Journal of Echocardiography (2019) 17:147–156
https://doi.org/10.1007/s12574-018-0404-6

ORIGINAL INVESTIGATION

Prognostic value of exercise stress echocardiography in patients with secondary mitral regurgitation: a long-term follow-up study

Tomomi Suzuki[1] · Masaki Izumo[1] · Kengo Suzuki[1] · Dan Koto[1] · Maya Tsukahara[1] · Kanako Teramoto[1] · Yukio Sato[1] · Mika Watanabe[1] · Kei Mizukoshi[1] · Ryo Kamijima[1] · Manabu Takai[1] · Seisyou Kou[1] · Tomoo Harada[1] · Sachihiko Nobuoka[2] · Yoshihiro J. Akashi[1]

Received: 7 September 2018 / Revised: 9 October 2018 / Accepted: 22 October 2018 / Published online: 29 October 2018
© Japanese Society of Echocardiography 2018

Abstract

Background Secondary mitral regurgitation (MR) remains a challenging problem in the diagnosis and treatment of patients with heart failure. Although it is well known that secondary MR is dynamic, the impact of the severity of MR during exercise on long-term outcome has not been fully evaluated. The aim of the present study was to investigate the prognostic value of exercise stress echocardiography (ESE) in patients with secondary MR.

Methods This prospective study included 118 consecutive patients with secondary MR and left ventricular dysfunction (mean ejection fraction at rest: 38 ± 14%) who underwent semi-supine ESE. Their major cardiovascular events (MACE) including cardiac death were followed up for a median of 41.7 (range: 6–128) months.

Results MR significantly increased from rest to exercise (effective regurgitant orifice: 0.18 ± 0.09 vs. 0.25 ± 0.12 cm^2, $P < 0.001$). The prevalence of severe MR was higher during exercise than those at rest (37% vs. 56%, $P < 0.001$). During follow-up, MACE occurred in 49 patients (41.5%) including 12 cardiac deaths. Cox proportional-hazard multivariate analysis revealed that older age and MR severity during exercise were significantly associated with increased risk of MACE (hazard ratio: 1.04 and 8.4, respectively, both $P < 0.05$).

Conclusions ESE provides prognostic information in patients with secondary MR that is useful for predicting long-term outcome.

Keywords Secondary mitral regurgitation · Echocardiography · Exercise stress echocardiography · Heart failure

Introduction

From a public health perspective, valvular heart disease, which has a poor prognosis, affects entire communities in developed countries [1]. Secondary mitral regurgitation (MR) occurs in 11% to 59% [2, 3] of patients after a myocardial infarction and is present in >50% of patients with dilated cardiomyopathy [4–6]. Despite this high prevalence, secondary MR remains as a challenging issure in the diagnostic workup and treatment of patients with heart failure. It is well known that secondary MR is dynamic, [7–14] however, current therapy is primarily focused on resting conditions and the impact of MR severity during exercise on long-term outcome has not been fully evaluated. Therefore, we aimed to investigate the prognostic value of exercise stress echocardiography (ESE) in patients with secondary MR.

Methods

Study population

This prospective single-center study included 138 consecutive patients with secondary MR and reduced left ventricular ejection fraction (LVEF < 50%) who underwent ESE using semi-supine bicycle ergometer between April 2006 and August 2017 at St. Marianna University School of Medicine Hospital. Of these, ten patients who underwent mitral valve

✉ Masaki Izumo
heartizumo@yahoo.co.jp

[1] Division of Cardiology, Department of Internal Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 216-8511, Japan

[2] Department of Clinical Laboratory, St. Marianna University School of Medicine, Kawasaki, Japan

surgery, eight patients who were lost to follow-up, and two patients with poor image quality for quantifying MR were excluded. Finally, 118 patients (mean age: 64 ± 14 years, 24% female) were enrolled. All patients were in a stable condition at the time of enrollment and none of them met the following exclusion criteria, (1) more than mild aortic regurgitation, mild or greater aortic stenosis or severe tricuspid regurgitation, (2) history of myocardial infarction < 6 months prior, (3) evidence of inducible ischemia; and (4) extensive myocardial ischemia requiring coronary angiography and revascularization. This study was approved by the institutional review board at St. Marianna University School of Medicine (No. 1288). All patients provided written informed consent before study enrollment.

Exercise echocardiography

After a comprehensive Doppler echocardiography at rest, a symptom-limited bicycle exercise test was performed in the semi-supine position on a dedicated tilting exercise table. Patients started with an initial workload of 10 W maintained for 3 min; the workload was increased every 3 min by 10 W. Blood pressure and heart rate were recorded every 1 min. Two-dimensional and Doppler echocardiography was available throughout the exercise test.

Echocardiographic measurements

Echocardiographic examinations were performed with commercially available ultrasound system (Vivid E9; GE Vingmed Milwaukee, WI, USA or iE33, Philips, Andover, MA, USA). All echocardiographic and Doppler data were obtained at rest and at peak exercise in digital format and stored on a workstation for offline analysis (EchoPAC, version 12; GE Vingmed Milwaukee, WI, USA). All measurements were averaged over three cardiac cycles. MR was quantified according to the proximal isovelocity surface area (PISA) method at rest and during exercise; effective regurgitant orifice (ERO) and regurgitant volume (RV), which indicates the severity of secondary MR. The PISA radius was measured from at least three frames with optimal flow convergence. The most appropriate negative aliasing velocity to obtain PISA was selected offline on the workstation. The PISA radius was measured in mid-systole. RV and ERO were calculated with standard formulas [15]. According to the guidelines, severe secondary MR was defined as an ERO of 0.20 cm^2 [16]. We also quantified MR evaluated by volumetric method only at rest. The diameter of the left ventricular (LV) outflow tract (inner edge) was measured only at rest in the parasternal long-axis view. The mitral and aortic stroke volumes were calculated as the pulsed-wave Doppler time–velocity integral × the area of the annulus of the mitral and aortic valves, respectively. RV (quantitative Doppler echocardiography) was calculated as the difference between the mitral and aortic stroke volumes. ERO was measured as RV/VTI of the regurgitant jet [16]. The biplane Simpson method was used to measure LV end-diastolic volume (LVEDV) and end-systolic volume (LVESV), stroke volume, EF, and left atrial (LA) maximal volume. Mitral E- and A-wave velocities were measured with pulsed-wave Doppler, and e' wave velocity was obtained by tissue Doppler imaging in the septal position of the mitral annulus. These measurements were repeated at exercise before or just after the eventual fusion of E and A. Systolic pulmonary artery pressure (SPAP) was derived from the regurgitant jet of tricuspid regurgitation using systolic transtricuspid pressure gradient calculated by the modified Bernoulli equation ($P4v^2$, where v is maximal tricuspid regurgitant jet velocity in m/s) and the addition of right atrial pressure. Mean right atrial pressure was estimated based on the most recent ASE recommendation [17]. Right atrial pressure was assumed to be constant from rest to exercise. Mitral valve tenting height and tenting area were measured by the apical long-axis view at mid-systole. Mitral valve tenting height was defined as the distance from the mitral annular plane to mitral leaflet coaptation point. The mitral valve tenting area was measured by the area enclosed between the annular plane and mitral leaflets.

Study endpoints

The primary study endpoint was cardiac death during follow-up and the secondary endpoint was major adverse cardiovascular events (MACE) defined as cardiac death, and hospitalization for heart failure.

Statistical analysis

The results are expressed as mean ± standard deviation (SD) or percentage unless otherwise specified. Data for the MACE and no-MACE groups were compared by Student's *t* test, Chi-squared test, or Fisher exact test as appropriate. Pearson's correlation coefficient was used to evaluate the correlation between two parameters. Probabilities of event-free survival among the severe and non-severe groups were obtained using Kaplan–Meier analysis and compared using the two-sided log-rank test. The effect of clinical, resting and exercise echocardiographic parameters was assessed using the Cox proportional-hazard model in univariate and multivariate analyses. Variables with a univariate value of $P < 0.1$ were incorporated into the multivariate models. ERO was entered into the multivariate model without RV as MR severity because of collinearity. Sequential Cox models were performed to determine the incremental prognostic benefit of exercise echocardiographic parameters over clinical and resting echocardiographic data. A statistically significant

increase in the global log-likelihood χ^2 of the model defined the incremental prognostic value. P values < 0.05 were considered as statistically significant. Both the interobserver and intraobserver variabilities for ERO and RV were obtained according to the blind analysis of twenty-eight random images by two independent observers at two different time points. The results were analyzed by both an intraclass correlation coefficient for absolute agreement (ICCa) and the Bland–Altman method. Statistical analyses were performed with SPSS 22.0 software (SPSS, Inc., Chicago, IL, USA).

Results

Clinical and echocardiographic features

Table 1 shows the clinical characteristics of the study population (mean age: 64 ± 14 years, 24% female). None of the patients, at the time of the study, had suspected significant coronary artery disease requiring myocardial revascularization. Among the 118 patients, 49 patients (41.5%) developed MACE during follow-up (12 cardiac death and 37 heart failure hospitalization). We found no differences in clinical characteristics between the MACE and no-MACE groups except for systolic blood pressure at peak exercise.

In the entire cohort, MR significantly increased from rest to exercise (0.18 ± 0.09 vs. 0.25 ± 0.12 cm^2, $P < 0.001$, Fig. 1). The prevalence of severe secondary MR was significantly higher at peak exercise than at rest (37% vs. 56%, $P < 0.001$). Table 2 shows resting and exercise echocardiographic findings. Although the MACE group had significantly greater LV volumes and lower LVEF than the no-MACE group (all $P < 0.05$), there were no significant differences in E wave velocity, E/e', and SPAP between the two groups at rest. During exercise, LV volumes, E/e' and SPAP were significantly greater in the MACE group than in the no-MACE group. Despite similar resting MR severity and tethering parameters of the mitral valve between the two groups, the MACE group had greater tenting height and area, ERO, and RV during exercise than the no-MACE group.

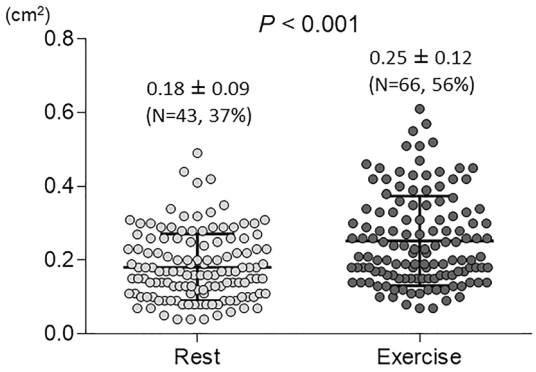


Fig. 1 Effective regurgitant orifice at rest and peak exercise in the whole cohort. Mitral regurgitation (MR) significantly increased from rest to exercise. The number and percent indicate the number and percentage of patients with severe secondary MR

Table 1 Baseline characteristics

	All (n = 118)	No MACE (n = 69)	MACE (n = 49)	P value
Age, (years)	64 ± 14	64 ± 15	63 ± 14	0.522
Female, n (%)	28 (24)	18 (26)	11 (22)	0.691
Blood pressure and heart rate at rest				
Systolic BP, (mmHg)	112 ± 24	113 ± 20	111 ± 24	0.624
Diastolic BP, (mmHg)	72 ± 14	73 ± 14	70 ± 15	0.565
Heart rate, (beats/min)	68 ± 12	67 ± 10	68 ± 12	0.686
Blood pressure and heart rate at peak exercise				
Systolic BP, (mmHg)	156 ± 35	162 ± 36	141 ± 30	0.029
Diastolic BP, (mmHg)	79 ± 14	80 ± 15	77 ± 14	0.591
Heart rate, (beats/min)	113 ± 24	115 ± 25	110 ± 21	0.733
Etiology				
Ischemic cardiomyopathy, n (%)	45 (38)	27 (39)	18 (37)	0.822
Medications				
ACEI/ARB, n(%)	105 (89)	60 (87)	45 (91)	0.802
β-blocker, n (%)	95 (81)	57 (83)	38 (78)	0.331
Diuretics, n (%)	101 (86)	60 (86)	41 (84)	0.841

MACE major cardiovascular event, *BP* blood pressure, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin II receptor blocker

Table 2 Echocardiographic findings at rest and peak exercise

	All ($n=118$)	No MACE ($n=69$)	MACE ($n=49$)	P value
Rest				
LVEDV, (ml)	168 ± 64	161 ± 64	176 ± 57	0.017
LVESV, (ml)	111 ± 59	101 ± 55	120 ± 62	0.013
LVEF, (%)	34.0 ± 13.8	37.2 ± 17.4	31.8 ± 12.6	0.043
S', (cm/s)	5.1 ± 1.6	5.4 ± 1.7	4.9 ± 1.3	0.073
LAVi, (ml)	47.5 ± 29.5	51.0 ± 30.8	44.1 ± 28.0	0.600
E wave velocity, (cm/s)	80.0 ± 30.1	77.5 ± 28.4	89.2 ± 32.7	0.547
E', (cm/s)	6.3 ± 2.7	5.9 ± 2.4	6.4 ± 3.4	0.937
E/E'	14.5 ± 6.8	13.5 ± 6.7	15.1 ± 6.1	0.188
SPAP, (mmHg)	34.0 ± 10.0	34.1 ± 10.2	34.9 ± 10.4	0.138
Tenting height, (mm)	7.0 ± 2.0	6.8 ± 2.0	7.2 ± 2.1	0.277
Tenting area, (cm^2)	1.4 ± 0.5	1.3 ± 0.5	1.5 ± 0.5	0.280
ERO (PISA), (cm^2)	0.18 ± 0.09	0.19 ± 0.09	0.17 ± 0.09	0.843
RV (PISA), (ml)	26.9 ± 15.1	28.8 ± 14.0	24.8 ± 15.5	0.991
ERO (volumetric), (cm^2)	0.19 ± 0.11	0.20 ± 0.12	0.18 ± 0.10	0.723
RV (volumetric), (ml)	29.8 ± 16.7	30.8 ± 17.8	27.9 ± 15.3	0.841
Exercise				
LVEDV, (ml)	176 ± 64	171 ± 64	188 ± 66	0.028
LVESV, (ml)	113 ± 59	106 ± 57	124 ± 58	0.019
LVEF, (%)	35.5 ± 14.6	38.5 ± 12.7	34.0 ± 12.2	0.004
S', (cm/s)	5.5 ± 2.2	5.8 ± 1.9	5.0 ± 2.0	0.176
E wave velocity, (cm/s)	129 ± 32	131 ± 34	127 ± 28	0.302
E', (cm/s)	7.4 ± 3.5	7.7 ± 3.8	6.4 ± 2.4	0.420
E/E'	18.6 ± 8.6	17.5 ± 9.5	20.1 ± 7.8	0.046
SPAP, (mmHg)	53.3 ± 14.4	51.0 ± 13.4	57.0 ± 15.6	0.015
Tenting height, (mm)	8.0 ± 2.5	7.5 ± 2.3	9.0 ± 2.9	0.013
Tenting area, (cm^2)	1.6 ± 0.5	1.5 ± 0.5	1.9 ± 0.6	0.006
ERO, (cm^2)	0.25 ± 0.12	0.23 ± 0.10	0.30 ± 0.14	< 0.001
RV, (ml)	34.0 ± 19.2	32.2 ± 14.1	44.1 ± 21.4	< 0.001

MACE major cardiovascular events, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *LVEF* left ventricular ejection fraction, *LAVi* left atrial volume index, *SPAP* systolic pulmonary artery pressure, *ERO* effective regurgitant orifice area, *RV* regurgitant volume

Clinical outcomes

During a median follow-up of 41.7 (range: 6–128) months, 12 patients (10.1%) developed the primary endpoint (cardiac death), and 49 patients (41.5%) reached the secondary endpoint (MACE; 12 cardiac death and 37 heart failure hospitalization). The Cox-hazard multivariate analysis showed that older age (HR: 1.036, $P=0.032$) and ERO during exercise (HR: 8.402, $P=0.012$) were independently associated with an increased risk of MACE (Table 3). In the entire cohort, the cardiac death-free survival rates were 97 ± 4%, 90 ± 7%, 82 ± 12%, and 72 ± 14% and MACE-free survival rates were 90 ± 8%, 78 ± 12%, 62 ± 15%, and 39 ± 17% at 1, 3, 5, and 7 years, respectively. Figure 2 illustrates the cardiac death and MACE-free survival rates of the study population stratified according to the severity of secondary MR at rest (A and C) and exercise (B and D). Patients with severe secondary MR during exercise had significantly lower rates of cardiac death and MACE-free survival than those without severe secondary MR; we could not stratify the cardiac death-free survival rate according to the resting severity of secondary MR. Receiver-operating characteristic curve analysis revealed that exercise ERO was more accurate in predicting MACE during follow-up than resting ERO (area under the curve: 0.692 vs. 0.504). Figure 3 shows the incremental benefit of exercise echocardiographic parameters in the prediction of MACE. The addition of exercise echocardiographic parameters significantly improved the prognostic power of a model containing clinical and resting echocardiographic variables (model 1: age, resting LVEF and LVESV, $\chi^2=15.9$; model 2: plus resting ERO, $\chi^2=16.9$, $P=0.324$; model 3: plus exercise LVESV, $\chi^2=19.8$, $P=0.038$; model 4: plus exercise ERO, $\chi^2=29.6$, $P=0.020$). Figure 4 shows

Table 3 Univariate and multivariate analyses for predicting major cardiovascular event

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.024	1.002–1.048	0.032	1.036	1.002–1.064	0.032
Female sex	0.983	0.651–1.713	0.953			
Ischemic cardiomyopathy	0.824	0.436–1.472	0.618			
Resting parameters						
LVESV	1.005	1.001–1.021	0.010	1.003	0.987–1.021	0.583
LVEF	0.988	0.950–1.010	0.080	1.032	0.872–1.094	0.412
E/e'	1.030	0.986–1.102	0.214			
SPAP	1.028	0.994–1.080	0.094	1.040	0.948–1.108	0.120
ERO	3.12	0.512–26.20	0.130			
Exercise parameters						
LVESV	1.010	1.001–1.016	0.014	1.004	0.984–1.022	0.662
LVEF	0.950	0.946–0.998	0.016	0.942	0.822–1.014	0.242
E/e'	1.052	1.015–1.084	0.002	0.992	0.944–1.042	0.524
SPAP	1.032	1.006–1.048	0.014	1.020	0.961–1.030	0.210
ERO	16.20	6.82–33.42	< 0.001	8.402	1.980–41.70	0.012

Abbreviations are shown in Table 2

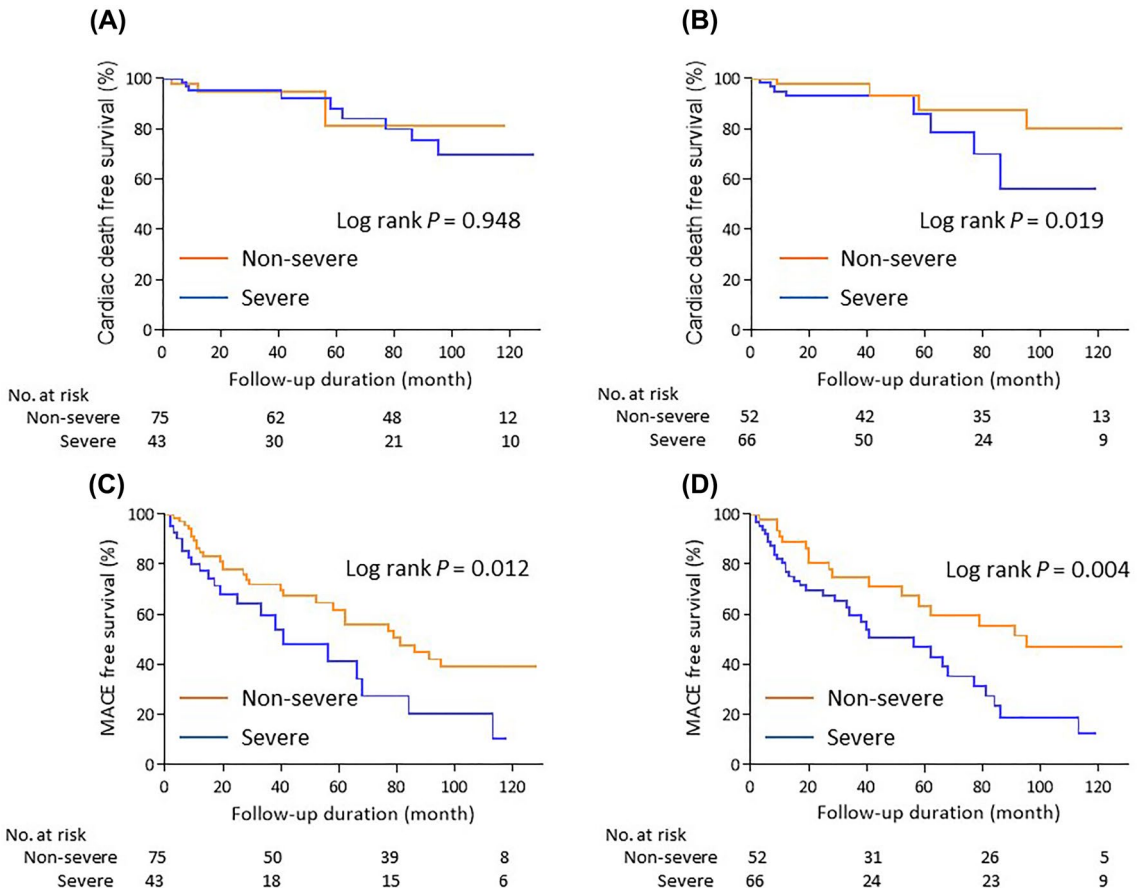
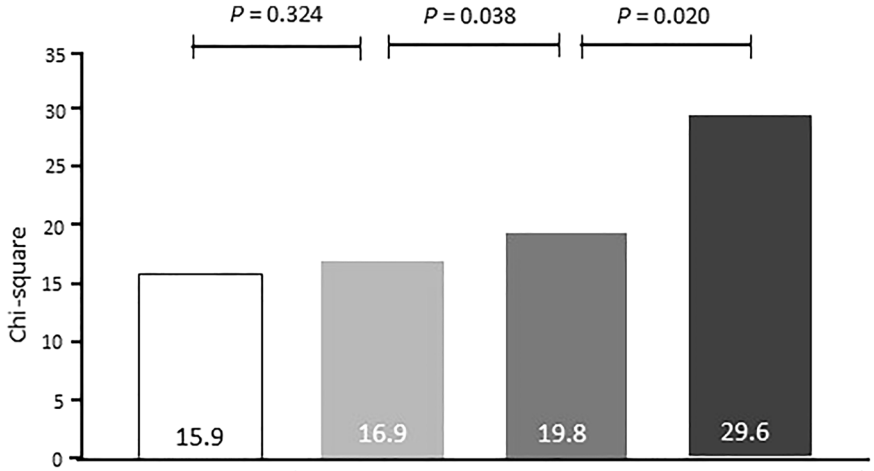


Fig. 2 Kaplan–Meyer analysis of cardiac death (**a**, **b**) and major cardio-cerebrovascular events (**c**, **d**) free survival in patients with and without severe secondary mitral regurgitation at rest (**a**, **c**) and during exercise (**b**, **d**)



	Age + resting LVEF and LVESV	+ resting ERO	+ exercise ESV	+ exercise ERO
Age	1.043 (1.012-1.091) P=0.004	1.045 (1.013-1.072) P=0.003	1.046 (1.012-1.082) P=0.004	1.036 (1.002-1.068) P=0.024
LVEF rest	1.005 (0.951-1.061) P=0.923	1.003 (0.954-1.071) P=0.916	1.005 (0.960-1.052) P=0.844	1.011 (0.965-1.059) P=0.611
LVESV rest	1.010 (1.000-1.021) P=0.062	1.009 (0.998-1.020) P=0.081	1.008 (0.990-1.020) P=0.394	1.006 (0.992-1.020) P=0.418
ERO rest		5.218 (0.164-15.23) P=0.331	5.260 (0.181-15.50) P=0.330	3.330 (0.024-5.980) P=0.336
LVESV exercise			1.015 (1.002-1.026) P=0.020	1.022 (0.980-1.044) P=0.082
ERO exercise				9.920 (6.280-16.20) P=0.001

Fig. 3 Incremental value of exercise stress echocardiographic parameters to clinical and resting echocardiographic data. The figure illustrates the global χ^2 of sequential Cox models incorporating clinical (age), resting left ventricular (LV) end-systolic volume (ESV) and ejection fraction (EF), effective regurgitant orifice area (ERO), exercise LVESV and exercise ERO

the representative cases of the MACE (A) and no-MACE (B) groups.

Reproducibility

The intraobserver variabilities assessed using the ICCa were 0.93 (95% CI, 0.89–0.95, $n=28$) for ERO, and 0.94 (95% CI, 0.89–0.97, $n=28$) for RV. The interobserver variabilities were 0.90 (95% CI, 0.78–0.95) for ERO, and 0.88 (95% CI, 0.76–0.94) for RV. The Bland–Altman method showed that interobserver and intraobserver variabilities were 0.04 ± 0.05 and 0.02 ± 0.04 cm^2 for ERO, 1.9 ± 7.0 and 2.7 ± 4.2 ml for RV, respectively.

Discussion

Although it is well known that secondary MR is dynamic, and depends on the loading conditions, current diagnostic workup and therapeutic strategies are mainly based on resting conditions. The main findings of this study were that (1) the prevalence of severe secondary MR was significantly higher during exercise than at rest, (2) patients with MACE had significantly greater MR severity during exercise despite similar MR severity at rest, (3) MR severity during exercise was significantly associated with MACE, and (4) ESE provided incremental prognostic value in patients with secondary MR.

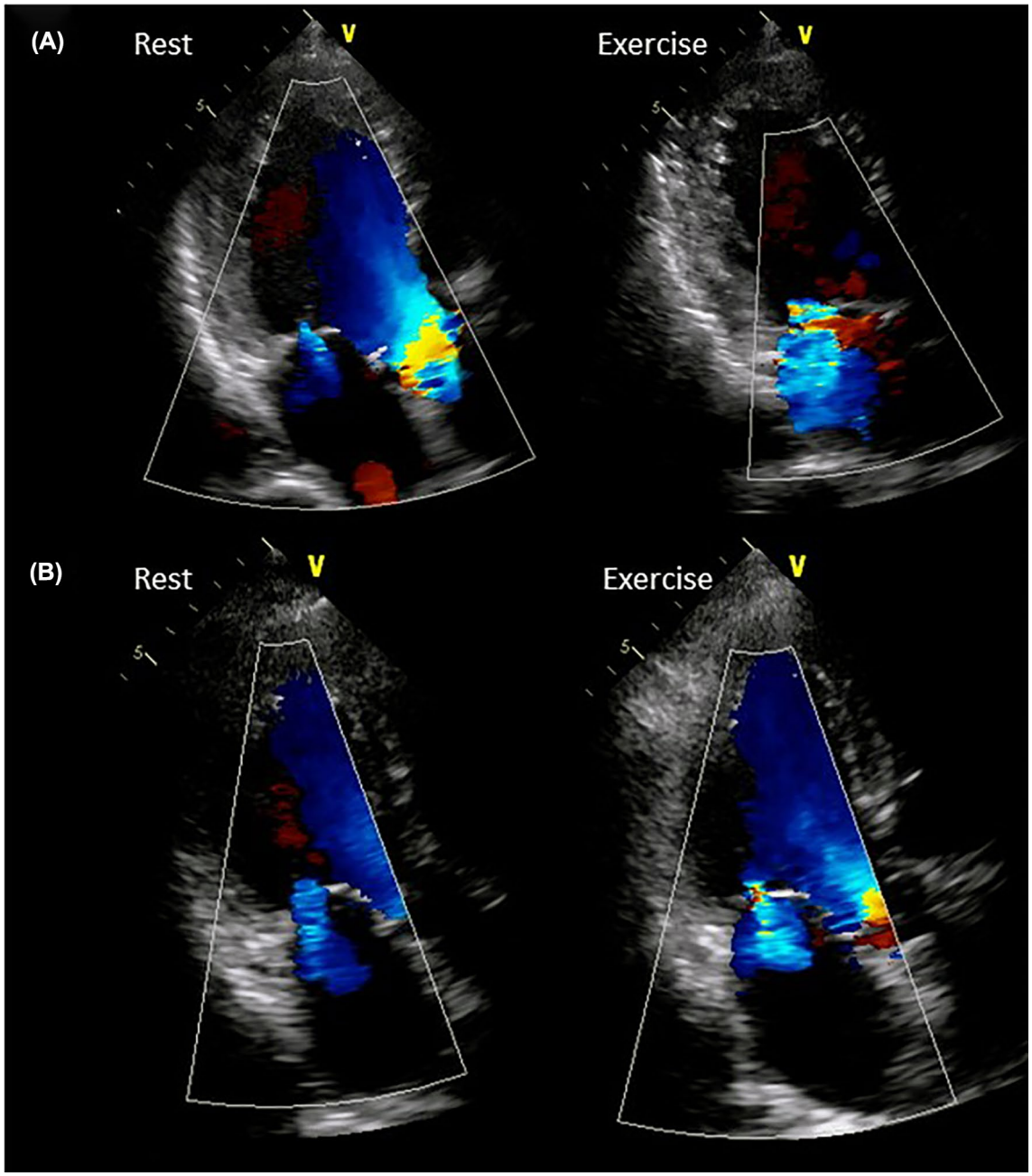


Fig. 4 Two representative MACE (**a**) and no MACE (**b**) cases. **a** 73 patients with non-ischemic cardiomyopathy. Exercise echocardiography showed severe secondary mitral regurgitation (MR) at peak exercise (right panel) despite of mid MR at rest (left panel). **b** 76 patients with ischemic cardiomyopathy. Exercise echocardiography showed that secondary MR was not increased during exercise

Mechanisms of exercise-increased secondary MR

In healthy individuals, the cardiovascular system adapts to meet increased oxygen demands of peripheral muscles. [18] During dynamic exercise, multiple muscle groups contract to achieve joint movement; this activity is associated with vasodilation in the intramuscular vasculature, reduction in systemic vascular resistance, and increased venous return due to the skeletal muscle pump. [19] Also, dynamic exercise is associated with no (or transient) increase in LVEDV and a concomitant decrease in LVESV. This results in a substantially increased stroke volume, LVEF and cardiac output. [20] In patients with ischemic or non-ischemic cardiomyopathy, LV response to dynamic exercise may differ from that of the healthy individuals. [21] Both the volume and pressure loading result in exercise-induced LV dilatation, whereas LVEF remains unchanged. Significant increases in systemic venous resistance are generally not observed during

dynamic exercise; however, failure of adequate arterial dilatation during exercise occurs. [22] In addition, exercise may result in dyssynchronous contraction of the left ventricle. [12, 13] Previous studies demonstrated increases in secondary MR in > 50% of patients with ischemic and non-ischemic cardiomyopathy. [7–14] Neither LV volumes nor LVEF at rest are a reliable predictor of exercise-increased secondary MR. In fact, with respect to exercise-induced LV dilatation, changes in shape (local remodeling) of LV may play more critical role than changes in the actual volume. [7, 13] An increase in left ventricular sphericity, which correlates with greater papillary muscle distance, may have a pronounced effect on mitral geometry even without a significant change in volume. In contrast, an increase in left ventricular volume caused by apical dilatation of the cavity (which does not involve the papillary muscles) will have no effect on mitral valve geometry. Therefore, it is not surprising that, when looking at variables at rest that can predict worsening of MR during exercise, left ventricular sphericity and papillary muscle dyssynchrony are more useful, as is mitral valve tenting, which reveals an already strained balance between closing and tethering forces. [13, 23] In addition, progressive annular dilation during exercise may be a contributor to exercise-induced MR in a majority of cases and is most predictive in non-ischemic cardiomyopathy. [11].

Prognostic importance of secondary MR during exercise

The present study is the first to examine the incremental prognostic value of ESE for secondary MR evaluated using very long-term follow-up. Our results indicate that patients with severe (ERO ≥ 0.20 cm^2) secondary MR during exercise have a worse outcome including both cardiac death and MACE. An earlier study reported that all-cause mortality in patients with heart failure and secondary MR follows a graded correlation with respect to MR severity, with ERO > 0.20 cm^2 already implying poor outcome. [24] This value contrasts to the 0.40 cm^2 cut-off traditionally used in primary MR. Although the occurrence of secondary MR is also a marker of underlying heart disease, the lower ERO threshold in secondary MR could also be rooted in the typically dynamic nature of secondary MR, which is frequently underestimated at rest. Our observations emphasize the importance of ESE in the setting of secondary MR. We could stratify patients into the MACE-free survival but not cardiac death-free survival according to resting severity during long-term follow-up. In our study, 27 patients (22%) with non-severe secondary MR at rest progressed to severe secondary MR during exercise and one-third of these patients developed cardiac death during follow-up. In contrast, none of the 22 patients (nine with severe MR at rest) with a decrease in MR during exercise developed cardiac death during long-term follow-up. Piérard and Lancellotti [25] demonstrated that exercise-induced MR deterioration, by augmenting backward flow and pulmonary vascular congestion, may contribute to the development of acute pulmonary edema. They also noted that a significant increase in ERO during exercise (defined as an increase > 0.13 cm^2) is observed in 30% of patients with HF and associated with increased mortality and readmissions. [7, 26] The link between severe MR during exercise and cardiac events could involve several mechanisms. [27] Intermittent increases in MR severity during daily life activities can acutely increase left atrial and pulmonary vascular pressures contributing to worsening of dyspnea and flash pulmonary edema. [10, 28] Acute increase in pulmonary systolic artery pressure as estimated by the exercise-induced changes in transtricuspid pressure gradient was also an independent predictor of cardiac events. [29] In our study, exercise ERO correlated well with systolic pulmonary artery pressure during exercise ($R = 0.435$, $P < 0.001$). Other factors can play a role, such as pulmonary vascular compliance. Repetitive transient increase in MR may also worsen LV volume overload and contribute to myocardial disease progression [30]. Chronic volume overload is also associated with a high incidence of ventricular tachyarrhythmias [31, 32]. Impaired LV contractile reserve, a marker of more severe disease, leads to inadequate cardiac adaptation to exercise. Dynamic MR is also a determinant of rapid increase in QRS duration at short-term follow-up; this may subsequently induce permanent electromechanical dyssynchronization [32]. LV asynchrony further deteriorates LV systolic function which in turn reduces mitral valve closing force and accelerates the progression to refractory heart failure [33, 34]. Dynamic MR is also associated with poor exercise capacity [35, 36]. Exercise capacity is one of the important factors in patients with heart failure.

Study limitations

This investigation has several limitations. First, despite of its large number of subjects with secondary MR, this study was a single-center analysis. A large population, multicenter study is, thus, warranted. Second, this study included both ischemic and non-ischemic cardiomyopathy even the increase in LVEDV during exercise is reported to be greater in ischemic cardiomyopathy compared to idiopathic dilated cardiomyopathy [21], which may be directly related to the extent of myocardial scar [37], a finding of particular importance for the exercise dynamics of secondary MR. However, previous dynamic exercise studies demonstrate increases in secondary MR in > 50% of patients with HF, both with ischemic and non-ischemic etiology [7–14]. None of the patient included in the present study had evidence of exercise-induced myocardial ischemia, and the prevalence of severe secondary MR during exercise was not different

between the ischemic and non-ischemic cardiomyopathy group (55.1 vs 51.1%, $P=0.533$); the prognostic effect of exercise-induced secondary MR was also similar. Third, the cardiac death-free survival rate in this population was lower than that in previous studies. [7, 24, 25] We hypothesized that this discrepancy was caused by variations in patients' characteristics. We excluded patients with NYHA IV who could not perform an exercise test in the semi-supine position, the prevalence of resting PH was relatively low, and medical treatment for heart failure was adequately standardized in this study (i.e., over 80% of the study patients received βblockers and ACEi/ARBs). Finally, Doppler methods used to quantify MR have some pitfalls [38]. In the present study, a limitation of the PISA method is the measurement of the PISA radius at only one velocity and time point. Nevertheless, an earlier study validated the use of PISA and volumetric methods at rest and during exercise. [28].

Conclusions

Exercise-induced severe secondary MR provides incremental prognostic information that is useful for predicting long-term outcome. This study showed that the evaluation of secondary MR is important not only at rest but also during exercise.

Compliance with ethical standards

Conflict of interest Tomomi Suzuki, Masaki Izumo, Kengo Suzuki, Dan Koto, Maya Tsukahara, Kanako Teramoto, Yukio Sato, Mika Watanabe, Kei Mizukoshi, Ryo Kamijima, Manabu Takai, Seisyou Kou, Tomoo Harada, Sachihiko Nobuoka, and Yoshihiro J Akashi declare that they have no conflicts of interest.

Human rights statements and informed consent All procedure followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions. The participants were well informed prior to the test; written informed consent was obtained before enrollment.

References

1. Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368:1005–11.
2. Lamas GA, Mitchell GF, Flaker GC, et al. Clinical significance of mitral regurgitation after acute myocardial infarction: survival and ventricular enlargement investigators. Circulation. 1997;96:827–33.
3. Bursi F, Enriquez-Sarano M, Jacobsen SJ, et al. Mitral regurgitation after myocardial infarction: a review. Am J Med. 2006;119:103–12.
4. Trichon BH, Felker GM, Shaw LK, et al. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol. 2003;91:538–43.
5. Levine RA, Schwammenthal E. Ischemic mitral regurgitation on the threshold of a solution: from paradoxes to unifying concepts. Circulation. 2005;112:745–58.
6. Koelling TM, Aaronson KD, Cody RJ, et al. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. Am Heart J. 2002;144:524–9.
7. Lancellotti P, Lebrun F, Piérard LA. Determinants of exercise-induced changes in mitral regurgitation in patients with coronary artery disease and left ventricular dysfunction. J Am Coll Cardiol. 2003;42:1921–8.
8. Giga V, Ostojic M, Vujisic-Tesic B, et al. Exercise-induced changes in mitral regurgitation in patients with prior myocardial infarction and left ventricular dysfunction: relation to mitral deformation and left ventricular function and shape. Eur Heart J. 2005;26:1860–5.
9. Lancellotti P, Stainier PY, Lebois F, et al. Effect of dynamic left ventricular dyssynchrony on dynamic mitral regurgitation in patients with heart failure due to coronary artery disease. Am J Cardiol. 2005;96:1304–7.
10. Lapu-Bula R, Robert A, Van Craeynest D, et al. Contribution. of exercise-induced mitral regurgitation to exercise stroke volume and exercise capacity in patients with left ventricular systolic dysfunction. Circulation. 2002;106:1342–8.
11. Ennezat PV, Maréchaux S, Le Tourneau T, et al. Myocardial asynchronism is a determinant of changes in functional mitral regurgitation severity during dynamic exercise in patients with chronic heart failure due to severe left ventricular systolic dysfunction. Eur Heart J. 2006;27:679–83.
12. D'Andrea A, Caso P, Cuomo S, et al. Effect of dynamic myocardial dyssynchrony on mitral regurgitation during supine bicycle exercise stress echocardiography in patients with idiopathic dilated cardiomyopathy and "narrow" QRS. Eur Heart J. 2007;28:1004–11.
13. Izumo M, Lancellotti P, Suzuki K, et al. Three-dimensional echocardiographic assessments of exerciseinduced changes in left ventricular shape and dyssynchrony in patients with dynamic functional mitral regurgitation. Eur J Echocardiogr. 2009;10:961–7.
14. Yamano T, Nakatani S, Kanzaki H, et al. Exercise-induced changes of functional mitral regurgitation in asymptomatic or mildly symptomatic patients with idiopathic dilated cardiomyopathy. Am J Cardiol. 2008;102:481–5.
15. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the american society of echocardiography developed in collaboration with the society for cardiovascular magnetic resonance. J Am Soc Echocardiogr. 2017;30:303–71.
16. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2017;38:2739–91.
17. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010;23:685–713.
18. Laughlin MH. Cardiovascular response to exercise. Am J Physiol. 1999;277:S244–59.
19. Manou-Stathopoulou V, Goodwin CD, Patterson T, et al. The effects of cold and exercise on the cardiovascular system. Heart. 2015;101:808–20.
20. Libby P, Bonow RO, Mann DL, et al. Braunwald's heart disease: a textbook of cardiovascular medicine. Philadelphia: WB Saunders Co.; 2007. p. p579.

21. Shen WF, Roubin GS, Hirasawa K, et al. Left ventricular volume and ejection fraction response to exercise in chronic congestive heart failure: difference between dilated cardiomyopathy and previous myocardial infarction. Am J Cardiol. 1985;55:1027–31.
22. Sullivan MJ, Knight JD, Higginbotham MB, et al. Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure: muscle blood flow is reduced with maintenance of arterial perfusion pressure. Circulation. 1989;80:769–81.
23. Bertrand PB, Schwammenthal E, Levine RA, et al. Exercise dynamics in secondary mitral regurgitation: pathophysiology and therapeutic implications. Circulation. 2017;135:297–314.
24. Grigioni F, Enriquez-Sarano M, Zehr KJ, et al. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation. 2001;103:1759–64.
25. Piérard LA, Lancellotti P. The role of ischemic mitral regurgitation in the pathogenesis of acute pulmonary edema. N Engl J Med. 2004;351:1627–34.
26. Lancellotti P, Gérard PL, Piérard LA. Long-term outcome of patients with heart failure and dynamic functional mitral regurgitation. Eur Heart J. 2005;26:1528–32.
27. Izumo M, Akashi Y. Exercise echocardiography for structural heart disease. J Echocardiogr. 2016;14:21–9.
28. Lebrun F, Lancellotti P, Pie´rard LA. Quantitation of functional mitral regurgitation during bicycle exercise in patients with heart failure. J Am Coll Cardiol. 2001;38:1685–92.
29. Lancellotti P, Magne J, Dulgheru R, et al. Clinical significance of exercise pulmonary hypertension in secondary mitral regurgitation. Am J Cardiol. 2015;115:1454–61.
30. Dal-Bianco JP, Beaudoin J, Handschumacher MD, et al. Basic mechanisms of mitral regurgitation. Can J Cardiol. 2014;30:971–81.
31. Stein KM, Borer JS, Hochreiter C, et al. Prognostic value and physiological correlates of heart rate variability in chronic severe mitral regurgitation. Circulation. 1993;88:127–35.
32. Martinez-Rubio A, Schwammenthal Y, Schwammenthal E, et al. Patients with valvular heart disease presenting with sustained ventricular tachyarrhythmias or syncope: results of programmed ventricular stimulation and long-term follow-up. Circulation. 1997;96:500–8.
33. Hung J, Otsuji Y, Handschumacher MD, et al. Mechanism of dynamic regurgitant orifice area variation in functional mitral regurgitation: physiologic insights from the proximal flow convergence technique. J Am Coll Cardiol. 1999;33:538–45.
34. Breithardt OA, Sinha AM, Schwammenthal E, et al. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. J Am Coll Cardiol. 2003;41:765–70.
35. Takano H, Adachi H, Ohshima S, et al. Functional mitral regurgitation during exercise in patients with heart failure. Circ J. 2006;70:1563–7.
36. Izumo M, Suzuki K, Moonen M, et al. Changes in mitral regurgitation and left ventricular geometry during exercise affect exercise capacity in patients with systolic heart failure. Eur J Echocardiogr. 2011;12:54–60.
37. Mann DL, Scharf J, Ahnve S, et al. Left ventricular volume during supine exercise: importance of myocardial scar in patients with coronary heart disease. J Am Coll Cardiol. 1987;9:26–34.
38. Enriquez-Sarano M, Seward JB, Bailey KR, et al. Effective regurgitant orifice area: a noninvasive Doppler development of an old hemodynamic concept. J Am Coll Cardiol. 1994;23:443–51.