1.5 cm; moderate [2+] to 1.5–3.0 cm; moderate-severe [3+] to 3.0–4.5 cm; and severe [4+] to ≥4.5 cm), as well as adjunctive criteria, including jet area/density, vena contracta,

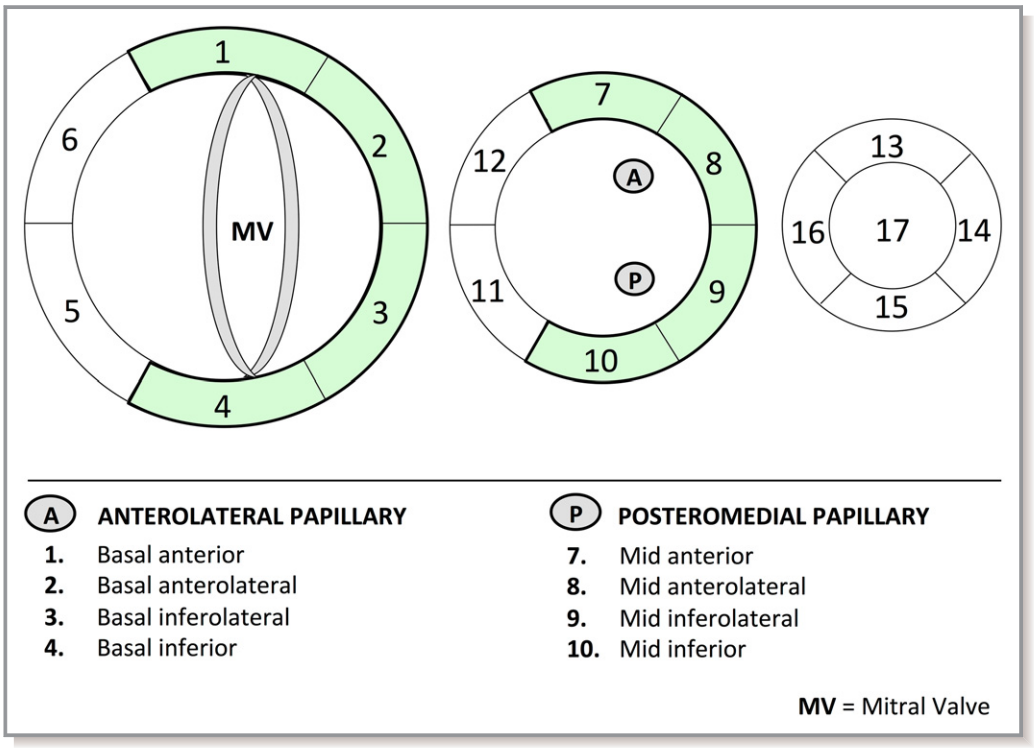

Figure 1. Mitral apparatus partitions. Bullseye plot (17-segment model) illustrating left ventricular (LV) segments subtended within the mitral apparatus, as defined adjacent to the anterolateral and posteromedial papillary muscles. For the anterolateral papillary muscle, LV perfusion/wall motion was assessed within the basal to mid anterior and anterolateral segments. For the posteromedial papillary muscle, LV perfusion/wall motion was assessed within the basal to mid inferior and inferolateral segments. MV indicates mitral valve.

and pulmonary vein flow pattern.[17] In all cases, advanced (moderate or greater) MR was further confirmed quantitatively (via dedicated image analysis) based on regurgitant fraction (≥30%), regurgitant volume (≥30 mL), and/or (in cases without mitral valve prolapse–associated nonholosystolic MR) effective regurgitant orifice area (≥0.20 cm^2).

In patients with advanced MR, primary echo images were retrieved from archives and reviewed for MR cause: Degenerative MR was classified if prolapse/redundant chordae, rheumatic heart disease, or marked annular calcification was present. Functional MR was classified in the context of regional wall motion abnormalities, annular dilatation and/or perfusion deficits within the mitral apparatus (defined as shown in Figure 1), or global LV dysfunction. When features of both degenerative and functional MR were present, patients were classified as having mixed MR. Patients without identifiable causality for valvular insufficiency were classified as having idiopathic MR.

Ancillary analyses were performed to assess cardiac remodeling as a potential modifier of MR and effort tolerance: LV systolic function, geometry, and mass were quantified on the basis of linear dimensions in parasternal long axis, consistent with quantitative methods previously validated in necropsy-comparison and population-based outcome studies.[11,14,16] LA (left atrial) linear dimensions and volumes were measured in accordance with guidelines.[16] Pulmonary artery (PA) systolic pressure or PASP, was calculated on the basis of tricuspid regurgitant velocity and inferior vena cava caliber and respirophasic variability.

Statistical Analyses

Continuous variables were compared between groups using the Student *t* test (expressed as mean±SD); multiple group comparisons were made using 2-way ANOVA, for which post hoc testing was performed to compare individual groups. Categorical variables were compared using χ^2 or Fisher's exact tests (if <5 groups per cell). Univariate and multivariate linear regressions were used to identify structural and functional predictors of effort tolerance (dependent variable), which was assessed on the basis of METs measured during exercise treadmill testing; multivariate models were constructed via selection of variables most significant in univariate analysis. Calculations were performed using SPSS (SPSS Inc, Chicago, IL). Two-sided $P<0.05$ was deemed indicative of statistical significance.

Results

Study Population

The study population comprised 3267 patients who underwent exercise MPI and echo within a mean±SD interval of 6±8 days; 81% had evaluation by both modalities within 1 week. MR was present in nearly one third (28%) of patients, including 176 (5%) with advanced (moderate or greater) MR.

Table 1 reports population characteristics, including comparisons between patients with and without MR. As shown, MR was associated with age and CAD (both $P<0.01$). Further stratification of advanced MR demonstrated additional marked differences, as evidenced by a 2- to 3-fold higher incidence of prior surgical revascularization versus patients with mild or no MR (both $P<0.001$).

Table 1 also demonstrates that presence and severity of MR strongly paralleled adverse LV remodeling: LV systolic function significantly decreased and chamber size significantly increased stepwise among MR groups (all $P<0.001$), irrespective of whether quantified by echo or single-photon emission computed tomography (SPECT) MPI. Consistent with this, MPI demonstrated patients with MR to have significantly greater aggregate perfusion defect severity on both stress and rest imaging ($P<0.001$). Notably, although LV perfusion defects subtending both the anterolateral and posteromedial papillary muscles were significantly greater among patients with advanced versus mild MR, the magnitude of posteromedial defects on stress imaging was 3-fold greater (mean±SD, 2.4±4.1 versus 1.6±3.5; $P=0.02$) than the magnitude of anterolateral defects (mean±SD, 0.8±1.8 versus 0.4±1.4; $P=0.02$), with similar magnitude of difference evident on rest MPI.

Effort Tolerance

Table 2 examines exercise tolerance and hemodynamic response in relation to strata of MR. As shown, mean exercise duration decreased stepwise between groups ($P\leq0.001$), corresponding to a 0.3 absolute decrement in workload (METs) between patients with mild versus no MR (mean±SD, 9.8±3.0 versus 10.1±3.0; $P=0.02$), the magnitude of which increased 4-fold (absolute change, 1.2 METs) between patients with advanced versus mild MR (mean±SD, 8.6±3.0 versus 9.8±3.0; $P<0.001$). Although patients with advanced MR had significantly higher baseline PA systolic pressure (mean±SD, 37±9 mm Hg) versus those with mild MR (mean±SD, 32±7 mm Hg) or no MR (mean±SD, 30±7 mm Hg; both $P<0.001$), advanced MR was independently associated with impaired effort tolerance (B=−0.95 [95% CI, −1.44 to −0.46]; $P<0.001$), even after controlling for magnitude of PA systolic pressure.

As shown in Table 2, decreased effort tolerance among patients with MR was accompanied by blunted hemodynamic response. Despite slight decrements in baseline heart rate and increments in systolic blood pressure, patients with MR

Table 1. Population Characteristics

Characteristics	Overall (n=3267)	No MR (n=2343)	Mild MR (n=748)	*P* Value (None vs Mild)	Advanced MR (n=176)	*P* Value (Advanced vs Mild)
Age, y	64±12	63±11	67±12	<0.001*	71±12	<0.001*
Male sex, % (n)	57 (1854)	58 (1353)	54 (403)	0.06	56 (98)	0.67
Body mass index, kg/m^2	29±6	29±6	27±5	<0.001*	27±5	0.12
Atherosclerosis risk factors, % (n)						
Diabetes mellitus	26 (858)	27 (637)	24 (178)	0.07	24 (43)	0.86
Hypertension	63 (2062)	62 (1454)	66 (495)	0.04*	64 (113)	0.62
Tobacco use	7 (217)	8 (178)	4 (33)	0.003*	3 (6)	0.55
Hypercholesterolemia	65 (2121)	65 (1528)	64 (478)	0.51	65 (115)	0.72
Family history of CAD	27 (876)	27 (628)	28 (211)	0.45	21 (37)	0.05
COPD	4 (123)	4 (90)	3 (23)	0.33	6 (10)	0.09
Known coronary artery disease, % (n)	27 (877)	25 (592)	31 (228)	0.005*	32 (57)	0.62
Prior myocardial infarction	10 (322)	9 (214)	12 (91)	0.02*	10 (17)	0.35
Prior PCI	16 (533)	16 (370)	18 (136)	0.12	15 (27)	0.37
Prior CABG	6 (185)	5 (109)	6 (47)	0.08	17 (29)	<0.001*
Atrial fibrillation, % (n)	3 (87)	2 (37)	4 (33)	<0.001*	10 (17)	0.006*
Indication for stress testing, % (n)						
Chest pain	52 (1684)	54 (1271)	46 (340)	<0.001*	42 (73)	0.34
Dyspnea	31 (1016)	30 (712)	32 (242)	0.31	35 (62)	0.47
Medications, % (n)						
Aspirin	54 (1763)	54 (1262)	54 (402)	0.96	56 (99)	0.55
Thienopyridines	10 (331)	10 (234)	12 (86)	0.24	6 (11)	0.04*
β Blocker	37 (1214)	34 (796)	43 (322)	<0.001*	55 (96)	0.006*
ACE/ARB inhibitor	40 (1314)	40 (931)	41 (309)	0.44	42 (74)	0.86
Statin	55 (1791)	53 (1244)	59 (441)	0.005*	60 (106)	0.76
Imaging						
Echocardiography						
LV ejection fraction, %	62±9	63±8	61±10	0.01*	55±14	<0.001*
LV dysfunction (EF <50%), % (n)	10 (263)	7 (138)	12 (74)	<0.001*	34 (51)	<0.001*
LV end-diastolic volume, mL/m^2	63±16	61±14	66±18	<0.001*	77±24	<0.001*
LV dilation (LVEDV), % (n)[†]	30 (993)	26 (609)	38 (283)	<0.001*	57 (101)	<0.001*
LV end-systolic volume, mL/m^2	25±12	23±10	26±13	<0.001*	36±23	<0.001*
LV dilation (LVESV), % (n)[†]	22 (703)	18 (423)	26 (195)	<0.001*	48 (85)	<0.001*
SPECT						
LV ejection fraction, %	63±11	64±10	62±12	<0.001*	57±15	<0.001*
LV dysfunction (EF <50%), % (n)	10 (317)	7 (172)	14 (101)	<0.001*	25 (44)	<0.001*
LV end-diastolic volume, mL/m^2	46±16	44±14	48±18	<0.001*	60±27	<0.001*
LV end-systolic volume, mL/m^2	20±12	19±10	22±13	<0.001*	29±21	<0.001*
Global myocardial perfusion						
Summed stress score	3.1±6.6	2.6±5.9	3.8±7.6	<0.001*	6.6±9.0	<0.001*
Summed rest score	2.2±5.3	1.7±4.6	2.8±6.1	<0.001*	5.2±8.1	<0.001*

Continued

Table 1. Continued

Characteristics	Overall (n=3267)	No MR (n=2343)	Mild MR (n=748)	*P* Value (None vs Mild)	Advanced MR (n=176)	*P* Value (Advanced vs Mild)
Regional perfusion (anterolateral)						
Summed stress score	0.4±1.4	0.4±1.3	0.4±1.4	0.19	0.8±1.8	0.02*
Summed rest score	0.2±0.9	0.2±0.8	0.2±1.0	0.06	0.6±1.5	0.009*
Regional perfusion (posteromedial)						
Summed stress score	1.2±2.9	1.0±2.4	1.6±3.5	<0.001*	2.4±4.1	0.02*
Summed rest score	0.9±2.5	0.7±2.0	1.3±3.1	<0.001*	2.1±3.7	0.02*
Left atrial volume, cm^3/m^2	31±10	29±9	34±10	<0.001*	44±14	<0.001*
Pulmonary artery pressure, mm Hg	31±8	30±7	32±7	<0.001*	37±9	<0.001*
Pulmonary hypertension, % (n)‡	23 (505)	19 (271)	26 (158)	0.001*	49 (76)	<0.001*

Data are given as mean±SD unless otherwise indicated. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; LV, left ventricular; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; MR, mitral regurgitation; PCI, percutaneous coronary intervention; SPECT, single-photon emission computed tomography.
*$P<0.05$.
†LVEDV >74 mL/m^2 (men) and >61 mL/m^2 (women); LVESV >31 mL/m^2 (men) and >24 mL/m^2 (women).
‡Pulmonary artery systolic pressure ≥35 mm Hg.

Table 2. Exercise Physiological Parameters

Parameters	Overall	No MR	Mild MR	*P* Value (None vs Mild)	Advanced MR	*P* Value (Advanced vs Mild)
Exercise duration, min	7.9±2.9	8.1±2.8	7.6±2.9	0.001*	6.7±2.8	<0.001*
Peak treadmill stage achieved	2.5±1.0	2.6±1.0	2.4±1.0	0.002*	2.1±0.9	<0.001*
Workload (METs)	9.9±3.0	10.1±3.0	9.8±3.0	0.02*	8.6±3.0	<0.001*
Heart rate, bpm						
Rest	71±12	72±12	70±13	<0.001*	70±12	0.89
Peak stress	140±23	142±22	138±24	<0.001*	130±27	<0.001*
Heart rate change	69±23	70±22	68±23	0.02*	60±26	<0.001*
% Predicted maximum heart rate	90.1±13	90±13	90±14	0.48	87±17	0.07
Pharmacologic conversion, % (n)†	16 (507)	14 (329)	19 (139)	0.003*	22 (39)	0.28
Systolic blood pressure, mm Hg						
Rest	127±17	126±17	128±18	0.002*	132±18	0.03*
Peak stress	168±27	169±27	165±27	0.002*	161±31	0.04*
Blood pressure change	41±26	43±25	38±26	<0.001*	29±28	<0.001*
ECG response						
≥1-mm ST depression, % (n)	20 (641)	18 (421)	24 (177)	0.001*	24 (43)	0.84
Maximal ST depression, mm	0.3±0.8	0.3±0.7	0.4±0.9	<0.001*	0.5±0.9	0.70
Clinical response, % (n)						
Chest pain	5 (163)	5 (113)	5 (40)	0.57	6 (10)	0.86
Shortness of breath	13 (436)	14 (323)	11 (83)	0.06	17 (30)	0.03*
Duke treadmill score	6.0±5.3	6.4±5.1	5.2±5.9	<0.001*	4.2±6.1	0.07

Data are given as mean±SD unless otherwise indicated. Bpm indicates beats per minute; MET, metabolic equivalent of task; MR, mitral regurgitation.
*$P<0.05$.
†Failure to attain 85% of predicted maximum heart rate [(220−age)×0.85].

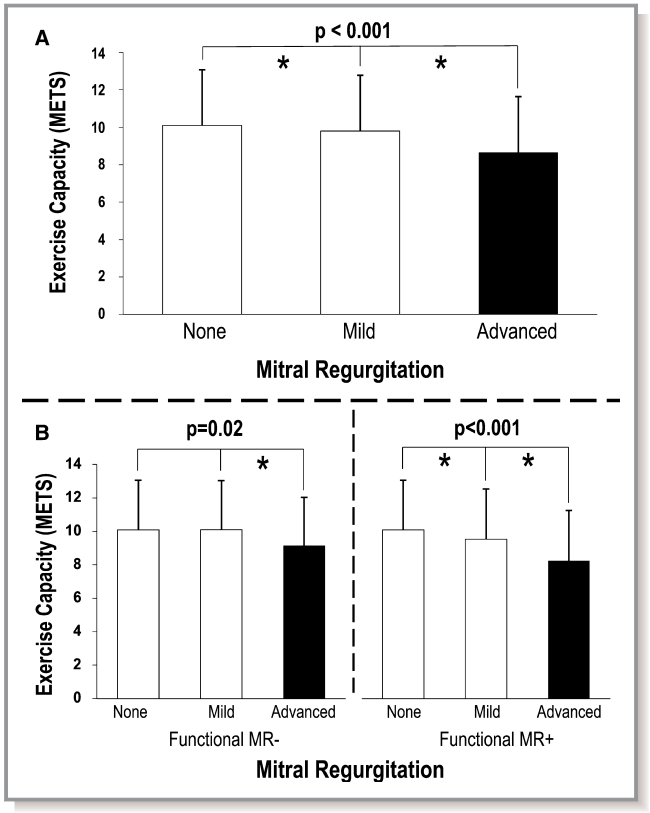

Figure 2. Effort tolerance in relation to mitral regurgitation (MR) severity. Exercise capacity (mean±SD) stratified in relation to graded severity of MR. Note stepwise decrements in metabolic equivalents of task (METs) in relation to MR severity among the overall population (**A**) as well as among patients with (**B**, right) or without (**B**, left) functional MR. For comparisons within MR strata, patients with both functional and degenerative/idiopathic MR demonstrated significant decrements in effort tolerance among patients with advanced (moderate or greater) MR compared with those with lower (mild) MR, although the magnitude of difference was nearly 1.5-fold greater for the functional MR (change=1.29 METs) compared with the degenerative/idiopathic MR (change=0.95 METs) subgroup. Advanced (moderate or greater) MR is denoted by black bars (other strata are denoted by white bars). **P*<0.05.

demonstrated significantly lower exercise-induced augmentation of both parameters (all *P*<0.05). Symptom status paralleled blunted hemodynamic response, as evidenced by a significant increase in prevalence of exercise-induced dyspnea among patients with advanced MR (17% versus 11%; *P*=0.03).

MR Severity and Cause

MR cause was classified as functional in 52% (n=478) and degenerative in 22% (n=202) of affected patients (26% idiopathic): Among patients with degenerative MR, mitral annular calcification was most common (41%), followed by prolapse/myxomatous (34%) and rheumatic disease (10%).

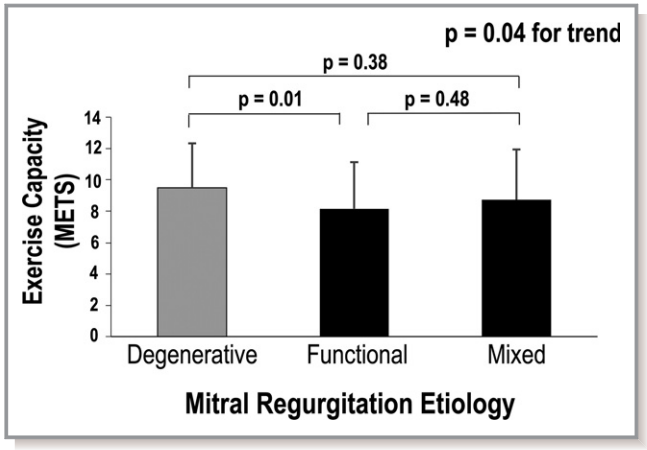

Figure 3. Advanced mitral regurgitation (MR) cause. Exercise capacity (mean±SD) among subtypes of advanced MR, demonstrating lower workload achieved among patients with functional MR (*P*=0.01) corresponding to greater adverse left ventricular remodeling (Table 3). Among patients with concomitant functional and degenerative MR components (eg, prolapse and mitral apparatus ischemia), effort tolerance was similar to isolated functional MR (*P*=0.48). MET indicates metabolic equivalent of task.

Figure 2 stratifies effort tolerance in relation to MR grade among the overall population, as well as among subgroups with (n=478) and without (n=446) functional MR. MR severity was associated with stepwise decrements in effort (METs) in both groups, which were most marked among patients with advanced (moderate or greater) MR compared with others (both *P*<0.05). Although clinically reported CAD was nearly 1.6-fold more common among patients with functional MR compared with those with degenerative MR (38% versus 24%), and nearly 3-fold more common among respective subgroups with advanced MR (48% versus 17%; both *P*≤0.001), effort tolerance decreased stepwise in relation to MR severity even when excluding patients with degenerative MR and epicardial CAD (*P*=0.02 for trend).

Figure 3 compares effort tolerance between patients with advanced MR as grouped by MR cause, illustrating that effort tolerance was significantly lower among patients with functional MR compared with degenerative MR (*P*=0.01). In multivariate analysis, functional MR was associated with impaired effort tolerance (B=−0.39 [95% CI, −0.62 to −0.17]; *P*=0.001) independent of MR severity. Table 3 reports exercise parameters between advanced MR groups. As shown, decreased workload among patients with advanced functional MR was accompanied by significantly lower heart rate augmentation (*P*<0.05) and a trend toward decreased achievement of target heart rate, more frequent conversion to pharmacologic stress testing, and lower blood pressure augmentation (all *P*≤0.1).

Exercise and hemodynamic differences between MR groups were highly associated with differences in LV remodeling. For

Table 3. Exercise Physiological Parameters in Relation to Advanced MR Cause

Advanced MR (n=176)	Overall (n=176)	Functional MR^{-} (n=79)	Functional MR^{+} (n=97)	*P* Value
Exercise				
Exercise duration, min	6.7±2.8	7.1±2.7	6.4±2.8	0.14
Peak treadmill stage achieved	2.1±0.9	2.3±0.9	2.1±0.9	0.13
Workload (METs)	8.6±3.0	9.2±2.9	8.2±3.0	0.04*
Heart rate, bpm				
Rest	70±12	69±13	71±12	0.36
Peak stress	130±27	133±26	127±28	0.14
Heart rate change	60±26	64±24	56±27	0.048*
% Predicted maximum heart rate	87±17	90±16	85±18	0.08
Pharmacologic conversion, % (n)[†]	22 (39)	17 (13)	27 (26)	0.10
Systolic blood pressure, mm Hg				
Rest	132±18	132±17	132±19	0.77
Peak stress	161±31	165±31	157±31	0.10
Blood pressure change	29±28	33±28	26±27	0.10
Exercise ECG response				
≥1-mm ST depression, % (n)	24 (43)	23 (18)	26 (25)	0.65
Maximal ST depression, mm	0.5±0.9	0.4±0.8	0.5±1.0	0.38
Exercise clinical response, % (n)				
Chest pain	6 (10)	5 (4)	6 (6)	1.00
Shortness of breath	17 (30)	19 (15)	16 (15)	0.54
Duke treadmill score	4.2±6.1	4.8±5.7	3.6±6.4	0.26

Data are given as mean±SD unless otherwise indicated. Bpm indicates beats per minute; MET, metabolic equivalent of task; MR, mitral regurgitation.
*P<0.05.
[†]Failure to attain 85% of predicted maximum heart rate [(220−age)×0.85].

age and sex, results demonstrated that patients with advanced functional MR were of similar age (mean±SD, 71±12 versus 72±12 years; P=0.52) but were more commonly men (72% versus 35%; P<0.001) than other patients with advanced MR. Table 4 demonstrates that despite more common male sex, patients with advanced functional MR had a 1.5- to 2.2-fold increment in sex-adjusted criteria for LV dilation on echo, paralleling greater prevalence of impaired LV systolic dysfunction (ejection fraction <50%) on both echo and SPECT, as well as a trend toward higher incidence of severe MR (16% versus 8%; P=0.08) and increased LA size.

Independent Predictors of Effort Tolerance

Univariable regression analysis was used to discern relative impact of clinical and imaging variables on effort, so as to inform development of multivariable models. As shown in Table 5, univariable analysis demonstrated age, chronic obstructive pulmonary disease, (female) sex, and diabetes mellitus to be most associated with decreased effort (all P<0.001). For imaging variables, advanced MR was strongly associated with impaired effort tolerance, as was LV end-systolic volume (a marker of ventricular dysfunction in MR), LV ejection fraction, and magnitude of stress and rest LV perfusion defects (all P<0.01).

Table 6 presents multivariable modeling, testing the association of MR with effort after controlling for LV functional and ischemia-based indexes. Imaging variables selected for inclusion in the model were those most strongly associated with MR in univariate analysis, which were tested together with age, body size (body mass index), and chronic obstructive pulmonary disease. As shown, advanced MR was associated with impaired effort tolerance (P=0.01) after controlling for age, clinical indexes, stress perfusion defects, and impaired LV function. Applied clinically, advanced MR was associated with an absolute reduction in exercise tolerance of >1 MET, which remained significant after controlling for LV dysfunction and clinical characteristics. Independent association between advanced MR and effort tolerance was unchanged with substitution of other clinical variables (diabetes mellitus,

Table 4. Imaging Parameters in Relation to Advanced MR Cause

Advanced MR (n=176)	Overall (n=176)	Functional MR$^-$ (n=79)	Functional MR$^+$ (n=97)	*P* Value
Echocardiography				
MR grade (moderate/greater than moderate), %	88/12	92/8	84/16	0.08
LV ejection fraction, %	55±14	62±8	48±15	<0.001*
LV dysfunction (EF <50%), % (n)	34 (51)	10 (7)	54 (44)	<0.001*
LV end-diastolic volume, mL/m^2	77±24	65±14	86±26	<0.001*
LV dilation (LVEDV), % (n)†	57 (101)	46 (36)	67 (65)	0.004*
LV end-systolic volume, mL/m^2	36±23	25±9	46±26	<0.001*
LV dilation (LVESV), % (n)†	48 (85)	29 (23)	64 (62)	<0.001*
SPECT				
LV ejection fraction, %	57±15	66±9	50±15	<0.001*
LV dysfunction (EF <50%), % (n)	25 (44)	5 (4)	41 (40)	<0.001*
LV end-diastolic volume, mL/m^2	60±28	47±15	70±31	<0.001*
LV end-systolic volume, mL/m^2	29±21	19±11	37±23	<0.001*
Left atrial volume, cm^3/m^2	44±14	42±13	46±14	0.13
Pulmonary artery pressure, mm Hg	37±9	36±7	38±11	0.18
Pulmonary hypertension, % (n)‡	49 (76)	46 (30)	52 (46)	0.40

Data are given as mean±SD unless otherwise indicated. EF indicates ejection fraction; LV, left ventricular; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; MR, mitral regurgitation; SPECT, single-photon emission computed tomography.
*P<0.05.
†LVEDV >74 mL/m^2 (men) and >61 mL/m^2 (women); LVESV >31 mL/m^2 (men) and >24 mL/m^2 (women).
‡Pulmonary artery systolic pressure ≥35 mm Hg.

hypertension, hypercholesterolemia, and smoking) as well as β-blocker use for age.

Discussion

This is the first study to examine the impact of MR on effort tolerance while controlling for variables that can impact both MR itself as well as exercise capacity, including LV dysfunction and ischemia. Key findings are as follows: First, among a broad cohort of 3267 patients with known or suspected CAD, effort capacity during exercise MPI decreased stepwise in relation to severity of MR, paralleled by significant impairments in heart rate and blood pressure augmentation (all P<0.05), as well as increased exercise-induced dyspnea (P<0.05). Second, exercise capacity varied in relation to MR cause, and was lower in patients with functional MR independent of MR severity. Impaired effort tolerance with functional MR was strongly related to adverse LV remodeling, as evidenced by greater LV dilation and LV systolic dysfunction, as quantified on echo and SPECT. Third, advanced (moderate or greater) MR was independently associated with impaired effort tolerance (P=0.01) after controlling for age, clinical indexes, stress perfusion defects, and impaired LV function. Applied clinically, advanced MR was associated with an absolute reduction in exercise tolerance of >1 MET, which remained significant after controlling for LV function and clinical characteristics.

For mechanism, we speculate that our observed independent association between MR and impaired effort tolerance stems from impact of MR on LA compliance and PA pressure. Although our study did not perform stress echo to assess dynamic changes in MR or PA pressure, prior studies have shown that both functional and degenerative MR can increase during exercise, as can PA systolic pressure.[6,7,11,21] Prior studies in patients with functional MR have also shown that exercise-induced MR is paralleled by dynamic changes in adverse LV remodeling, as evidenced by increased LV sphericity.[6,7] Accordingly, a dynamic cycle can result whereby MR begets MR, resulting in progressive increments in LA volume that increase PA pressure, increase LV preload, and impair LV diastolic filling, each of which can impede effort tolerance. Our study demonstrated stepwise association between MR and LV ischemia, as evidenced by a 1.5-fold increase in summed stress score among patients with mild versus no MR and a 1.7-fold increase among patients with advanced versus mild MR (both P<0.001). Regional LV perfusion deficits among patients with MR were most pronounced adjacent to the posteromedial papillary muscle, supporting a mechanistic link between ischemia in LV myocardium underlying the mitral valve and MR. Prior studies

Table 5. Univariable Regression Analyses for Exercise Tolerance (METs)

Variable	B	95% CI	*P* Value
Clinical			
Age (per 10-y increment)	−0.90	(−0.97 to −0.81)	<0.001*
Male sex	1.28	(1.08 to 1.48)	<0.001*
Known CAD	0.04	(−0.20 to 0.27)	0.76
Diabetes mellitus	−0.98	(−1.22 to −0.75)	<0.001*
Hypertension	−0.93	(−1.14 to −0.72)	<0.001*
Tobacco use	−0.06	(−0.48 to 0.35)	0.76
Hypercholesterolemia	−0.24	(−0.46 to −0.03)	0.03*
Family history CAD	0.48	(0.24 to 0.71)	<0.001*
COPD	−1.53	(−2.07 to −1.00)	<0.001*
Medications			
Aspirin	−0.28	(−0.48 to −0.07)	0.008*
Thienopyridines	−0.09	(−0.43 to 0.25)	0.60
β Blocker	−0.78	(−0.99 to −0.57)	<0.001*
ACE/ARB inhibitor	−0.53	(−0.74 to −0.33)	<0.001*
Statin	−0.48	(−0.68 to −0.27)	<0.001*
Imaging			
Echocardiography			
LV ejection fraction, per 10% decrement	−0.27	(−0.39 to −0.15)	<0.001*
LV end-diastolic volume, per 10 mL/m^2	0.00	(−0.07 to 0.06)	0.97
LV end-systolic volume, per 10 mL/m^2	−0.14	(−0.24 to −0.05)	0.003*
SPECT			
LV ejection fraction, per 10% decrement	−0.01	(−0.11 to 0.08)	0.80
LV end-diastolic volume, per 10 mL/m^2	0.12	(0.05 to 0.18)	<0.001*
LV end-systolic volume, per 10 mL/m^2	0.12	(0.03 to 0.21)	0.007*
Mitral regurgitation			
MR grade	−0.52	(−0.69 to −0.35)	<0.001*
Advanced MR	−1.36	(−1.80 to −0.93)	<0.001*
Global myocardial perfusion			
Summed stress score	−0.04	(−0.06 to −0.03)	<0.001*
Summed rest score	−0.04	(−0.06 to −0.02)	<0.001*

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LV, left ventricular; MET, metabolic equivalent of task; MR, mitral regurgitation; SPECT, single-photon emission computed tomography.
*P<0.05.

Table 6. Multivariable Regression Analyses for Exercise Tolerance (METs)

	Model-Adjusted R^2=0.246, P<0.001		
Variable	B	95% CI	*P* Value*
Age (per 10-y increment)	−0.93	(−1.02 to −0.85)	<0.001
Male sex	1.55	(1.34 to 1.75)	<0.001
COPD	−0.88	(−1.41 to −0.34)	0.001
BMI	−0.13	(−0.15 to −0.11)	<0.001
LV ejection fraction (per 10% decrement)	−0.28	(−0.17 to −0.40)	<0.001
Summed stress score	−0.50	(−0.67 to −0.32)	<0.001
Advanced MR†	−0.55	(−0.99 to −0.11)	0.01

BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; LV, left ventricular; MET, metabolic equivalent of task; MR, mitral regurgitation.
*P<0.05.
†Independent association between advanced MR and effort tolerance was unchanged with substitution of other clinical variables (diabetes mellitus, hypertension, hypercholesterolemia, and smoking) as well as β-blocker use for age.

have established that LV ischemia itself can cause transient increases in LV chamber size.[22] In this context, it is possible that ischemia-induced alterations in LV remodeling, resulting in chamber dilation that impairs valve coaptation, can increase MR, alter LA and LV filling, and thus impede effort tolerance.

It is important to recognize that our perfusion data in this study are derived from exercise SPECT, which enabled us to test the association between MR and effort tolerance while controlling for both LV function and ischemia. Although SPECT is widely used as a primary test to assess LV perfusion, it can be suboptimal for assessing physiological ischemia in patients with prior coronary artery bypass grafting, and for differentiating between profoundly ischemic (ie, hibernating) and infarcted myocardium, as established by techniques such as cardiac magnetic resonance. Further studies are warranted to better elucidate the relative contribution of ischemia and infarction to MR, as well as to assess dynamic changes in MR itself and PA pressure as causal factors for impaired effort tolerance in patients with MR.

Our study, which shows the impact of MR on exercise to be independent of LV dysfunction, extends prior research that has shown a link between MR and impaired effort. Szymanski et al, studying 77 patients with functional MR undergoing exercise stress testing, reported effort tolerance in METs to correlate negatively with MR severity, as assessed via vena contracta (r=−0.674, P<0.001) and regurgitant area (r=−0.575, P<0.001).[5] Prior studies have also linked MR to other indexes of impaired exercise capacity, including decreased peak O_2 consumption (VO_2).[6] However, given that MR itself can result from LV dysfunction and myocardial injury (ischemia and infarction), uncertainty persisted as to whether the link between MR and impaired effort was primarily attributable to valvular regurgitation or a secondary consequence of adverse LV remodeling. Our current results demonstrate that the

impact of MR on effort intolerance augments that of LV dysfunction and ischemia, supporting the concept that MR itself impedes cardiovascular adaptations to increased workload.

Several limitations of this study should be noted. First, advanced MR was confirmed on the basis of a variety of quantitative indexes (regurgitant volume/fraction and rarely effective regurgitant orifice area) rather than a uniform quantitative parameter. On the other hand, prior research has shown limitations of individual quantitative parameters for MR,[23] undermining application of a strict uniform criterion in large-scale populations, as included in our study. Second, although our study used echo criteria for MR, other approaches (such as cardiac magnetic resonance) have been used for this purpose[23]: Although our results could have varied somewhat had cardiac magnetic resonance been used to assess MR, echo is well validated and widely used for this purpose and use of cardiac magnetic resonance could have resulted in a more selected population. In this context, our findings on independent links between echo-evidenced MR and impaired effort tolerance are broadly generalizable to clinical practice and population-based research. In addition, although our results demonstrate an association between MR and impaired effort independent of LV function and remodeling, it is possible that other clinical factors (not reflected in available data) may have modified this. For example, although MR was associated with shorter effort duration after controlling for clinically reported chronic obstructive pulmonary disease and smoking status, subtle pulmonary impairments may have been present in some patients with MR, in whom altered lung capacity could have contributed to decreased effort. By extension, MR itself likely resulted in dynamic augmentation in PA pressure during exercise, providing a mechanism that contributed to impaired exercise capacity. Finally, our study tested MR in relation to a surrogate end point of effort tolerance rather than hard clinical end points, such as mortality. However, prior studies have shown MR itself to strongly predict clinical prognosis and have shown risk for adverse outcomes to increase in parallel with presence and severity of MR.[5,21,24,25]

In conclusion, findings of the current study demonstrate MR to impede effort tolerance independent of LV ischemia and dysfunction, as well as age and clinical indexes. Further studies are warranted to assess dynamic changes in MR and PA pressure as causal factors for impaired effort tolerance in patients with MR. Given our finding that MR severity was strongly related to LV ischemia (a potentially reversible condition), findings of the current study highlight the need for future tailored research to test efficacy of targeted interventions (including revascularization of ischemic but viable segments within the mitral valve apparatus) to reduce MR and improve clinical symptom status.

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Disclosures

None.

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