

# Changes in mitral regurgitation and left ventricular geometry during exercise affect exercise capacity in patients with systolic heart failure

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## Aims

Exercise may dramatically change the extent of functional mitral regurgitation (MR) and left ventricular (LV) geometry in patients with chronic heart failure (CHF). We hypothesized that dynamic changes in MR and LV geometry would affect exercise capacity.

## Methods and results

This study included 30 CHF patients with functional MR who underwent symptom-limited bicycle exercise stress echocardiography and cardiopulmonary exercise testing for quantitative assessment of MR (effective regurgitant orifice; ERO), and pulmonary artery systolic pressure (PASP). LV sphericity index was obtained from real-time three-dimensional echocardiograms. The patients were stratified into exercised-induced MR (EMR;  $n = 10$ , an increase in ERO by  $\geq 13 \text{ mm}^2$ ) or non-EMR (NEMR;  $n = 20$ , an increase in ERO by  $< 13 \text{ mm}^2$ ) group. At rest, no differences in LV volume and function, ERO, and PASP were found between the two groups. At peak exercise, PASP and sphericity index were significantly greater (all  $P < 0.01$ ) in the EMR group. The EMR group revealed lower peak oxygen uptake (peak  $\text{VO}_2$ ;  $P = 0.018$ ) and greater minute ventilation/carbon dioxide production slope ( $\text{VE}/\text{VCO}_2$  slope;  $P = 0.042$ ) than the NEMR group. Peak  $\text{VO}_2$  negatively correlated with changes in ERO ( $r = -0.628$ ) and LV sphericity index ( $r = -0.437$ ); meanwhile,  $\text{VE}/\text{VCO}_2$  slope was well correlated with these changes ( $r = 0.414$  and  $0.364$ , respectively). A multivariate analysis identified that the change in ERO was the strongest predictor of peak  $\text{VO}_2$  ( $P = 0.001$ ).

## Conclusion

Dynamic changes in MR and LV geometry contributed to the limitation of exercise capacity in patients with CHF.

## Keywords

Functional mitral regurgitation • Exercise • Echocardiography • Three-dimensional echocardiography • Sphericity

## Introduction

It has been investigated the contribution of the heart and peripheral muscle to determination of exercise capacity in patients with chronic heart failure (CHF).<sup>1,2</sup> Exercise intolerance is partly related to maximal pumping capacity, such as maximal stroke volume and cardiac output. Many patients with left ventricular

(LV) systolic dysfunction have functional mitral regurgitation (MR) which adversely influences ventricular function and prognosis in patients with CHF.<sup>3–6</sup> Exercise may dramatically change the presence and extent of functional MR; an increase in functional MR during exercise independently affects outcomes in such patients.<sup>7</sup> Dynamic changes in the severity of MR may compromise a normal increase in forward stroke volume and reduce maximal

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cardiac output.<sup>8</sup> Dynamic variation in MR orifice area is probably related to dynamic changes in mitral valve configuration at both ends of tethered leaflets, dynamic LV dyssynchrony, and changes in LV shape during exercise.<sup>9</sup> It has not been fully elucidated the contribution of changes in LV geometry and the severity of MR to stroke volume adaptation during exercise. Nowadays, three-dimensional echocardiography provides better evaluation of LV geometry and shape.<sup>9,10</sup> No clinical studies have assessed the effects of exercise on three-dimensional LV geometry in systolic heart failure. Here, we investigated our hypothesis whether exercise-induced changes in functional MR and LV geometry might affect exercise capacity in patients with CHF.

## Methods

### Subjects

This prospective study included 36 clinically stable CHF patients with LV systolic dysfunction (ejection fraction <45%). Of these, one patient with primary mitral valve disease and five patients with poor quality images were excluded from the study. Of the remaining 30 patients, 10 patients were in New York Heart Association functional class I, 19 in class II, and 1 in class III. All patients were clinically stable; they had no changes in the prescribed medications within the last 3 months before enrolment. Ischaemic disease was determined when a patient had either previous myocardial infarction (>6 months) or significant coronary artery disease (>75% stenosis in one of the major epicardial coronary arteries); 12 patients had ischaemic heart disease and 18 had idiopathic dilated cardiomyopathy. Nineteen patients had a narrow QRS complex (<120 ms) and 11 had a wide QRS complex (>120 ms). This study also included 15 age-matched healthy controls with no specific medical history or organic cardiovascular disease. This study was performed in accordance with the ethical principles set forth in the Declaration of Helsinki. The study protocol was approved by the St Marianna University School of Medicine Institutional Committee on Human Research (No. 1288). Written informed consent was obtained from all participants before enrolment.

### Exercise testing

All participants underwent a symptom-limited graded bicycle exercise test using a StrengthErgo240™ (SE240; Mitsubishi Electric Corporation, Tokyo, Japan) in a semi-supine position on a tilting exercise table to obtain two- and three-dimensional echocardiograms at baseline and at peak exercise. After an initial 3 min workload at 10 W, the intensity was increased in 5 W every minute. All echocardiographic images were obtained at rest and within 3 min before the peak exercise and digitally stored. Single-lead electrocardiograms and blood pressure were recorded every minute. The participants were asked to declare their perceived exertions of the chest and legs separately according to the 6–20 category scale during the test.<sup>11</sup> The criteria to halt the test were chest pain, severe dyspnoea, severe fatigue, sustained hypotension, sustained ventricular tachycardia, short runs of three or more ventricular premature contractions, pallor, or dizziness.

### Echocardiography

Data were acquired during a breath hold at the end of expiration. The averages of three consecutive beats at rest and at peak exercise were used in each parameter. Data were subsequently transferred to an offline computer for the analysis using commercially available software (3DQ ADV, QLAB, Version 4.2, Philips Medical Systems).

### Two-dimensional echocardiography

An iE33 (Philips, Andover, MA, USA) with a 2.5–5 MHz imaging probe was used for two-dimensional echocardiography. An exercise-induced change on echocardiogram was defined as an absolute difference between the values at peak exercise and at rest ( $\Delta$  value). Functional MR was quantified according to the proximal isovelocity surface area method. Effective regurgitant orifice (ERO) and regurgitant volume were evaluated. The patients were stratified into exercise-induced MR (EMR;  $\Delta$ rest – peak exercise ERO  $\leq$  13 mm<sup>2</sup>) or non-EMR (NEMR;  $\Delta$ rest – peak exercise ERO < 13 mm<sup>2</sup>) group based on the cut-off point adopted in the previous study.<sup>7</sup> LV end-diastolic pressure elevation during exercise was identified by the ratio of the early diastolic transmitral velocity to the early diastolic tissue velocity (*E/E'*).<sup>12,13</sup> Pulmonary artery systolic pressure (PASP) during exercise was estimated in the presence of tricuspid regurgitation. PASP was calculated as follows: PASP = 4(velocity)<sup>2</sup> + 5 mm/Hg, where velocity presents the maximum velocity of tricuspid regurgitation jet in metre per second and 5 mm/Hg in the equation was the estimated right atrial pressure.<sup>14</sup>

### Three-dimensional echocardiography

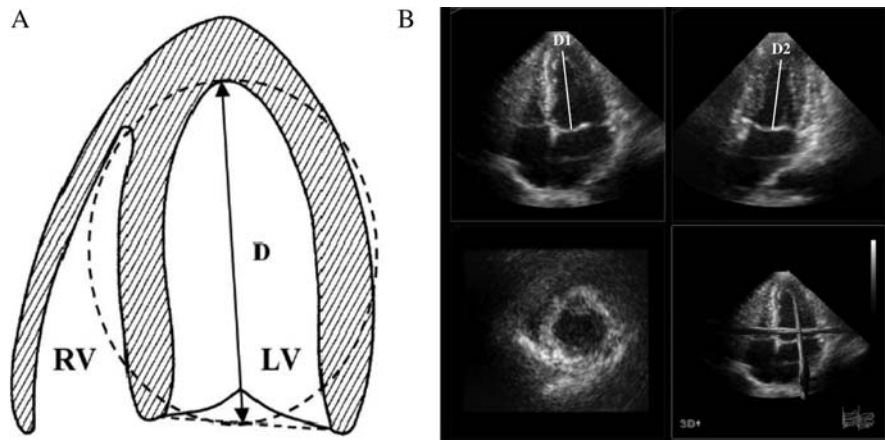
A harmonic real-time three-dimensional echocardiography with a matrix-array transducer (X3-1, 1.9/3.8 MHz) depicted the entire LV cavity within the pyramidal scan volume. A real-time three-dimensional data set equipped with a wide-angle acquisition (93 × 80°) mode could obtain four wedge-shaped subvolumes (93 × 20° each) during four consecutive cardiac cycles. Global LV volume, end-systolic volume index, end-diastolic volume index, and global ejection fraction were calculated. The three-dimensional sphericity index was calculated from the end-systolic volume divided by the volume of a sphere with a diameter corresponding to the major end-systolic LV long axis. The LV long axis was obtained as the longest distance between the centre of the mitral annular and the endocardial apex (Figure 1).<sup>10</sup>

### Cardiopulmonary exercise testing

All participants underwent cardiopulmonary exercise testing using a MAT-2500 treadmill (Fukuda Denshi Co., Tokyo, Japan) within 2 weeks before/after exercise echocardiography. After an initial 3 min rest on the treadmill and 3 min warm-up (speed 1.6 km/h; grade 0%), the patients underwent the testing at a gradually increasing intensity (load increased at 1 min intervals). Standard 12-lead electrocardiography (ML-5000, Fukuda Denshi Co.) was continuously monitored; the heart rate was measured with R–R interval. Systolic blood pressure was measured at 1 min intervals. An expired gas analysis was performed throughout the test on a breath-by-breath basis with an AE-280 cart (Minato Medical Science, Osaka, Japan). Peak oxygen uptake (peak VO<sub>2</sub>) and the minute ventilation/carbon dioxide production (VE/VCO<sub>2</sub>) slope were measured. An apparent levelling off of oxygen uptake (an oxygen uptake plateau in spite of increasing exercise intensity) was used as a sign to terminate the exercise testing.

### Statistical analysis

Data are expressed as mean  $\pm$  SD. Mean values of parameter between measurements at rest and during exercise were compared using Student's *t*-test; correlations between two parameters were assessed by a univariate linear regression analysis. Statistical significance was set at *P* < 0.05. A linear regression analysis determined cofactors associated with changes in MR during exercise; a stepwise multiple linear regression analysis was also performed. All continuous variables were included in the multivariable model. Statistical analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA).



**Figure 1** (A) Three-dimensional sphericity index. This figure shows the left ventricular cavity, where  $D$  is the left ventricular end-systolic major long axis. The formula:  $4/3 \times \pi \times (D/2)^3$ . The spherical volumes in millilitres can be calculated, where  $D$  is the diameter (cm). The three-dimensional sphericity index is calculated by  $ESV / \{4/3 \times \pi \times (D/2)^3\}$ , a modification of the equation used in Mannaerts et al.<sup>10</sup> (B) Four-tile image display of the dynamic three-dimensional data set with two near perpendicular long axes (top left and right), a short axis (bottom left), and a cubical display with the corresponding cutplanes (bottom right). The measurements of  $D$  are shown. The left ventricular long axis ( $D1$  or  $D2$ ) was obtained from the three-dimensional echocardiographic data set as the longest distance between the centre of the mitral annulus and the endocardial apex. The longest  $D$ s were used in the four-chamber view ( $D1$ ) and two-chamber view ( $D2$ ).

**Table 1** Baseline characteristics

	EMR	NEMR	P-value
Age	60.8 ± 9.5	55.3 ± 12.6	0.333
Sex			
Male	8	18	0.081
Female	2	2	0.072
NYHA class	2.1 ± 0.3	1.5 ± 0.5	0.002
BNP (pg/mL)	229.2 ± 243.9	220.6 ± 179.8	0.928
QRS (ms)	102.3 ± 52.3	126.0 ± 34.1	0.232
Peak blood pressure (mmHg)	125.6 ± 20.7	150.2 ± 24.3	0.027
Peak heart rate (bpm)	112.3 ± 20.4	116.9 ± 23.6	0.373
ESE duration (min)	8.9 ± 3.1	13.7 ± 3.9	0.008
ESE peak load (W)	41.6 ± 9.4	64.5 ± 19.7	0.008
Aetiology			
DCM	7	11	0.104
PMI	3	9	0.126
Medication			
ACEI	6	12	0.352
ARB	3	7	0.736
β-Blocker	7	13	0.535
Diuretics	7	15	0.766

EMR, exercise-induced mitral regurgitation; NEMR, non-EMR; NYHA, New York Heart Association; BNP, brain natriuretic peptide; DCM, dilated cardiomyopathy; PMI, previous myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ESE, exercise echocardiography. P-value, EMR vs. NEMR.

Inter- and intra-observer variabilities for measurements of ERO,  $E/E'$ , and sphericity index were obtained by analysis of 10 random images by two independent blinded observers who analysed the

images twice on different days. The limits of agreement were calculated by the Bland–Altman analysis.

## Results

### Baseline and exercise characteristics

Baseline characteristics are summarized in Table 1. None of them experienced chest pain or manifested ST segment depression or had new or worsening wall motion abnormality during the exercise testing.

Exercise remarkably increased the amount of MR in 10 patients (33%) in the EMR group. During the test, systolic blood pressure and heart rate significantly increased in all participants ( $P < 0.001$ ), although the increment was greater in the controls and the NEMR group. The EMR group demonstrated shorter exercise duration ( $P = 0.008$ ) and lower peak load ( $P = 0.008$ ) than the controls and the NEMR group. We found no differences in systolic blood pressure, brain natriuretic peptide, aetiology, and prescribed medications between the EMR and NEMR groups.

### Exercise-induced changes in left ventricular shape

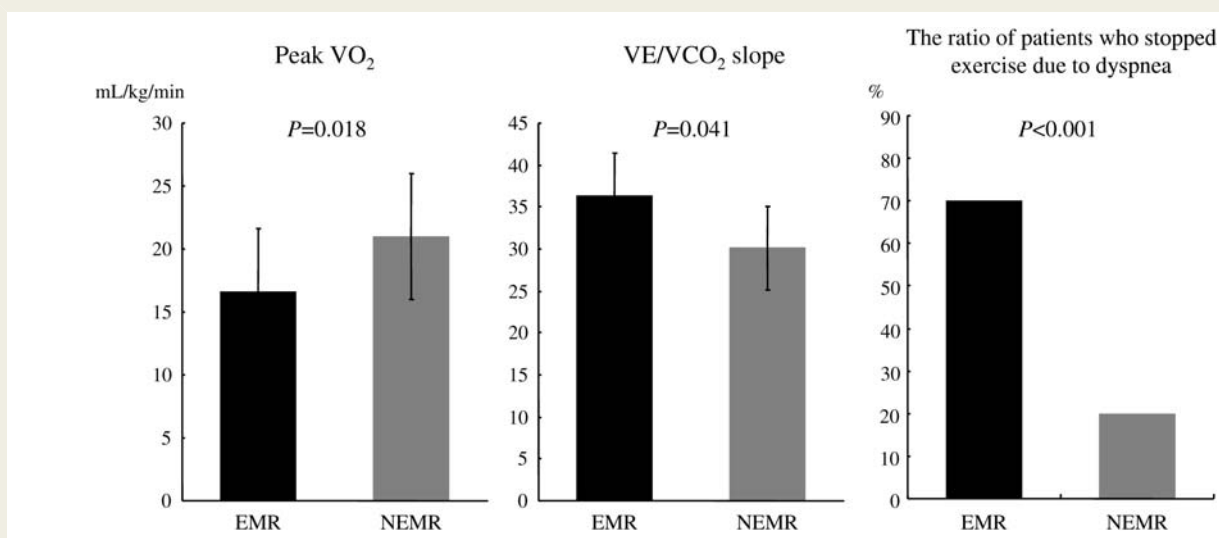
During exercise, the changes in the end-systolic volume index, end-diastolic volume index, and ejection fraction were similar in the EMR and NEMR groups (Table 2). The LV sphericity index significantly increased in the EMR group ( $P = 0.026$ ), whereas it remained unchanged in the NEMR ( $P = 0.459$ ) and control ( $P = 0.526$ ) groups. At rest, no differences in ERO,  $E/E'$ , PASP, and mitral deformation parameters (coaptation distance and tenting area) were found between the two groups. The EMR group revealed significantly greater  $E/E'$ , PASP, and mitral deformation parameters (all  $P < 0.01$ ) at peak exercise.

**Table 2** Echocardiographic changes during exercise

	Rest			Exercise		
	Control	EMR	NEMR	Control	EMR	NEMR
EDVI (mL/m <sup>2</sup> )	47.8 ± 7.3	106.71 ± 46.6	94.2 ± 28.0	52.5 ± 8.8 <sup>†</sup>	121.4 ± 33.1	100.3 ± 25.8
ESVI (mL/m <sup>2</sup> )	18.2 ± 2.9	69.4 ± 41.7	56.1 ± 24.0	16.0 ± 3.3 <sup>†</sup>	81.2 ± 29.8	59.7 ± 24.9
EF (%)	61.4 ± 5.8	34.5 ± 10.0	40.2 ± 10.7	69.4 ± 3.2 <sup>†</sup>	36.9 ± 9.8 <sup>†</sup>	41.3 ± 10.5
SVI (mL/m <sup>2</sup> )	30.1 ± 6.8	36.8 ± 13.7	34.2 ± 11.6	36.7 ± 7.1 <sup>†</sup>	38.2 ± 14.6	38.6 ± 17.7
Coaptation distance (mm)	7.0 ± 1.0	14.4 ± 2.8	12.3 ± 3.4	5.9 ± 2.1	18.1 ± 2.9 <sup>*†</sup>	12.3 ± 3.2
Annular diameter (mm)	26.1 ± 2.2	34.1 ± 3.4	35.0 ± 6.4	26.1 ± 1.7	39.3 ± 5.3 <sup>*†</sup>	35.0 ± 5.1
Tenting area (cm <sup>2</sup> )	1.0 ± 0.3	2.6 ± 0.5	2.2 ± 0.7	0.9 ± 0.4	3.6 ± 0.8 <sup>*†</sup>	2.2 ± 0.7
Sphericity index	0.23 ± 0.04	0.33 ± 0.10*	0.25 ± 0.09	0.23 ± 0.04	0.41 ± 0.09 <sup>*†</sup>	0.26 ± 0.08
RV (mL)	–	23.7 ± 6.8	16.7 ± 111.7	–	51.3 ± 15.2 <sup>*†</sup>	17.7 ± 9.3
ERO (mm <sup>2</sup> )	–	19.6 ± 4.8	14.0 ± 6.6	–	37.1 ± 6.8 <sup>*†</sup>	15.3 ± 6.8
E/E'	8.7 ± 2.5	13.7 ± 9.2	14.3 ± 7.3	9.0 ± 2.5	20.8 ± 5.4 <sup>*†</sup>	14.7 ± 7.5
PASP (mmHg)	30.0 ± 6.7	34.6 ± 10.8	33.8 ± 11.3	40.4 ± 8.7	53.8 ± 10.4 <sup>*†</sup>	41.5 ± 11.4

EDVI, end-diastolic volume index; ESVI, end-systolic volume index; EF, ejection fraction; SVI, stroke volume index; RV, regurgitant volume; ERO, effective regurgitant orifice; E/E', the ratio of the early diastolic transmitral velocity to the early diastolic tissue velocity; PASP, pulmonary artery systolic pressure. The other abbreviations are shown in Table 1.

\*Significant difference ( $P < 0.05$ ) EMR vs. NEMR. <sup>†</sup> $P < 0.05$  at peak exercise vs. at rest.

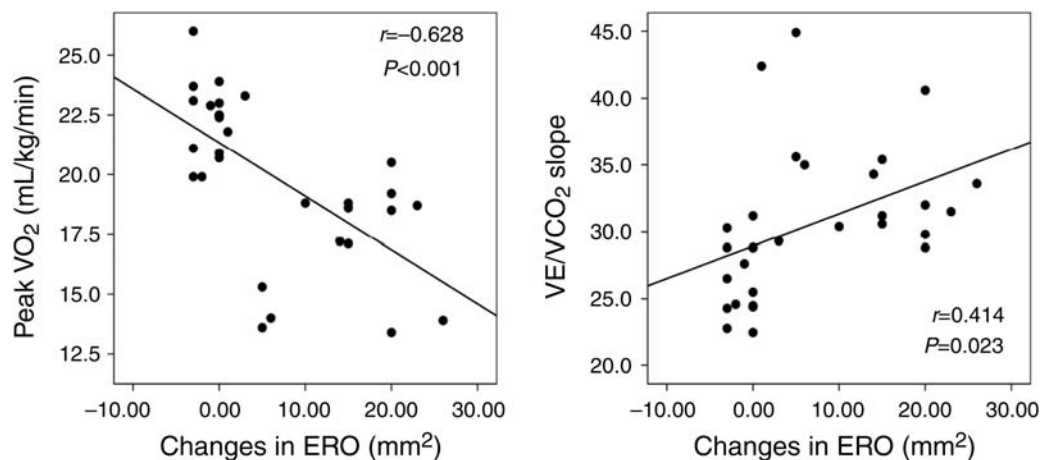


**Figure 2** The exercised-induced mitral regurgitation group revealed significantly lower exercise capacity than the non-exercised-induced mitral regurgitation group. The number of patients who stopped exercise because of dyspnoea was greater in the exercised-induced mitral regurgitation group.

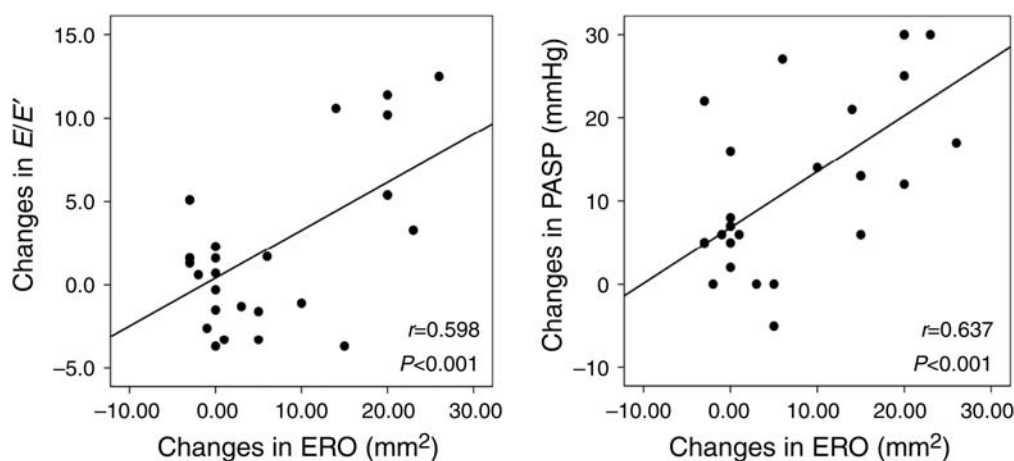
## Determinants of exercise capacity

The EMR group revealed lower peak VO<sub>2</sub> (16.6 ± 5.1 vs. 21.0 ± 3.6 mL/min,  $P = 0.018$ ) and greater VE/VCO<sub>2</sub> slope (36.4 ± 9.5 vs. 30.1 ± 6.1,  $P = 0.041$ ) than the NEMR group (Figure 2). The number of patients who stopped exercise because of dyspnoea was greater in the EMR group (seven patients, 70%) than the NEMR group (four patients, 20%,  $P < 0.001$ ). The rest–exercise differences in ERO correlated negatively with peak VO<sub>2</sub> ( $r = -0.628$ ,  $P = 0.001$ ) and weakly with the VE/VCO<sub>2</sub> slope

( $r = 0.414$ ,  $P = 0.023$ ; Figure 3). The increased ERO was well correlated with the changes in E/E' ( $r = 0.598$ ,  $P = 0.001$ ) and trans-tricuspid pressure gradient ( $r = 0.637$ ,  $P < 0.001$ ), respectively (Figure 4). The rest–exercise differences in the LV sphericity index correlated negatively with peak VO<sub>2</sub> ( $r = -0.437$ ,  $P = 0.018$ ) and weakly with the VE/VCO<sub>2</sub> slope ( $r = 0.364$ ,  $P = 0.040$ ; Figure 5). The dynamic changes in ERO strongly predicted limited exercise capacity according to a multivariate analysis (Table 3).



**Figure 3** Relationship between changes in ERO and peak oxygen uptake or the minute ventilation/carbon dioxide production slope. ERO, effective regurgitant orifice.



**Figure 4** Relationship between changes in ERO and those in  $E/E'$  or PASP. ERO, effective regurgitant orifice;  $E/E'$ , the ratio of the early diastolic transmitral velocity to the early diastolic tissue velocity; PASP, pulmonary artery systolic pressure.

## Reproducibility of echocardiographic measurements

The inter- and intra-observer variabilities were  $r = 0.96$  and  $0.94$  for ERO,  $r = 0.92$  and  $0.84$  for  $E/E'$ , and  $r = 0.88$  and  $0.84$  for the sphericity index, respectively. The Bland–Altman method was also adopted for the analysis of echocardiographic measurements; the inter- and intra-observer variabilities were  $4.2$  and  $6.1$   $\text{mm}^2$  for ERO,  $1.2$  and  $2.0$  for  $E/E'$ , and  $0.03$  and  $0.03$  for the sphericity index, respectively.

## Discussion

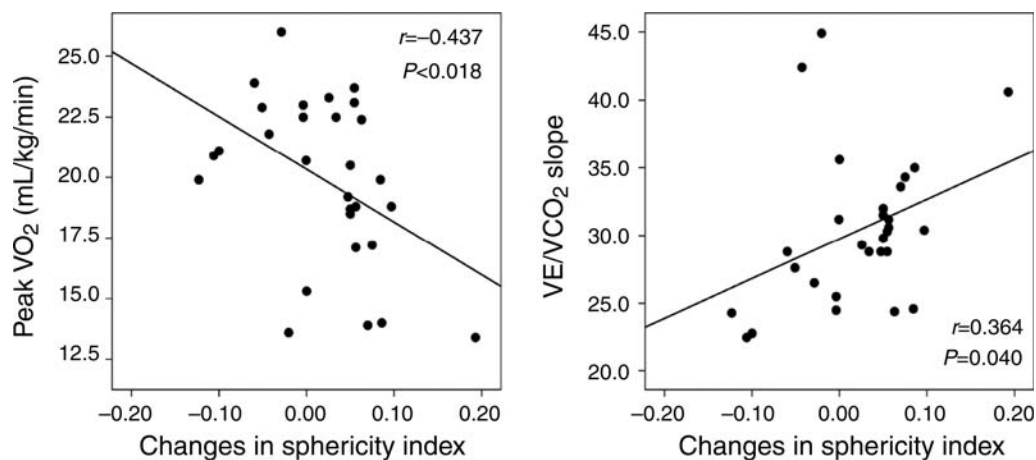
This study focused on dynamic changes in LV shape and functional MR. An increase in MR during exercise contributes to exercise

intolerance and exercise capacity in patients with systolic heart failure.

## Dynamic changes in mitral regurgitation and left ventricular geometry

LV adaptation to exercise depends on multiple factors in patients with CHF. Exercise may change LV shape more spherically, which increases mitral valve tethering and worsens MR. Progressive distortion of LV architecture leads to apical and lateral displacement of papillary muscles, which in turn causes tethering and restrictive motion of the mitral leaflets, thus contributes to mitral valvular miscoaptation. Some studies have demonstrated that exercise-induced LV sphericity provokes mitral valve deformation (tethering) and increases mitral tenting area through excessive leaflet tension, resulting in the exacerbation of functional MR.<sup>8,9,15</sup>





**Figure 5** Relationship between changes in the sphericity index and peak oxygen uptake or the minute ventilation/carbon dioxide production slope.

**Table 3** Multivariable analysis for predicting exercise capacity

	Peak VO <sub>2</sub>		VE/VCO <sub>2</sub> slope	
	r <sup>2</sup>	P-value	r <sup>2</sup>	P-value
Changes in ERO	0.487	0.001	0.345	0.029
Changes in LV sphericity	0.195	0.374	0.176	0.264
Changes in E/E'	0.088	0.676	0.107	0.167
Changes in PASP	0.371	0.032	0.198	0.073

Peak VO<sub>2</sub>, peak oxygen uptake; VE/VCO<sub>2</sub> slope, the minute ventilation/carbon dioxide production slope; LV, left ventricular. The other abbreviations are shown in Table 2.

## Influence of exercise-induced mitral regurgitation on exercise capacity

When a healthy individual exercises in a supine position, end-diastolic volume slightly increases, whereas end-systolic volume significantly decreases. An increase in stroke volume and LV ejection fraction augments cardiac output.<sup>16</sup> In a failing heart with depressed LV contractility, the Frank–Starling law or an enhancement of regional contractile state maintains its cardiac output within a homeostatic range. This induces a further increase in end-diastolic volume, which leads to abnormally high pulmonary capillary pressure and dyspnoea.<sup>17</sup> The presence of exercise-induced changes in functional MR may affect not only cardinal symptom but also exercise capacity in patients with CHF. Exercise-induced changes in the severity of functional MR limit an expected increase in forward stroke volume during exercise; hence, maximal cardiac output. In three-dimensional echocardiography, stroke volume includes both forward stroke volume and regurgitant volume. In the present study, three-dimensional echocardiography showed no differences in ejection fraction and stroke volume during the exercise testing between the EMR and NEMR groups. The EMR

group, which revealed the greater regurgitant volume, had the lower forward stroke volume and peak VO<sub>2</sub>/body weight than the NEMR group. The present study demonstrated that the EMR group had the greater VE/VCO<sub>2</sub> slope than the NEMR group. An elevated VE/VCO<sub>2</sub> slope is a reflection of the pathophysiological mechanism, an abnormal ventilatory response to exercise in heart failure patients.<sup>18</sup> The EMR group also had the greater E/E' and pulmonary artery pressure than the NEMR group. Meanwhile, the dynamic changes in MR correlated with the E/E' and pulmonary artery pressure, which explains the number of patients who terminated exercise because of dyspnoea was greater in the EMR group than the NEMR group. Exercise-induced dynamic MR can probably increase left atrial and pulmonary artery pressure, resulting in right ventricular overload, a shift of the interventricular septum to the left, and a further decrease in LV distensibility. It also aggravates pulmonary congestion and affects pulmonary gas changes.

## Determinants of exercise capacity

In the present study, dynamic changes in ERO, rather than changes in LV sphericity index, well predicted exercise capacity. Dynamic changes in ERO may directly limit forward stroke volume during exercise and increase left atrial pressure. Exercise-induced MR is one of the final findings among the central (LV spherical and mitral deformation changes) and peripheral (lower muscle volume) factors.

## Study limitations

This study excluded patients in New York Heart Association class IV who had more severe MR. Since echocardiography was performed at rest and during the maximal symptom-limited exercise testing, it was uncertain what effects would be produced by a lesser degree of exertion. It has been suggested that exercise three-dimensional echocardiography has lower acquisition time and the possibility of image multiple parallel planes in each view.<sup>19</sup>

## Conclusion

The result of this study leads us to believe that both dynamic increases in MR and dynamic changes in LV shape limit exercise capacity in patients with CHF.

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**Conflict of interest:** none declared.

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