Functional Mitral Regurgitation During Exercise in Patients With Heart Failure

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Background  Functional mitral regurgitation (MR) is common in patients with chronic heart failure (CHF) and left ventricular dysfunction. The severity of CHF is expressed in terms of exercise tolerance, so MR during exercise would affect the severity of heart failure. However, it is not well known how much MR increases during exercise, or if it is related with severity of heart failure.

Methods and Results  Seventeen subjects underwent dynamic cycle exercise at steady-state levels of 80% and 150% of anaerobic threshold (AT). During each exercise level, the MR jet and left atrial (LA) area were measured, and the degree of MR was expressed as the ratio (MR/LA). The MR/LA increased slightly at 80% AT (rest: 15.5±7.8%, 80% AT: 21.7±9.3%, p<0.05). It increased more at 150% AT (29.2±11.6%, p<0.01). The MR/LA at both 80% and 150% AT weakly correlated with peak oxygen consumption/heart rate (r=-0.509). They showed a weakly positive correlation with the ventilatory equivalent/CO2 production slope (r=0.340).

Conclusions  MR during exercise increases as stroke volume worsens during exercise, so evaluation of MR during exercise is important in the management of patients with CHF. (Circ J 2006; 70: 1563–1567)

Key Words: Cardiopulmonary exercise testing; Echocardiography; Functional mitral regurgitation

Methods

Study Population

The study population consisted of 17 consecutive men with heart failure (mean age: 64±8 years, range: 58–73 years) who met the following inclusion criteria: (1) New York Heart Association class I or II heart failure, and (2) mild to moderate degree of MR on color Doppler echocardiography while resting (Table 1). Patients with primary mitral valve disease, prosthetic mitral valve or evidence of inducible myocardial ischemia, chronic obstructive pulmonary disease or other non-cardiac conditions that limit

Table 1 Clinical Characteristics and Baseline Left Ventricular Function

| Age (years) | 64±8 |
| MR grade at rest | Mild: 9, moderate: 8 |
| Left ventricular function | |
| Ejection fraction (%) | 35±15 |
| End-diastolic dimension (mm) | 57±9 |
| Cardiopulmonary exercise test | |
| Anaerobic threshold (ml·min⁻¹·kg⁻¹) | 10.0±4.0 (5.1–15.1) |
| Peak VO2/HR (ml/beat) | 7.5±2.9 (3.0–13.3) |
| VE/VO2 slope | 38.0±8.0 (26.1–47.7) |
| Cause of heart failure | |
| Ischemic heart disease | 5 |
| Dilated cardiomyopathy | 8 |
| Hypertensive heart disease | 4 |
| Medication | |
| ß-blocker | 5 |
| ACE inhibitor or ARB | 11 |

Data are mean ± SD. Mild MR, mitral regurgitation (MR)/left atrial (LA) <20%; moderate MR, 20–40% of MR/LA; VO2/HR, oxygen consumption/heart rate; VE/VO2, ventilatory equivalent/CO2 production; ACE, angiotensin converting enzyme inhibitor; ARB, angio-tensin receptor blocker.
exercise capacity were not included. The causes of heart failure were ischemic heart disease in 5 patients, non-ischemic dilated cardiomyopathy in 8 patients, and hypertensive heart disease with left ventricular (LV) dilatation in the remaining 4 patients. Ischemic heart disease was defined by the presence of a documented previous myocardial infarction, or previously had >50% angiographic luminal narrowing of a proximal major epicardial coronary artery, which was successfully relieved by coronary intervention. Each subject was informed of the investigative nature of the study, which was approved by the institutional ethics committee.

**Exercise Testing**

All patients performed a symptom-limited dynamic bicycle exercise test, and 2 constant work rate studies using a stationary cycle ergometer (Rocor 500P, Load, Delft, The Netherlands). None of the patients experienced angina pectoris, syncope, or showed ischemic ST changes or severe arrhythmias during exercise testing. Oxygen consumption (VO$_2$), CO$_2$ production (VCO$_2$), and ventilatory equivalent (VE) were measured continuously using a breath-by-breath gas analyzer (Minato AE300S, Minato Ikagaku, Osaka, Japan). The first test was used for determining the anaerobic threshold (AT), peak VO$_2$, peak VO$_2$/heart rate (HR), and VE/VCO$_2$ slope, as previously reported. AT was determined by the V-slope method, and the VE/VCO$_2$ slope was determined by linear regression analysis. During this test, the initial workload was set at 0 W, and the exercise intensity was increased by 1 W every 6 s. In each case, patients were encouraged to perform maximal exercise.

To evaluate the change in MR during exercise, 2 exercise tests were performed 1 week later. The first test was performed at a steady-state level of 80% of AT and the second test was performed at 150% of AT. All tests were performed while upright. Because the heart disease was stable and subjects performed no physical training during this period, there was no training effect at the 2nd test.

**Echocardiography**

Echocardiographic studies (SONOS 5500, Philips Medical Systems, Best, Netherlands) were performed 2 min after beginning exercise. The MR jet area and left atrial (LA) area at end-systole (Fig 1) were measured by the area trace method on the 4-chamber view and their ratio (MR/LA) was calculated as previously reported. The degree of MR was determined by MR/LA: <20% is mild, 20–40% is moderate, and >40% is severe. The MR/LA at rest and during exercise were obtained from the same view.

LV dimensions were measured on the 4-chamber view at end-diastole and the LV ejection fraction (LVEF) was calculated by Simpson’s method.

**Statistical Analysis**

All data are expressed as the mean ± standard deviation (SD). A value of p<0.05 was considered statistically significant. Correlation coefficients were calculated using the regression analysis method. One-way analysis of variance was used to determine the statistical significance and the Bonferoni test was used for posthoc analysis.

**Results**

**Exercise Tolerance**

All patients performed cardiopulmonary exercise testing until exhaustion, but none showed evidence of myocardial ischemia during exercise. As shown in Table 2, exercise tolerance varied from Weber class A to D, most of the patients were classified into class C. The peak oxygen pulse (VO$_2$/HR), which reflects the SV at peak exercise, was also moderately impaired. Because the average value of peak VO$_2$/HR for a 170-cm tall, 64-year-old man is approximately 12 ml/beat, these patients’ cardiac function during exercise was about 60% of the normal value.

**Echocardiographic Changes During Exercise**

As shown in Table 2, MR/LA increased at 80% of the AT as compared with the resting value (rest: 15.5±7.8%, 80% AT: 21.7±9.3%, p<0.05) and it further increased at 150% of the AT (150% AT, 29.2±11.6%, p<0.01). The LV dimensions were measured on the 4-chamber view at end-diastole and the LV ejection fraction (LVEF) was calculated by Simpson’s method.
end-diastolic dimension stayed constant until 80% AT, but increased at 150% AT, which was significantly higher (p<0.05) than the resting value.

The exercise-induced change in MR was inversely correlated (r=-0.509) with peak VO2/HR (Fig 2), which suggests that as MR worsens the increase in SV attenuates. The change in MR correlated positively with the VE/VCO2 slope, although the correlation was weak (r=0.3401, Fig 3).

Exercise-induced changes in MR showed no correlation with the resting LVEF (Fig 4).

Exercise tolerance, represented by the AT, showed no correlation with the degree of worsening of MR during exercise (Fig 5).

**Discussion**

The 2 main findings of this study are as follows.

1. The severity of functional MR increased in every patient with exercise, both at a level near the AT and at an intensity greater than the AT. The degree of exaggeration of MR was greater when the exercise intensity was greater.

2. The exercise-induced changes in the severity of functional MR correlated with SV during exercise.

**Mechanisms of Exercise-Induced MR**

Although functional MR is frequently observed in patients with LV dysfunction, the mechanisms responsible for its presence and severity are incompletely understood. Several factors, including LV size, extent of emptying, mitral annular diameter, papillary muscle function and LA size, have been implicated. At an exercise intensity of 80% AT, MR was found to increase, although the LV end-diastolic dimension did not increase. Thus, in this situation, LV dilation does not account for the worsening of MR. Therefore, the reason why MR worsens requires more investigation. There is a possibility that the increase in the systolic dimension causes worsening of MR. It is reported that as the end-systolic volume increases, the effective regurgitant orifice (ERO) increases. However, in this paper, the correlation coefficient was greater between the ERO and the end-diastolic volume than with the end-systolic volume. Therefore, it is assumed that the impact of the systolic dimension is not as great when the diastolic dimension fails to affect the increasing MR.
At an intensity of 150% AT, the LV dimension increased to a greater extent. Some studies suggest that in heart disease papillary muscle dysfunction causes tethering of the mitral valve as a result of remodeling of LV, and that this is the main mechanism of functional MR. In our study, we used LV dilatation as a measure of the degree of LV remodeling, which means that, at an exercise level of 150% AT, an increase in the LV dimension seems to be one of the mechanisms responsible for worsening of tethering and thus worsening functional MR.

There was no correlation between the worsening of MR and the LVEF. LVEF is calculated from LV diastolic and systolic ventricular cross-sectional areas at rest, the so-called Simpson’s method. This means that LVEF does not equal the EF, because the SV can be preserved when the left ventricle is enlarged. Furthermore, it has been reported that the EF does not correlate with exercise tolerance. In the present study, there was no correlation between AT and LVEF (Fig 6); that is, the EF does not represent SV, especially during exercise. Therefore, in the present study, the LVEF did not have any correlation with MR during exercise.

Clinical Implications

Exercise-induced changes in the severity of functional MR correlated with peak VO₂/HR, which reflects the SV at peak exercise. The results of our study indicate that worsening of functional MR during exercise contributes to the limitation of cardiac function during exercise. Specifically, in subjects with worsening of MR during exercise, in order to maintain a sufficient SV, cardiac work must be enhanced, which may lead to greater cardiac damage and worsening of the patient’s prognosis.

The exercise-induced changes in the severity of functional MR showed only a weak correlation with the VE/VCO₂ slope, which is mainly determined by the degree of ventilation–perfusion, and in the clinical setting this is determined not only by SV but also by respiratory function and muscle function. Because exercise-induced MR may be reflected by SV during exercise, the correlation was weak in the present study.

The worsening of MR did not induce a deterioration of the AT, which is determined by many factors. CO is, of course, 1 of the important determinant factors, but skeletal muscle function, endothelial cell function, as well as autonomic nervous function, affect exercise tolerance. Therefore, although MR worsened with exercise, and SV did not increase sufficiently, it did not directly affect exercise tolerance.

Worsening of functional MR was observed during exercise at an intensity lower than the AT. The exercise intensity at the AT is moderate and 50–60% of the peak work load. This intensity is widely used for exercise training for patients with heart disease in cardiac rehabilitation programs. However, we demonstrated that MR worsens at this intensity, although exercise tolerance is unaffected. Therefore, one must be careful when prescribing exercise therapy to monitor whether MR becomes greater or not during exercise. Also, treatment of functional MR, such as angiotensin-converting enzyme inhibitors, β-blockers and spironolactone, to improve remodeling is important even if the functional MR is not severe.

There is 1 report describing a few subjects whose ERO of MR decreased during exercise. None of the present subjects showed an improved degree of MR. The discrepancy is related to differences in the baseline diseases. The previous study reported that a decrease in the ERO during exercise occurs mainly in patients with inferior myocardial infarction, which none of the present patients had, so in the present study there was no improvement in MR by exercise.

Study Limitations

This study included only 17 patients. Furthermore, the color Doppler appearance of the MR jet is influenced by several factors, such as the gain settings, packet size, aliasing velocities, and frame rate. Also, despite good agreement between the MR/LA area and MR severity under resting conditions, it has been suggested that this parameter may be less accurate during exercise. In addition, for eccentric jets, the area may vary with the imaging plane, leading to underestimation of the MR severity.

Conclusion

Our data suggest that exercise-induced changes in the severity of functional MR may contribute to limited SV in patients with heart failure. Even though exercise training is performed at the intensity of the AT, exaggeration of functional MR must be considered and evaluated carefully.

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References

and diastolic filling in idiopathic or ischemia dilated cardiomyopathy.


