**Mechanisms and Clinical Implications of Asymptomatic Mitral Regurgitation in Patients With Left Ventricular Dysfunction**

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**Background**  Functional mitral regurgitation (MR) is common in patients with chronic heart failure (CHF). During exercise, hemodynamic changes such as elevation of blood pressure and an increase in the left ventricular end-diastolic dimension may increase MR. Severity of CHF is reflected by exercise tolerance and, therefore, MR during exercise is supposed to indicate the severity of heart failure. The degree of MR increase and left ventricle (LV) shape was quantified during exercise in CHF patients and were compared with exercise tolerance.

**Methods and Results**  Twenty patients with CHF (mean age: 63 years) underwent dynamic cycle exercise at steady-state levels of 80% and 150% of the anaerobic threshold (AT). The MR jet area and left atrial (LA) area were measured during exercise and the ratio of MR/LA was calculated. The LV shape was assessed by calculating the ratio of the major to the minor axis. The MR/LA ratio increased during exercise (rest: 16.9±6.5%, 80% AT: 21.9±8.9%, 150% AT: 30.9±11.2%; p<0.01) and the LV shape became more spherical (rest: 1.34±0.10, 80% AT: 1.31±0.10, 150% AT: 1.23±0.11; p<0.05). There was a negative correlation between MR/LA ratio and the ratio of the major to the minor axis (−0.722, r<0.01).

**Conclusions**  MR during exercise increases as the severity of CHF increases. Functional MR is correlated with the shape of the LV. (Circ J 2008; 72: 115–119)

**Key Words:** Echocardiography; Exercise; Heart failure

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**Table 1 Clinical Characteristics and Baseline LV Function**

<table>
<thead>
<tr>
<th>Clinical data</th>
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<tbody>
<tr>
<td>Age (years)</td>
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<tr>
<td>MR grade at rest</td>
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<tr>
<td>LV function</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
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<tr>
<td>End-diastolic dimension (mm)</td>
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<tr>
<td>Cardiopulmonary exercise test</td>
</tr>
<tr>
<td>Anaerobic threshold (ml·min⁻¹·kg⁻¹)</td>
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<tr>
<td>Peak VO₂/HR (ml/beat)</td>
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<tr>
<td>VE/VCO₂ slope</td>
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<tr>
<td>Cause of heart failure</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
</tr>
<tr>
<td>Medication</td>
</tr>
<tr>
<td>β-blocker</td>
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<td>ACEI or ARB</td>
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</table>

Data are expressed as the mean±SD.

LV, left ventricular; MR, mitral regurgitation; mild MR, MR/left atrial (LA) <20%; moderate MR, MR/LA=20–40%; VO₂, oxygen consumption; VE, minute ventilation; VCO₂, CO₂ production; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
eter, papillary muscle function, and left atrial (LA) size, are implicated.\textsuperscript{13–16} Also, recent studies have suggested that remodeling of the LV is one of the main mechanisms of functional MR.\textsuperscript{17,18}

Here, we investigated LV deformation and studied how it relates to functional MR during exercise in patients with chronic heart failure (CHF).

**Methods**

**Study Population**

The study population comprised 20 consecutive male patients with heart failure (mean age: 63±8 years, range: 58–73 years) who met the following inclusion criteria: (1) symptoms of New York Heart Association class I or II; and (2) mild-to-moderate MR as determined by color Doppler echocardiography under resting conditions (Table 1). Patients with primary mitral valve disease, prosthetic mitral valves, evident inducible myocardial ischemia, chronic obstructive pulmonary disease, or other non-cardiac conditions that limit exercise capacity were excluded. In 6 patients, heart failure was caused by ischemic heart disease, non-ischemic dilated cardiomyopathy was the cause in 11 patients, and hypertensive heart disease with LV dilatation in 3 patients. Ischemic heart disease was defined by the presence of a documented previous myocardial infarction, or a previous luminal narrowing (≥50%) of a proximal major epicardial coronary artery that had undergone successful coronary intervention. Each patient was informed about the nature of the study, which was approved by the ethics committee of our institution.

**Exercise Testing**

All patients underwent a symptom-limited dynamic exercise test and 2 constant work rate studies, using a stationary cycle ergometer (Rehcor 500P; Lode, Groningen, The Netherlands). None of the patients experienced angina pectoris or syncope, or showed ischemic ST changes or severe arrhythmia during exercise testing. Oxygen consumption (\(\dot{V}O_2\)), CO\(_2\) production (\(\dot{V}CO_2\)), and minute ventilation (\(\dot{V}E\)) were continuously measured using a breath-by-breath gas analyzer (Minato AE300S; Minato Ikagaku, Osaka, Japan). The first test was used to determine the anaerobic threshold (AT), peak \(\dot{V}O_2\), peak \(\dot{V}O_2/HR\), and \(\dot{V}E/\dot{V}CO_2\) slope, as described elsewhere.\textsuperscript{19} AT was determined by the V-slope method\textsuperscript{20} and \(\dot{V}E/\dot{V}CO_2\) slope was determined by linear regression analysis.\textsuperscript{21} During this test, the initial workload was set at 0 W and the intensity of exercise was increased by 1 W every 6 s. All patients were encouraged to perform maximal exercise. To evaluate changes of MR during exercise, 2 steady-state exercise tests were performed 1 week later. The first test was performed at an intensity of 80% of AT and the second test was at 150% of AT. All tests were performed in the upright position. As the state of heart disease is stable and subjects performed no physical training during this period, there was no training effect at the second test.

**Echocardiographic Study**

Echocardiographic studies (SONOS 5500; Philips Medical Systems, Andover, MA, USA) were performed 2 min after the beginning of exercise. The MR jet area and the LA area at the time of the mid-systolic phase (Fig 1) were measured by the area trace method on a 4-chamber view and their ratio (MR/LA) was calculated as described elsewhere.\textsuperscript{22} The degree of MR is determined by the MR/LA ratio, whereby <20% is mild, 20–40% is moderate, and >40% is severe. The MR/LA ratio at rest and during exercise was obtained from the same view.

LV shape was calculated using the ratio of the major to the minor axis at end-diastole on the 4-chamber view.\textsuperscript{23} In the present study, the ratio of the major to the minor axis of the end-diastole LV ventricle is defined as the sphericity index.

**Statistical Analysis**

All data are expressed as the mean±SD. Values of p<0.05 were considered statistically significant. Correlation coefficients were calculated by regression analysis. One-way analysis of variance was used to determine the statistical significance and Bonferroni analysis was used for post-hoc analysis.
Results

Patient Characteristics and Exercise Tolerance

All patients performed cardiopulmonary exercise testing until exhaustion. No patient showed myocardial ischemia during the tests. As shown in Table 1, their exercise tolerance was moderately impaired. Although they varied from Weber class A to D, most of the subjects were class C. Peak \( V\cdotO_2/HR \), which reflects the stroke volume during exercise, was also moderately impaired. Mean body height and age in the present study were 170 cm and 63 years, and the average value of peak \( V\cdotO_2/HR \) was approximately 12 ml/beat.24 Therefore, these patients’ cardiac function during exercise was about 60% of normal.

Echocardiographic Changes During Exercise

As shown in Table 2, the ratio of MR jet area to LA area increased significantly during exercise at 80% AT (rest: 16.9±6.5%, 80% AT: 21.9±8.9%; p<0.05) and increased further during exercise at 150% AT (30.9±11.2%; p<0.01). To determine the effect of morphological factors on the increase of MR during exercise, we quantified the LV end-diastolic dimension and end-diastolic sphericity index. The LV end-diastolic dimension remained constant at 80% AT; however, it increased at an exercise intensity of 150% AT (Table 2). The end-diastolic sphericity index showed a similar result, remaining constant at 80% AT and decreasing at 150% AT (Table 2).

The degree of exercise-induced MR change (\( \Delta MR \)) correlated negatively (\( r=-0.500, p<0.01 \)) with peak \( V\cdotO_2/HR \) (Fig 2). This result suggests that, as MR worsens, the increase of stroke volume is attenuated. \( \Delta MR \) correlated positively with \( VE/VCO_2 \) slope, although the correlation was small (\( r=0.242 \)). Exercise-induced changes in MR showed no correlation with ejection fraction or AT.

The exercise-induced changes of MR severity was found to correlate with exercise-induced changes of end-diastolic sphericity index (\( r=-0.722, p<0.01 \); Fig 3).

Discussion

In the present study, we found the following: (1) The severity of functional MR increased in almost all patients during exercise, both at the work intensity of the AT and at an intensity greater than the AT. The increase in MR was greater when the exercise intensity was greater. (2) The exercise-induced changes in the severity of functional MR affected exercise capacity. (3) The exercise-induced changes in the severity of functional MR were related to the sphericity of the LV.

We have reported that functional MR increases as exercise intensity increases. Although previous studies have also described the relationship between MR and exercise, almost all used only single work rate exercise. The present study is the first to investigate the relationship between exercise intensity and functional MR severity.

The present study suggests that functional MR correlated negatively with peak \( V\cdotO_2/HR \). Considering that peak \( V\cdotO_2/HR \) is determined by the peak stroke volume, an impaired increase of stroke volume due to increased MR may be the main reason for the reduction in peak \( V\cdotO_2/HR \) and for the negative correlation between functional MR and peak \( V\cdotO_2/HR \).

There was a weak correlation between functional MR and \( VE/VCO_2 \) slope. Although the \( VE/VCO_2 \) slope partly depends on pulmonary blood flow and cardiac output, it mainly depends on physiological dead space, which in turn, is determined only by cardiac output. Therefore, this confirmed the apparently weak correlation between functional MR and \( VE/VCO_2 \) slope.
There was no correlation between MR and LV ejection fraction. The LV ejection fraction is calculated from LV diastolic and systolic cross-sectional area at rest (Simpson’s method). This means that the ejection fraction does not equal the stroke volume because the stroke volume can be preserved when the LV is enlarged. Furthermore, it has been reported that the ejection fraction is not correlated with exercise tolerance. Therefore, ejection fraction may not be a predictor of worsening MR.

**Mechanisms of Worsening Functional MR During Exercise**

Although functional MR is frequently observed in patients with LV dysfunction, the mechanisms that determine its presence and severity are incompletely understood. Previous studies have suggested that several factors, including LV size, extent of emptying, mitral annular diameter, papillary muscle function, and LA size, are implicated; although some cases do not have functional MR with dilatation of the mitral annular diameter alone. Other studies have suggested that papillary muscle dysfunction worsens tethering of the mitral valve even though recent studies suggest that papillary muscle dysfunction because of ischemic heart disease decreases tethering of the mitral valve. The present study suggests that worsening of functional MR correlated only with the shape of the LV; that is, remodeling of the LV seemed to be the main mechanism of functional MR.

It is possible that the increase in the systolic dimension caused worsening of MR. Lancellotti and colleagues reported that, as the end-systolic volume increases, the effective regurgitant orifice (ERO) increases. However, in their paper, the correlation coefficient was greater between the ERO and the end-diastolic volume than the end-systolic volume. Therefore, it is assumed that the impact of the systolic dimension is not great.

There is one report of a decrease in the ERO during exercise in a few subjects. The present study’s results show that no subject exhibited improved MR during exercise. The discrepancy is due to differences in the underlying disease. In the study by Lancellotti et al., a decrease in the ERO during exercise occurred mainly in patients with inferior myocardial infarction. In the present study, there was no patient with inferior myocardial infarction and, so, no patient showed an improvement in MR during exercise.

**Clinical Implications**

The exercise-induced changes in the severity of functional MR correlated with peak VO₂/HR. Peak VO₂/HR reflects the stroke volume at peak exercise. The results of the present study show that worsening of functional MR during exercise contributes to the limitation of cardiac function during exercise, even in patients who exhibit only mild to moderate MR at baseline. Impaired cardiac output during exercise might contribute to the worsening of the VE/VO₂ slope, despite the weak correlation coefficient. In contrast, functional MR worsens as peak VO₂ decreases. Exercise tolerance is determined by many factors, cardiac output being one of the most important, but skeletal muscle, endothelial cell, and autonomic nervous function are also involved. Therefore, although MR worsened with exercise, and decreased the stroke volume, it did not directly regulate exercise tolerance in this situation. Worsening of functional MR is observed during exercise of a lower intensity than the AT. The AT represents moderate intensity and 50–60% of the peak workload, and is widely used for anaerobic exercise in patients with heart disease. However, from the present study, it was observed that MR worsens at this intensity although exercise tolerance is not affected. Therefore, care must be taken when prescribing exercise therapy, as MR may be increased.

The results suggest that, as functional MR reduces exercise capacity, treatment of functional MR by diminishing remodeling of the LV might improve LV function during exercise. Pharmaceutical intervention such as ß-blockers, angiotensin-converting enzyme inhibitors (ACEI) or spironolactone would seem to be important, but in the subjects of the present study functional MR remained despite taking an ACEI and/or a ß-blocker. This means that pharmaceutical intervention is not sufficient to prevent LV remodeling. Surgical intervention is the next option for the treatment of functional MR when LV function worsens during exercise despite medical treatment. Mitral valve replacement can completely prevent worsening of functional MR; however, it is important to preserve the continuation of the mitral annulus, leaflet, chordae tendineae, and papillary muscle. As thrombosis and the side effects of warfarin are serious problems in mitral valve replacement, mitral valvoplasty is better. However, annuloplasty can treat coaptation of the mitral valve leaflet but cannot treat tethering of the mitral valve. Indeed, annuloplasty worsens tethering of the posterior leaflet and is the cause of postoperative MR. New surgical approaches to improve tethering are under development and are urgently needed.

**Study Limitations**

The present study had only 20 subjects. The color Doppler appearance of MR jets is influenced by several parameters, such as gain setting, packet size, aliasing velocity, and frame rate. Also, despite good agreement between the MR/LA ratio and MR severity under resting conditions, it has been suggested that this parameter may be less accurate during exercise. In addition, eccentric jets may vary according to the imaging plate, leading to underestimation of MR severity.

**Conclusions**

The data suggest that exercise-induced changes in the severity of functional MR may contribute to impaired exercise capacity in patients with CHF. Although the exercise training was performed at an intensity of the AT or lower, exaggeration of functional MR sometimes occurs; therefore, it must be evaluated carefully.

The data also suggest that functional MR correlated only with the shape of the LV; that is, remodeling of the LV seemed to be the main mechanism of functional MR.

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**References**


