Cardiopulmonary Exercise Testing Determination of Functional Capacity in Mitral Regurgitation

Physiologic and Outcome Implications

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OBJECTIVES
This study was designed to evaluate prevalence, determinants, and clinical outcome implications of reduced functional capacity (FC) in patients with organic mitral regurgitation (MR).

BACKGROUND
Evaluation of FC by exercise testing is rarely performed in MR because little is known about the clinical determinants and outcome implications of FC.

METHODS
Cardiopulmonary exercise testing (CPET) was prospectively performed in 134 asymptomatic patients with organic MR to assess FC (peak oxygen consumption \(\text{VO}_2\)) simultaneously to Doppler-echocardiographic quantitation of MR (effective regurgitant orifice [ERO]) and left ventricular (LV) systolic and diastolic function.

RESULTS
Peak \(\text{VO}_2\) was 26 ± 6 ml/kg/min (96 ± 16% of age-predicted), but varied widely (57% to 145% of predicted) and was markedly reduced (≤84% of predicted) in 19% of patients. Although ERO of MR was univariately associated with reduced FC (26 vs. 9% with ERO ≥40 vs. <40 mm²), independent determinants of reduced FC were LV diastolic function (higher E/E' ratio, \(p = 0.006\)), atrial fibrillation (\(p = 0.01\)), and lower forward stroke volume (\(p = 0.03\)). Clinical events (death, heart failure, new atrial fibrillation) and clinical events or surgery were more frequent with than without reduced FC (3 years, 36 ± 14% vs. 13 ± 4%,\(p = 0.02\); and 66 ± 11% vs. 29 ± 5%, \(p = 0.001\), respectively), even adjusting (risk ratios 1.80 and 1.54 respectively, both \(p < 0.03\)) for age and ERO.

CONCLUSIONS
In asymptomatic organic MR, FC quantitatively assessed by CPET is unexpectedly markedly reduced in one out of every four to five patients. Reduced FC is independently determined by consequences rather than severity of MR and predicts increased subsequent clinical events. Therefore, CPET frequently reveals functional limitations not detected clinically and is an important tool in managing patients with organic MR.

The management of patients with mitral regurgitation (MR) is based, in great part, on functional limitations occurring with activity (1). In asymptomatic patients, no limitation is clinically detected, but this subjective assessment does not account for the physical activity level of patients who are often sedentary. Recent outcome studies reported notable risks incurred by subsets of asymptomatic patients with MR (2,3), and guidelines underscore the importance of “a well established estimation of exercise tolerance” and recommend exercise testing to objectively assess exercise tolerance (1). However, the incremental information provided by exercise testing in asymptomatic patients with organic MR is uncertain, and this test is rarely performed (4). Few reports objectively define functional capacity (FC) in MR; they involved limited numbers of patients (5–7) and did not analyze FC’s link to clinical outcome.

Defining FC determinants in organic MR is a vexing problem. Although some patients with severe MR complain of no functional limitation, others with similar MR develop severe functional limitations (2,3,8). Increasing evidence, particularly based on Doppler tissue imaging (9), links diastolic function to exercise capacity (10,11), but such evidence is lacking in MR. Cardiopulmonary exercise testing (CPET) with determination of gas exchange provides quantitative, objective, and noninvasive evaluation of FC and allows risk stratification in patients with congestive heart failure (12). Cardiopulmonary exercise testing accounts for the expected decrease in FC capacity with age and gender (13).

One of our aims was to prospectively and objectively assess FC by CPET in asymptomatic patients with organic MR. We also used a comprehensive echocardiographic quantification of MR severity, left ventricular (LV) and left
atrial (LA) remodeling, and LV systolic and diastolic function, to evaluate FC determinants. Our hypothesis was that FC reduction is frequent, is independently determined by diastolic LV dysfunction after adjusting for MR severity, and is a marker for subsequent clinical events.

METHODS

Study population. Between 1998 and 2004, asymptomatic patients with organic MR were prospectively and consecutively evaluated using quantitative echocardiography and CPET. Inclusion criteria were patients: 1) with pure, isolated MR and regurgitant volume (RVol) ≥30 ml/beat) (14) quantified by at least two methods; 2) with quantitative assessment of cardiac remodeling and LV systolic and diastolic function; 3) who performed a maximal exercise test, i.e., achieving their heart rate goal (≥85% of the age-predicted peak heart rate) or stopped because of symptoms of dyspnea, exhaustion, or hypotension; and 4) in whom echocardiography and CPET were performed during the same episode of care without intervening clinical change. Exclusion criteria were: 1) age ≥90 years; 2) history of congestive heart failure; 3) rheumatic mitral stenosis of any degree; 4) moderate or more severe lung disease; 5) exercise limited by angina; and 6) exercise testing stopped because of ischemia or severe arrhythmia.

Echocardiographic measurements. QUANTIFICATION OF MR. Degree of MR was quantified by at least two of the following three methods, which were systematically performed and were averaged to calculate RVol and effective regurgitant orifice (ERO): quantitative Doppler based on mitral and aortic stroke volumes, quantitative two-dimensional echocardiography based on LV stroke volume measurement, and the proximal isovelocity surface area method based on analysis of proximal flow convergence (14). Severe MR was defined by RVol ≥60 ml/beat or ERO ≥40 mm² (14).

EVALUATION OF DIASTOLIC FUNCTION. Mitral inflow was recorded at mitral leaflet tips, and velocities of early diastolic flow (E-wave), late diastolic flow (A-wave), E-wave deceleration time, and E/A ratio were measured. With Doppler tissue imaging, septal early diastolic tissue velocity (E') was recorded, and the E/E' ratio was calculated with at least three measurements averaged.

LV AND LA FUNCTION AND REMODELING ASSESSMENT. Measurements of LV size (LV end-diastolic and -systolic volume index), ejection fraction, and LV mass were performed as recommended by the American Society of Echocardiography (15). End-systolic wall stress calculation used estimated end-systolic pressure and echocardiographic LV geometry and wall thickness. Left atrial volume was measured by area-length method (16).

Cardiopulmonary exercise testing. Symptom-limited treadmill exercise testing with respiratory gas exchange analysis used modified Bruce protocol (2-min workloads, 2 W/min increments in work).

Electrocardiograms were continuously monitored and blood pressure was assessed the last 30 s of each 2-min workload. Patients were encouraged to exercise to exhaustion. Exercise duration was expressed in minutes and in percent of age- and gender-predicted value (13). Breath-by-breath minute ventilation (VE), carbon dioxide production (VCO₂), their ratio (VE/VCO₂), and oxygen consumption (VO₂) were measured using a Medical Graphics metabolic cart (St. Paul, Minnesota). Calibration used gravimetric quality gases before each test and physiologic calibration for weekly quality control. Peak VO₂ was the highest averaged 30-s VO₂ during exercise and was expressed as absolute peak-VO₂ or normalized peak VO₂ (percent of age, gender, and weight predicted) (13). Normalized peak-VO₂ was calculated offline, with FC considered markedly reduced with peak VO₂ ≤84% of predicted (17) and was not available to patients’ independent physicians, who conducted clinical management. The O₂-pulse, an estimate of stroke volume, was calculated as VO₂/heart rate. Quality of exercise effort was assessed by respiratory exchange ratio (RER) (17).

Statistical analysis. Data are presented as mean ± SD or percent. Comparisons between groups used analysis of variance (with Tukey-HSD test) or chi-square test as appropriate. Correlations to peak VO₂ were entered stepwise in the model. Outcome was analyzed using three end points: clinical events (death, heart failure or new severe symptoms, new atrial arrhythmia) under conservative management, indication for surgery, and the combined end point of clinical events or surgery. Event rates were estimated using the Kaplan-Meier method and compared between groups using the log-rank test. The association of FC with the end points was determined using the Cox proportional hazards method with and without adjustment to other determinants of outcome. A value of p < 0.05 was significant.
function of the capacity of the population overall and according to the functional capacity.

### RESULTS

Baseline characteristics. We prospectively enrolled 134 patients (63 ± 14 years, 63% men) with MR in whom mitral valve prolapse (with or without flail) was the main etiology (93%). Six patients (5%) were in atrial fibrillation. Quantitation of MR showed excellent correlation between methods (all r > 0.90), which were averaged for simplification. Mitral regurgitation was often severe (77 of 132 patients, 57%), with a wide range (RVol: 68 ± 24 ml/beats; range 30 to 146 ml/beats; ERO: 35 ± 14 mm², range 14 to 83 mm²). Ejection fraction was 73 ± 6% and was ≥55% in all patients. Mean E/E' ratio was 12 ± 5 and ≥15 (9) in 19%. Main clinical and echocardiographic characteristics are presented in Table 1 (left column).

### Table 1. Baseline Resting Characteristic of the Population Overall and According to the Functional Capacity

<table>
<thead>
<tr>
<th>Category</th>
<th>Variable Name, U</th>
<th>Overall (n = 134)</th>
<th>Normal FC (n = 108)</th>
<th>MR-Related FC (n = 18)</th>
<th>Extrinsic Component (n = 8)</th>
<th>p Value for the 3 Groups</th>
<th>Correlation to Percent of Predicted VO₂‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
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<tr>
<td>Age, yrs</td>
<td>63 ± 14</td>
<td>64 ± 13</td>
<td>57 ± 13</td>
<td>60 ± 22</td>
<td>0.15</td>
<td>0.16</td>
<td>0.08</td>
</tr>
<tr>
<td>Male gender</td>
<td>85 (63)</td>
<td>70 (65)</td>
<td>12 (67)</td>
<td>3 (38)</td>
<td>0.29</td>
<td>0.09</td>
<td>0.30</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26 ± 4</td>
<td>26 ± 4</td>
<td>26 ± 4</td>
<td>26 ± 4</td>
<td>0.90</td>
<td>-0.09</td>
<td>0.34</td>
</tr>
<tr>
<td>Beta-blocker therapy</td>
<td>31 (23)</td>
<td>27 (25)</td>
<td>3 (18)</td>
<td>1 (13)</td>
<td>0.59</td>
<td>0.02</td>
<td>0.84</td>
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<tr>
<td>Atrial fibrillation</td>
<td>6 (5)</td>
<td>4 (4)</td>
<td>2 (11)</td>
<td>0</td>
<td>0.30</td>
<td>0.24</td>
<td>0.0007</td>
</tr>
<tr>
<td>Hemodynamic</td>
<td></td>
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<tr>
<td>HR, beats/min</td>
<td>66 ± 10</td>
<td>64 ± 9</td>
<td>74 ± 10*</td>
<td>69 ± 7</td>
<td>0.0002</td>
<td>-0.29</td>
<td>0.0009</td>
</tr>
<tr>
<td>Forward stroke volume, ml</td>
<td>79 ± 16</td>
<td>81 ± 16</td>
<td>75 ± 18</td>
<td>68 ± 10</td>
<td>0.05</td>
<td>0.21</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>2.7 ± 0.5</td>
<td>2.7 ± 0.5</td>
<td>2.8 ± 0.4</td>
<td>2.6 ± 0.4</td>
<td>0.40</td>
<td>0.13</td>
<td>0.14</td>
</tr>
<tr>
<td>S-PAP, mm Hg</td>
<td>32 ± 9</td>
<td>32 ± 7</td>
<td>36 ± 16*</td>
<td>31 ± 9</td>
<td>0.14</td>
<td>-0.22</td>
<td>0.02</td>
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<tr>
<td>Cardiac remodeling</td>
<td></td>
<td></td>
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<tr>
<td>EDVI, ml/m²</td>
<td>108 ± 20</td>
<td>109 ± 19</td>
<td>112 ± 21</td>
<td>91 ± 17*</td>
<td>0.03</td>
<td>0.12</td>
<td>0.19</td>
</tr>
<tr>
<td>ESVI, ml/m²</td>
<td>29 ± 10</td>
<td>30 ± 10</td>
<td>31 ± 10</td>
<td>25 ± 9</td>
<td>0.34</td>
<td>0.01</td>
<td>0.89</td>
</tr>
<tr>
<td>LV mass/volume, g/ml</td>
<td>1.1 ± 0.2</td>
<td>1.1 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>1.1 ± 0.2</td>
<td>0.30</td>
<td>-0.13</td>
<td>0.16</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>73 ± 6</td>
<td>73 ± 6</td>
<td>73 ± 5</td>
<td>74 ± 6</td>
<td>0.95</td>
<td>0.05</td>
<td>0.61</td>
</tr>
<tr>
<td>ESWS/ESVI, g/cm²</td>
<td>5.3 ± 1.4</td>
<td>5.3 ± 1.5</td>
<td>5.0 ± 1.2</td>
<td>5.8 ± 1.7</td>
<td>0.53</td>
<td>0.02</td>
<td>0.79</td>
</tr>
<tr>
<td>LA index, ml/m²</td>
<td>68 ± 26</td>
<td>68 ± 23</td>
<td>80 ± 40</td>
<td>52 ± 24</td>
<td>0.03</td>
<td>-0.08</td>
<td>0.37</td>
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<tr>
<td>MR severity</td>
<td></td>
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<tr>
<td>RVol, ml/beat</td>
<td>68 ± 24</td>
<td>68 ± 24</td>
<td>79 ± 23</td>
<td>49 ± 16</td>
<td>0.01</td>
<td>-0.11</td>
<td>0.21</td>
</tr>
<tr>
<td>ERO, mm²</td>
<td>35 ± 14</td>
<td>34 ± 12</td>
<td>46 ± 16*</td>
<td>25 ± 8</td>
<td>0.0002</td>
<td>-0.23</td>
<td>0.01</td>
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<tr>
<td>Diastolic function</td>
<td></td>
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<tr>
<td>E/A ratio</td>
<td>1.4 ± 0.5</td>
<td>1.4 ± 0.5</td>
<td>1.5 ± 0.4</td>
<td>1.2 ± 0.3</td>
<td>0.28</td>
<td>-0.06</td>
<td>0.50</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>213 ± 40</td>
<td>215 ± 38</td>
<td>201 ± 46</td>
<td>208 ± 25</td>
<td>0.37</td>
<td>0.22</td>
<td>0.02</td>
</tr>
<tr>
<td>E'/E' ratio</td>
<td>12 ± 5</td>
<td>12 ± 4</td>
<td>14 ± 9*</td>
<td>11 ± 4</td>
<td>0.09</td>
<td>-0.30</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Data presented are number of patients (percent) or mean ± SD. p < 0.05 vs. patients with normal functional capacity; applies to patients without extraneous contribution to functional limitations.

DBP = diastolic blood pressure; EDVI = end-diastolic volume index; EF = ejection fraction; ERO = effective regurgitant orifice; ESVI = end-systolic volume index; ESWS = end-systolic wall stress; FC = functional capacity; HR = heart rate; LA = left atrium; RVol = regurgitant volume; SBP = systolic blood pressure; S-PAP = systolic pulmonary artery pressure; VO₂ = oxygen consumption.

Functional capacity in MR. Interval between CPET and echocardiography was 2 ± 3 days. Exercise testing was terminated because of symptoms in 132 patients and hypotension in 2 patients. Mean RER was 1.12 ± 0.08, confirming appropriate effort in most patients. Exercise testing characteristics are summarized in Table 2.

### COMPREHENSIVE ANALYSIS OF THE FUNCTIONAL CAPACITY

Absolute peak VO₂ was 26 ± 6 ml/kg/min with wide range (15.6 to 49.0 ml/kg/min) and expected negative correlation with age (r = –0.54, p < 0.0001), female gender (r = –0.29, p = 0.002), and body mass index (r = –0.29, p = 0.002). Normalized peak VO₂ was close to normal (96 ± 16% of predicted) and showed no correlation to age, gender, and body mass index (all p > 0.05), confirming appropriate adjustment. Nevertheless, normalized peak VO₂ varied widely, from 57% to 145% of predicted, even in patients with severe MR (57% to 145%).

Among the 126 asymptomatic patients with no extraneous component to FC limitations (orthopedic, uncomfortable on the treadmill, obesity), and 18 had no other cause than MR (MR-related reduced FC). Exercise effort measured by peak-VO₂ was similarly high with normal FC and with MR-related reduced FC (1.12 ± 0.08 vs. 1.14 ± 0.07, p = 0.32), whereas it was lower with extraneous component to FC limitations (1.05 ± 0.08, p = 0.02).

PEAK VO₂ VERSUS EXERCISE DURATION. The correlation between peak-VO₂ and exercise duration was good (r = 0.80, p < 0.0001), but exercise duration was dependent on age (r = –0.50, p < 0.0001) and gender (r = 0.29, p =
0.001), and no threshold of exercise duration predicted FC reduction with both sensitivity and specificity >80%. Sensitivity, specificity, and positive and negative predictive values of exercise duration ≤ 9.4 min were modest (72%, 64%, 93%, and 26%, respectively).

**Determinants of the FC.** Comparisons between patients with and without markedly reduced FC for baseline characteristics and correlations to normalized peak VO₂ are presented in the mid and right panels of Tables 1 and 2. Exercise effort assessed by RER, peak heart rate, and frequency of patients who reached their heart rate goal were not different between patients with reduced and normal FC (all p > 0.05). Lower double-product with reduced FC was related to lower peak systolic blood pressure. In MR-related markedly reduced FC, lower absolute peak VO₂, ml/kg/min p = 0.03; atrial fibrillation, p = 0.01) independently determined normalized peak VO₂. After adjustment for these variables, ERO showed no independent association with reduced FC. Including the eight patients with potential extraneous component to FC limitations, FC determinants were unchanged. Abnormal LV diastolic function (E/E’ ≥ 15 or <15 [9]), low stroke volume (≥ or < lower quartile), and atrial fibrillation exerted a cumulative effect on FC as patients with markedly reduced FC represented 11%, 15%, and 40% of those with 0, 1, and 2 abnormalities, respectively (p = 0.05).

**Clinical outcome.** During follow-up under conservative management of 288 patient-years (mean 2.2 ± 1.3 years), clinical events occurred in 20 patients (3 deaths, 15 congestive heart failure or occurrence of severe symptoms, and 2 atrial arrhythmias), corresponding to 4-year incidence of 26 ± 7% by Kaplan-Meier method. Ultimately, 42 patients underwent surgery for mitral regurgitation (12 for new symptoms and 30 based on patient and physician preference, supported by severity of MR, LV and LA remodeling, and progression), corresponding to four-year incidence of 43 ± 7%. Clinical events or mitral surgery occurred in a total of 50 patients, or 53 ± 8% at 4 years.

Patients with reduced FC displayed a higher three-year rate of clinical events than those with normal FC (36 ± 14% vs. 13 ± 4%, p = 0.02), even excluding patients with potential extraneous component to FC limitations (p = 0.049). Reduced FC was univariately associated with higher risk of clinical events (risk ratio [RR] 1.72 [95% confidence interval (CI) 1.01 to 2.76], p = 0.045) and remained so with almost unchanged RR after adjustment for age and ERO (RR 1.80 [95% CI 1.06 to 2.92], p = 0.03) and additionally for gender and EF (RR 1.78 [95% CI 1.04 to 2.87], p = 0.035). Longer exercise time
was univariately associated with lower risk of clinical events (RR 0.85 [95% CI 0.73 to 0.98], p = 0.03) but lost significance after adjustment for age and ERO (p = 0.11). Patients with reduced FC displayed a higher three-year incidence of mitral surgery than those with normal FC (53 ± 12% vs. 29 ± 5%, p = 0.03), even when patients with potential extraneous component to FC limitations were excluded from the comparison (p = 0.005). Patients with reduced FC also displayed a higher three-year rate of combined end point (clinical event or surgery) than those with normal FC (66 ± 11% vs. 29 ± 5%, p = 0.001) (Fig. 2), even excluding patients with potential extraneous component to FC limitations (p = 0.005). Reduced FC was univariately associated with higher risk of combined end point (RR 1.62 [1.18 to 2.19], p = 0.004) and remained so with almost unchanged RR after adjustment for age and ERO (RR 1.54 [1.10 to 2.09], p = 0.01), even after additional adjustment for gender and EF (RR 1.53 [1.10 to 2.09], p = 0.01).

### DISCUSSION

The present study is the first to evaluate FC quantitatively by peak VO2 during CPET simultaneously with quantification of MR, LA and LV remodeling, LV systolic and diastolic function, and ventilatory efficiency with exercise in a large series of patients with organic MR and to link FC to clinical outcome. In asymptomatic patients, FC showed a wide range from supranormal to markedly reduced. Mitral regurgitation severity (ERO) is modestly linked to FC, whereas LV diastolic dysfunction (high E/E'), reduced forward stroke volume and atrial fibrillation independently and cumulatively determined FC. Reduced FC is an independent marker of higher mid-term risk of clinical events or surgery. Therefore, CPET is an important tool in asymptomatic patients with organic MR to uncover FC reduction and to assess mechanisms leading to reduced FC, which predicts independently higher risk of clinical events. These

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results support the guidelines suggestion of wider use of exercise testing, particularly CPET in MR.

**Functional capacity in organic MR.** The only routine form of assessment of functional capacity in MR is based on symptoms occurring with exertion, despite the subjective nature of this assessment (1). However, asymptomatic patients with severe MR incur notable mortality under conservative management (2,3,8), raising the concern that lack of symptoms may underestimate disease severity. Although peak VO₂ is on average normal in asymptomatic patients, FC is frequently markedly reduced. Indeed, reduced FC is unexpectedly observed in one of every four to five asymptomatic patients with organic MR, underscoring the importance of exercise stress testing in classifying functional disability. Cardiopulmonary exercise testing not only detects reduced FC but also can help define the features of cardiac limitations, characterized by plateau in VO₂ and O₂-pulse with maximum exertional effort, contrasting with the pattern of reduced FC contributed to by extraneous components.

The determinants of FC reduction in MR have remained unclear with no definite association between peak VO₂ and RVol (6), whereas the link between ERO and reduced FC is stronger, possibly through its association to LA pressure (18). Nevertheless, the ERO-FC association is weak, suggesting that other factors are important contributors to reduced FC. Indeed, FC is affected by LV characteristics, but not by LV systolic function, as all end-systolic LV indices showed no association to FC. Conversely, diastolic function is a major FC determinant (10,11,19), now shown to also strongly influence FC in organic MR (7). High E/E’ ratio marks diastolic dysfunction with higher LV filling pressures (9,20) independent of MR (21). The impact of diastolic dysfunction on FC is also supported by univariate association between peak VO₂ and deceleration time, a marker of LV compliance. An important result of our study is that the link of reduced FC to diastolic dysfunction is not related to lack of LA adaptation, classically considered to explain preserved FC (22). Indeed, with reduced FC, LA is larger, and LA and LV enlargement compensating for MR progression (23) are overwhelmed, with diastolic LV filling alterations resulting in reduced FC. Other determinants of reduced FC are associated with reduced cardiac output, with lower exercise stroke volume demonstrated by lower peak O₂ pulse and lower O₂ pulse change with exercise. Reduced baseline forward stroke volume is associated with lower peak O₂ pulse (r = 0.50, p < 0.0001) and independently predicts reduced FC, probably through inability to sustain large forward stroke volume due to MR. Atrial fibrillation is important in MR and, through reduced cardiac output, links to lower FC even in the absence of symptoms. Although these individual FC determinants, which exert a cumulative effect leading to reduced FC, are linked to MR, they reflect not only the degree of MR but also the severity of MR consequences.

Ventilatory efficiency with exercise is an emerging contributor to reduced FC in cardiac diseases (24) that has not been evaluated in MR. Ventilatory inefficiency could not be linked to reduced FC in asymptomatic patients, but may contribute to FC limitations with advanced disease or heart failure (25).

**Clinical implications.** Mitral regurgitation has long had a benign reputation owing to its frequent asymptomatic presentation (2,3,8). However, the reality is more sobering, as even in asymptomatic patients, clinical outcome may be poor (3). It is unclear whether the risk attached to MR applies to all patients or whether high-risk and low-risk subsets can be defined to indicate surgical correction. The link between reduced FC and clinical outcome is essential in emphasizing the role of CPET in detecting such high-risk subsets. One in four to five patients displays markedly reduced FC unsuspected clinically and revealed only by CPET. In asymptomatic patients with organic MR, the indication of surgery is hotly debated (1). In asymptomatic patients, our study shows that FC reduction can be considerable with exercise level that may be only half of that expected for age. Markedly reduced FC (peak VO₂ < 84% of expected) is associated with a higher rate of events under medical management and should lead to prompt consideration of mitral valve surgery. Therefore, our data should lead to greater use of CPET in MR to detect objective FC limitation before patients develop heart failure, which is associated with poor postoperative outcome (26). Improvement of peak VO₂ after successful surgery remains uncertain (27,28), warranting future large prospective studies. Asymptomatic patients without markedly reduced FC display a notable event rate, and further studies are necessary to define risk stratification and benefit of surgery in these patients.

Cardiopulmonary exercise testing requires interpretation within clinical context of age, gender, and weight (29,30) and of extraneous limitations to define whether peak VO₂ reaches individually predicted maximum and whether FC reduction is MR-related. Peak VO₂ and exercise duration show significant correlation, but exercise time is insensitive in predicting FC (31) and may be less predictive of outcome. Therefore, CPET, if reliably feasible, should be, in our opinion, the preferred approach to exercise testing in MR.

**Study limitations.** Cardiopulmonary exercise testing was used to assess FC, but other exercise modalities may be used. Exertional changes in ventricular function (6,32) are of theoretical interest but raise quality control challenges, and detection of transient post-exercise MR and LV changes is tenuous. Conversely, CPET is standardized and directly applicable to clinical practice.

Diastolic function is difficult to analyze, particularly with MR (9,20). However, the E/E’ ratio is only weakly associated with RVol (r = 0.25) and shows stronger association to FC than RVol or ERO (Table 1). Univariate association of deceleration time to FC supports a diastolic dysfunction role in determining reduced FC in organic MR.

Complete coronary information is desirable, but coronary angiography has risks. Overt history of coronary disease, exertional angina, and exercise stopped by ischemia were excluded. In the 43 patients with subsequent coronary angiography, silent obstructive coronary disease tended to
be less frequent with (8%) than without (19%) reduced FC (p = 0.35). Thus, ischemia is unlikely to affect our results.

Reduced FC due to submaximal effort is denoted by low RER, as observed with extraneous component to FC limitations. Patients were strongly encouraged to exercise to exhaustion, as demonstrated by high RER. Whether such essential effort to reach peak performance explains the higher VO$_2$ obtained in the present versus limited previous data (27,28) will require further collaborative studies.

**Conclusions.** In asymptomatic patients with organic MR, the FC objectively and quantitatively assessed by CPET, while on average in the normal range, ranges widely from supranormal to markedly reduced. Approximately one of every four to five patients displays unexpected markedly reduced FC. Independent determinants of markedly reduced FC are impaired LV diastolic function, reduced forward stroke volume, and atrial fibrillation, and they exert a cumulative effect. Reduced FC is an independent predictor of subsequent high risk of clinical events and of surgical indication. Therefore, CPET is an important physiologic and clinical tool for management of patients with organic MR.

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Messika-Zeitoun et al. 2527

Functional Capacity in MR