

Original Article



# An Analysis of Myocardial Efficiency in Patients with Severe Asymptomatic Mitral Regurgitation

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## ABSTRACT

**BACKGROUND:** It is difficult to determine left ventricular systolic performance in patients with severe mitral regurgitation (MR) since left ventricular ejection fraction (EF) could be preserved until the end stages of the disease. Myocardial efficiency (MEf) describes the amount of external work (EW) done by the left ventricle per unit of oxygen consumed ( $mVO_2$ ). In the present study, we aimed to investigate MEf in patients with asymptomatic severe MR using a novel echocardiographic method.

**METHODS:** A total of 27 patients with severe asymptomatic MR and 26 healthy volunteers were included in this cross-sectional study. EW was measured using stroke volume and blood pressure, while  $mVO_2$  was estimated using double product and left ventricular mass.

**RESULTS:** There were no differences between the groups with regards to EF ( $66\% \pm 5\%$  vs.  $69\% \pm 7\%$ ), while MEf was significantly reduced in patients with severe MR ( $25\% \pm 11\%$  vs.  $44\% \pm 12\%$ ,  $p < 0.001$ ). This difference was maintained even after adjustment for age, gender and body surface area (adjusted  $\bar{x}$ : 0.44, 95% CI: 0.39–0.49 for controls and adjusted  $\bar{x}$ : 0.24, 95% CI: 0.19–0.29 for patients with severe MR). Further analysis showed that this reduction was due to an increase in total  $mVO_2$  in the severe MR group. MEf of the patients who were both on  $\beta$ -blockers and angiotensin converting enzyme inhibitors/angiotensin receptor blockers were higher than those who were not on any drugs, but this difference was not statistically significant ( $32\% \pm 15\%$  vs.  $23\% \pm 9\%$ ,  $p = 0.41$ ).

**CONCLUSIONS:** MEf was significantly lower in patients with asymptomatic severe MR and preserved EF.


**Keywords:** Mitral regurgitation; Echocardiography; Myocardial efficiency; Left ventricular function

## INTRODUCTION

Severe primary mitral regurgitation (MR) causes several changes in left ventricular (LV) physiology and morphology; including an increase in preload and afterload, LV dilation and eccentric hypertrophy and an increase in total cardiac output to preserve forward flow.<sup>1,2)</sup> While these compensatory changes could preserve adequate pump function for a prolonged period, such compensatory alterations are detrimental and ultimately lead to LV

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#### Conflict of Interest

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failure.<sup>3)</sup> Volumetric measures of LV systolic function, such as LV ejection fraction (LVEF), could be preserved until end-stage heart failure as the left atrium (LA) essentially provides a low-pressure reservoir to divert stroke volume (SV) away from the high-pressure aorta.<sup>3,4)</sup> Patients with severe primary MR, a LVEF < 60% and/or a LV end-systolic dimension > 40 mm have already developed LV systolic dysfunction, and 9%–18.4% of patients with a “normal” preoperative LVEF could suffer from postoperative LV systolic dysfunction following mitral valve surgery.<sup>5,7)</sup> Thus, earlier detection of LV systolic dysfunction could be useful to prevent postoperative LV systolic dysfunction in patients with severe primary MR.

Efficiency is a term used in mechanics to express the amount of work produced per unit of energy spent. Drawing an analogy from engines, myocardial efficiency (MEf) was proposed as a means to measure myocardial pump performance and is calculated by dividing the external work (EW) generated by the heart to total myocardial oxygen consumption ( $m\text{VO}_2$ ) of the myocardium.<sup>8)</sup> MEf could be measured invasively by cardiac catheterization or noninvasively using combined PET and echocardiography/cardiac MRI.<sup>8,9)</sup> The most common application of MEf in cardiovascular diseases is heart failure, where several studies had shown that MEf is reduced in patients with a reduced LV systolic performance, it is related with prognosis and cardiac resynchronization could improve MEf.<sup>10,11)</sup> In contrast, there are only a handful of studies that had investigated the usefulness of MEf in valvopathies, particularly in severe primary MR where it could offer incremental value over traditional measures of LV systolic performance.<sup>2,9)</sup>

We have hypothesized that MEf should be reduced in patients with severe primary MR even when the traditional indices of LV systolic function are preserved. In the present study, we aimed to investigate the changes in MEf and its principal components (EW and  $m\text{VO}_2$ ) in patients with severe MR, as well as the association of these mechanoenergetic parameters with other clinical and echocardiographic parameters, using a novel noninvasive way to calculate MEf.

## METHODS

### Patient selection

Patients with severe MR that underwent echocardiography in the study institution between years 2011 and 2012 were consecutively screened for inclusion to the present study. All patients above 18 years, with a primary etiology for mitral valve dysfunction (predominantly mitral valve prolapse or rheumatic valve disease), a LVEF  $\geq$  60% were included to the study in the absence of exclusion criteria. Exclusion criteria for the present study were a previous history or a new diagnosis of dilated, restrictive or hypertrophic cardiomyopathy, acute MR, secondary MR or less than severe MR (see below for echocardiographic definitions), any concomitant mitral or aortic valve stenosis or more than trace aortic regurgitation, more than moderate right sided valve stenosis or regurgitation, a previous diagnosis of pulmonary arterial hypertension, previous ischemic heart disease or more than 50% stenosis in any major coronary arteries, atrial fibrillation or any other persistent arrhythmia or presence of a paced rhythm. Patients with a previous diagnosis of hypertension were excluded only if they are actively treated for hypertension. Patients using angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) or beta blockers were not excluded if the patient did not have a prior diagnosis of hypertension. Thirty-two patients with severe MR were screened in the initial phase and 27 patients were found eligible for inclusion. Twenty-six volunteers were selected from the hospital staff to serve as the control group. All volunteers underwent a clinical and echocardiographic examination prior to inclusion to the study.

Demographic and clinical variables for patients were collected by direct interview and using institutional electronic medical database. Blood pressure (BP) was measured using an aneroid sphygmomanometer from both arms and the arm with the higher BP reading was accepted as reference. The measurement was repeated one minute after the initial measurement and an average of two measurements was accepted as the final reading. If the difference between the first and second reading was higher than 10 mmHg, a third measurement was obtained and an average of three measurements were used. The first and 5th Korotkoff sounds were used to define systolic blood pressure (SBP) and diastolic blood pressure (DBP). Mean BP was calculated as  $(SBP + 2 \times DBP)/3$ . BP measurements were obtained immediately before echocardiographic examinations. Heart rate (HR) was measured using the electrocardiography function on the echocardiography platform.

All participants gave their written consent before inclusion and the study was approved by a local ethics committee. The study was carried out according to the principles of Helsinki Declaration in 1975.

### Transthoracic echocardiography

All echocardiographic studies were performed with an ultrasound platform (Vivid 3, GE Healthcare Systems, Piscataway, NJ, USA) system equipped with a 2.5-MHz phased-array transducer. An average of three measurements were recorded as the final result. LV end-systolic and end-diastolic dimensions, as well as interventricular septal thickness and posterior wall thickness were measured from parasternal long-axis views. LV outflow tract (LVOT) diameter was measured from parasternal long-axis views using zoomed views of LVOT and is measured at the level of the origin of aortic valve leaflets. LVOT flow velocity was measured by locating posterior wall Doppler cursor at the level of the origin of aortic valve leaflets in apical long-axis views. Velocity-time integral (VTI) was obtained by tracing the velocity envelope. Using these measurements, forward SV was calculated by multiplying LVOT area with LVOT VTI. LV volumes, as well as LVEF were measured using modified Simpson method. LA volume was calculated using area-length method with LA tracings obtained from apical 4-chamber and 2-chamber views. Vena contracta was measured from apical long axis or 4-chamber views and defined as the narrowest portion of the MR flow. LV mass was calculated using Devereux formula.<sup>12)</sup>

Patients were diagnosed with severe MR in the presence of following: a vena contracta width of > 6 mm, a LA volume index of 28 ml/m<sup>2</sup> or more, echocardiographic evidence for structural mitral valve disease (i.e. features consistent with rheumatoid valvular disease or mitral valve prolapse) and at least one of the following: i) MR Doppler jet area  $\geq 10$  cm<sup>2</sup>, ii) MR jet area/LA area > 40%, iii) a dense MR waveform on continuous wave Doppler or iv) an early mitral inflow velocity of 1.5 m/s or more.

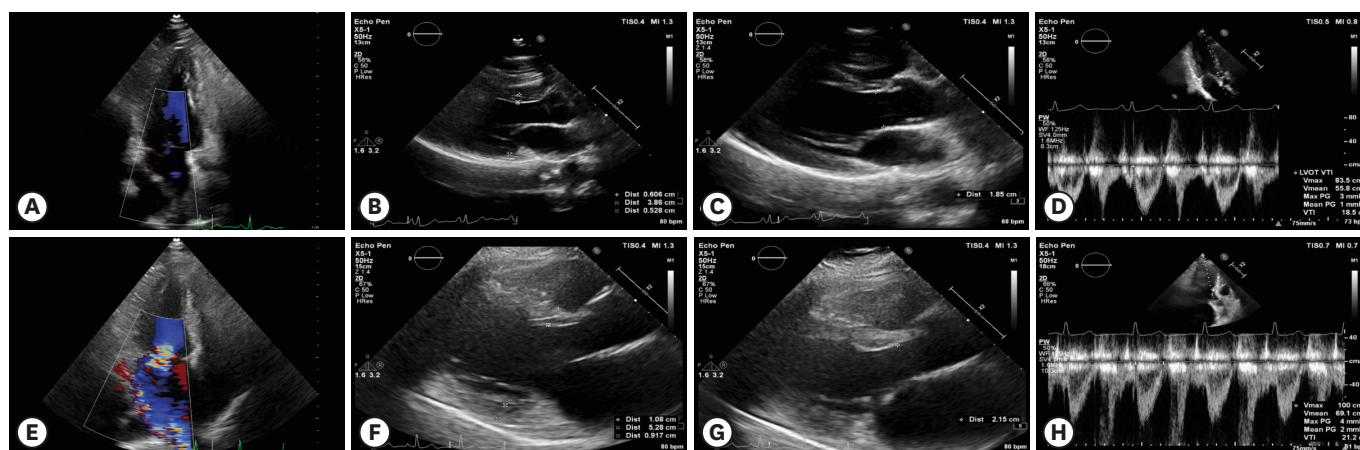
### Calculation of external work, total mVO<sub>2</sub> and myocardial efficiency

Myocardial oxygen consumption was estimated using Hellerstein and Wenger equation<sup>13)</sup>:

$$\text{Eq1 } m\text{VO}_2/100 \text{ g myocardium} = (\text{SBP} \times \text{HR} \times 1.4 \times 10^{-3}) - 6.3$$

MEf is calculated as defined before:

$$\text{Eq2 } (\text{SV} \times \text{MAP} \times \text{HR} \times 1.33 \times 10^{-4}) / (m\text{VO}_2 \times \text{LVM} \times 20)$$



**Figure 1.** Two case examples for calculation of myocardial efficiency in those with and without significant mitral regurgitation. Panels A-D show echocardiograms for an otherwise healthy 35-year-old female with a blood pressure of 100/60 mmHg. Trace mitral regurgitation can be seen in panel A. Her left ventricular external work and total myocardial oxygen consumption were calculated as 35.6 j and 63.1 j, yielding a myocardial efficiency of 56.4%. Panels E-H show a 46-year-old male patient followed up with rheumatic mitral valve disease and severe eccentric mitral regurgitation (E) with normal ejection fraction. His blood pressure was 130/60 mmHg at the time of echocardiographic examination. For the latter case, left ventricular external work and total myocardial oxygen consumption were calculated as 91.3 j and 330.4 j, resulting with a much lower myocardial efficiency (27.6%) as compared to the first case.

Where MAP is mean arterial pressure, LVM is total LV mass, and  $mVO_2$  is the minute oxygen consumption of the heart per gram myocardium. In this formula, the constant in the numerator and denominator represents the caloric equivalent of 1 mmHg • mL work and 1 mL  $O_2$ , respectively. The numerator of the formula was equal to minute EW and the denominator is equal to total  $mVO_2$ . Since the  $mVO_2$  equation given in Eq1 calculates  $mVO_2$  per 100 g of myocardium, this number was divided to 100 before calculating Eq2.

Case examples for “echocardiography-only” calculation of MEF were presented in **Figure 1**.

### Statistical analysis

Data was recorded on a spreadsheet and all statistical analyses were performed using JASP 0.9.2 (JASP Team (2018), JASP Version 0.9.2 for Microsoft Windows). Continuous variables were given as mean  $\pm$  SD and categorical variables were presented as percentages. For continuous variables, normality assumption and equality of variances were tested using Shapiro-Wilk and Levene tests, respectively. For data with a normal distribution, Student’s t test or t test with Welch correction was used. For data that were not normally distributed, Mann-Whitney U test was used. For categorical variables,  $\chi^2$  test with continuity correction were used. An ANCOVA model was constructed to analyze whether demographic variables (age, gender and body surface area [BSA]) had any confounding effect on MEF. Pearson or Spearman’s Rho bivariate correlation tests were used to analyze linear relationships between MEF and clinical/echocardiographic variables in patients with severe MR. Also, a secondary analysis was done in the severe MR group to understand the effects of ACE inhibitors/ARB and  $\beta$ -blockers on MEF and individual components of MEF. To study relative importance of  $mVO_2$  and total LV mass on MEF, a linear regression model was built and standardized coefficients ( $\beta$ ) were calculated.

## RESULTS

Demographic, anthropometric and clinical variables for severe MR and control groups were presented in **Table 1**. While there were no significant differences between groups, there was

**Table 1.** Demographic, anthropometric, clinical and echocardiographic data for study groups

Parameters	Control group (n = 26)	Study group (n = 27)	p value
Demographic, anthropometric and clinical variables			
Age	36.5 ± 8.9	41.3 ± 14.2	0.23
Gender (male)	9 (35%)	10 (37%)	1.0
Height (cm)	167.8 ± 8.5	164.3 ± 10.5	0.44
Weight (kg)	71.4 ± 12.9	68.3 ± 11.4	0.73
BSA (m <sup>2</sup> )	1.82 ± 0.20	1.76 ± 0.18	0.64
Systolic blood pressure (mmHg)	121.12 ± 9.21	128.19 ± 17.33	0.07
Diastolic blood pressure (mmHg)	75.73 ± 10.21	74.11 ± 12.42	0.61
Heart rate (bpm)	77.0 ± 7.8	88.0 ± 23.6	0.1
Coexisting diabetes	0 (0%)	3 (11%)	0.25
Coexisting CKD	0 (0%)	1 (4%)	1.0
Etiology of severe MR			N/A
Rheumatoid valve disease		14 (52%)	
Mitral valve prolapse		11 (41%)	
Other/undetermined		2 (7%)	
B-blocker use	0 (0%)	11 (41%)	< 0.001*
ACEi/ARB use	0 (0%)	7 (26%)	0.02*
Diuretic use	0 (0%)	1 (4%)	1.0
Echocardiographic variables			
LA volume index (mL/m <sup>2</sup> )	17.61 ± 4.33	60.67 ± 21.79	< 0.001*
LV end-diastolic volume (mL)	83.13 ± 18.88	121.91 ± 37.63	< 0.001*
LV end-systolic volume (mL)	28.07 ± 9.57	45.30 ± 17.42	< 0.001*
Interventricular septal thickness (cm)	0.70 ± 0.12	0.78 ± 0.11	0.001*
Posterior wall thickness (cm)	0.73 ± 0.11	0.79 ± 0.11	0.02*
LV mass (g)	122.93 ± 45.64	184.37 ± 56.16	< 0.001*
Conventional parameters of contractility			
LV ejection fraction (%)	0.69 ± 0.07	0.66 ± 0.05	0.29
Sm (m/s)	7.88 ± 1.14	8.07 ± 1.81	0.66

\*p values below 0.05.

ACEi/ARB: angiotensin converting enzyme inhibitors/angiotensin receptor blockers, BSA: body surface area, CKD: chronic kidney disease, LA: left atrium, LV: left ventricle, MR: mitral regurgitation, Sm: systolic velocity of lateral mitral annulus.

a trend towards higher SBP and HR in patients with severe MR, and 3 participants in severe MR group had diabetes and one patient had chronic kidney disease. As expected; mean LA volume, LV end-systolic and end-diastolic dimensions and LV mass were all higher in the severe MR group, but there were no differences between the groups with regards to LVEF or systolic velocity of lateral mitral annulus (**Table 1**).

### Myocardial energetics and efficiency in study groups

MEf was significantly lower in patients with severe MR as compared to the control group (**Table 2, Figure 2**). When individual components of MEf were analyzed, it was observed that this difference was mainly as a result of increased  $mVO_2$  rather than a reduction in EW, and both components of  $mVO_2$  – namely oxygen consumption per gram myocardium and total LV mass – were significantly higher in the severe MR group. While there were no significant differences with regards to EW or individual components of EW between groups, mean SV (but not stroke work) was lower in patients with severe MR (**Table 2, Figure 3**).

### Myocardial efficiency in study groups after adjustment for demographic and anthropometric confounders

In an ANCOVA model adjusted for age, gender and BSA; presence of severe MR was significantly associated with MEf (adjusted  $\bar{x}$  MEf for control patients: 0.44, 95% CI: 0.39–0.49; adjusted  $\bar{x}$  MEf for patients with severe MR: 0.24, 95% CI: 0.19–0.29). Other variables, including age (p = 0.52), gender (p = 0.83) or BSA (p = 0.97) had no significant association with MEf. Likewise, the interaction between study group and gender was not significant ( $P_{int} = 0.26$ ).

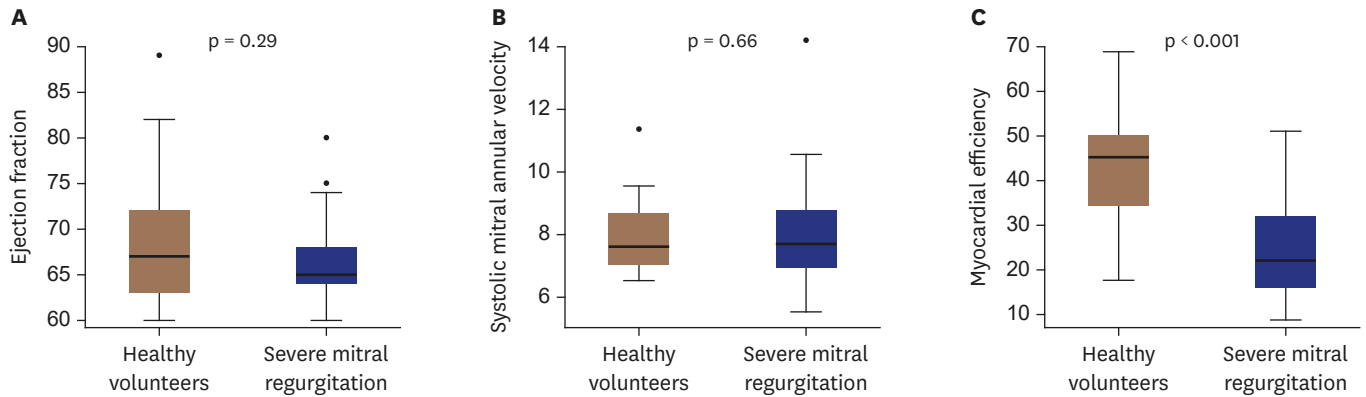
**Myocardial Efficiency in Mitral Regurgitation**

**Table 2.** Myocardial efficiency and individual components that were used to calculate myocardial efficiency in control and severe mitral regurgitation groups

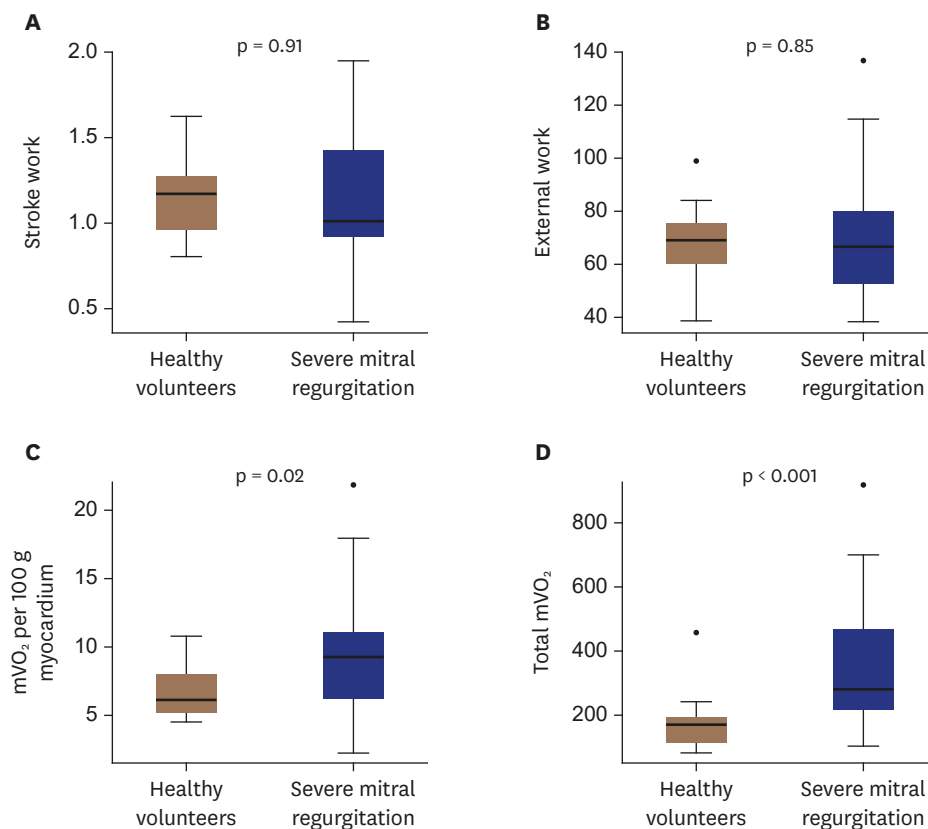
Parameters	Control group (n = 26)	Study group (n = 27)	p value
Stroke volume (mL)	70.76 ± 12.53	66.67 ± 17.15	0.30
Stroke work (j)	1.14 ± 0.21	1.15 ± 0.36	0.91
Minute external work (j)	65.96 ± 14.71	70.17 ± 23.15	0.85
mVO <sub>2</sub> (mL·min <sup>-1</sup> ·100g <sup>-1</sup> )	6.79 ± 1.93	9.48 ± 4.71	0.02*
Total mVO <sub>2</sub> (j)	166.58 ± 77.14	346.46 ± 202.71	< 0.001*
Myocardial efficiency (%)	44 ± 12	25 ± 11	< 0.001*

\*p values below 0.05.

mVO<sub>2</sub>: myocardial oxygen consumption.



**Figure 2.** Boxplot graphics for left ventricular ejection fraction (A), systolic velocity of lateral mitral annulus (B) and myocardial efficiency (C) between study groups. The only comparison that was statistically significant between groups was myocardial efficiency. Points show outlying cases.



**Figure 3.** Boxplot graphics for stroke work (A), minute external work (B), mVO<sub>2</sub> per 100 g of myocardium (C) and total mVO<sub>2</sub> (D) between groups. Note that there were no significant differences between groups with regards to the work being done, while oxygen consumption to generate this work was significantly higher in patients with mitral regurgitation, thus explaining the decrease in the myocardial efficiency in the latter group. Points show outlying cases. mVO<sub>2</sub>: myocardial oxygen consumption.

**Table 3.** Bidirectional correlations between myocardial efficiency and echocardiographic parameters in control and severe mitral regurgitation groups

Parameters	Control group		Study group	
	p value	Coefficient	p value	Coefficient
LA volume index	0.10	0.33	0.91	-0.02
LVEDV	0.51	-0.14	0.61	-0.10
LVESV	0.68	-0.09	0.14	-0.29
IVS thickness	< 0.01*	-0.50	0.05	-0.32
PW thickness	< 0.01*	-0.74	0.01*	-0.47
LVEF	0.46	-0.15	0.13	0.30
Sm	0.76	-0.06	0.18	0.27

\*p values below 0.05

IVS: interventricular septum, LA: left atrium, LVEDV: left ventricular end diastolic volume, LVEF: left ventricular ejection fraction, LVESV: left ventricular end systolic volume, PW: posterior wall, Sm: systolic velocity of the lateral mitral annulus.

### Relationship of myocardial efficiency with echocardiographic parameters in study groups

MEf did not correlate with LA volume index or with LV dimensions, as well as metrics of LV contractility in both study groups. The only parameter that had a significant correlation with MEf was LV wall thickness (both septal and posterior wall thickness) in both study groups, though the strength of this association (i.e. coefficient of correlation) was more prominent in healthy controls as compared to patients with MR (Table 3).

### Relative weights of mVO<sub>2</sub> and LV mass on myocardial efficiency in study groups

In healthy volunteers, linear regression equation for MEf was  $ME (\%) = 85.07 - 3.14 \times mVO_2 - 0.16 \times LV \text{ mass}$  and standardized coefficients ( $\beta$ ) for mVO<sub>2</sub> and total LV mass were -0.5 and -0.62. In patients with MR,  $ME (\%) = 53.43 - 1.35 \times mVO_2 - 0.09 \times LV \text{ mass}$ , where  $\beta$  for mVO<sub>2</sub> and total LV mass were -0.59 and -0.45.

### Effects of $\beta$ -blockage and combined ACE-inhibition/ $\beta$ -blockage on myocardial energetics in patients with severe mitral regurgitation

Five patients were on  $\beta$ -blockers and 6 patients were on both  $\beta$ -blockers and ACE inhibitors/ARB at the time of echocardiographic examination. While there were no significant differences between subgroups of patients, there was a trend towards higher EW and total mVO<sub>2</sub> in patients solely on  $\beta$ -blockers. In contrast, patients that were using both  $\beta$ -blockers and ACE inhibitors/ARBs had a tendency towards lower total mVO<sub>2</sub> and higher MEf, as compared to those not on either drug or only on  $\beta$ -blockers (Table 4).

## DISCUSSION

In the present study, we have investigated EW, mVO<sub>2</sub> and MEf in patients with asymptomatic severe MR using a novel echocardiographic method. Key findings from the present study were: i) MEf is approximately halved in patients with severe asymptomatic MR as compared

**Table 4.** Myocardial efficiency and individual components used to calculate myocardial efficiency in patients with severe mitral regurgitation that were either on  $\beta$ -blockers,  $\beta$ -blockers plus ACE inhibitors or angiotensin receptor blockers or not on any of these drugs

Parameters	No $\beta$ B or ACEi/ARB (n = 15)	$\beta$ B only (n = 5)	$\beta$ B + ACEi/ARB (n = 6)	p value
Stroke work (j)	1.10 $\pm$ 0.39	1.21 $\pm$ 0.21	1.17 $\pm$ 0.44	0.66
Minute EW (j)	66.60 $\pm$ 21.06	73.35 $\pm$ 17.28	65.34 $\pm$ 18.53	0.59
mVO <sub>2</sub> (mL·min <sup>-1</sup> ·100g <sup>-1</sup> )	9.47 $\pm$ 4.02	9.06 $\pm$ 2.64	7.82 $\pm$ 5.54	0.68
Total mVO <sub>2</sub> (j)	328.33 $\pm$ 151.25	408.27 $\pm$ 286.77	281.16 $\pm$ 220.73	0.39
Myocardial efficiency (%)	23 $\pm$ 9	22 $\pm$ 9	32 $\pm$ 15	0.41

ACEi/ARB: angiotensin converting enzyme inhibitors/angiotensin receptor blockers,  $\beta$ B: beta-blocker, EW: external work, mVO<sub>2</sub>: myocardial oxygen consumption.

to healthy volunteers, ii) The reason of this reduction is not a reduction in EW, but it is related with increased  $mVO_2$ , iii) the reduction in MEF could not be explained with other potential confounders; such as age, gender or BSA, iv) MEF did not correlate with conventional measures of LV contractility, such as LVEF or mitral annular systolic velocity and v) while total LV mass had a greater weight in determining  $mVO_2$  in healthy volunteers, oxygen consumption per gram myocardium is the primary determinant of  $mVO_2$  in patients with severe MR.

### Effects of mitral regurgitation on myocardial efficiency

MR redirects LV outflow to the low-pressure LA, thus causing an increase in total SV to compensate reduced forward flow. Thus, MR causes a predictable decrease in MEF but the degree of this reduction is not clear since there are only a few studies that have investigated MEF in patients with severe MR and these studies had limited sample sizes and used different methodologies to define MEF. Chow et al.<sup>2)</sup> had found that forward work metabolic index (WMI), which is an index representing MEF, is increased 35% after surgery with no change in total WMI. In another small study, MEF was increased from  $0.69 \pm 0.26$  to  $1.01 \pm 0.15$  ( $p < 0.05$ ) following mitral valve replacement, but the definition of MEF was not dependent on oxygen consumption in the latter study and therefore reflected the ratio of forward work to total work.<sup>14)</sup> A control group was notably absent in both studies and therefore the reduction in MEF at baseline could not be assessed.<sup>2)14)</sup> Our findings suggest that on average, MEF is approximately halved (54.5%) in patients with severe asymptomatic MR as compared to healthy volunteers. This reduction in MEF was a result of doubling in myocardial oxygen usage rather than a decline in minute EW. Further analysis of determinants of  $mVO_2$  has shown that this increase in total myocardial  $O_2$  utilization was not only secondary to an increase in LV mass but also due to an increase in  $mVO_2$  per gram of myocardium and  $O_2$  consumption per gram myocardium had more weight in determining total  $mVO_2$  in patients with severe MR. Increased cellular oxygen consumption leads to oxidative stress, which is considered as a major pathway for the development and progression of LV dysfunction and heart failure.<sup>15-17)</sup> In addition, there is data showing that myocardial oxygen utilization does not change after mitral valve replacement and morphological changes in the LV are not completely reversible in a subset of patients with chronic MR, thus suggesting that abnormal myocardial energetics might persist following correction of underlying hemodynamic abnormality.<sup>2)18)</sup> Reduced MEF and abnormal  $O_2$  utilization could in part explain development of LV dysfunction in chronic severe MR, though available findings are observational and indirect and thus needs further validation from further experimental studies.

### Mechanical efficiency as a potential surrogate marker of LV performance in severe mitral regurgitation

Numerous studies have shown that in patients with severe MR, LV systolic performance is impaired even before LVEF begins to decline and even a slight impairment of LVEF below 60% portends a poor prognosis following valve replacement or repair, thus underlying the need for better parameters to quantify LV contractility.<sup>19)20)</sup> MEF has the potential to offer further information regarding to overall mechanical performance of the LV, as a gradual reduction in MEF could be expected as the flow is diverted from aortic valve to mitral valve and compensatory structural changes (such as eccentric LV hypertrophy) begin to appear. In the present study, we have observed that average MEF was 24% in patients with severe asymptomatic MR after adjusting for age, gender and BSA; with 95% confidence intervals ranging from 19% and 29%. A further decline in MEF could be expected as LV systolic performance is gradually lost, and compensatory mechanisms begin to fail in the decompensated, symptomatic phase of the disease. While this latter hypothesis is the logical



extension of the present findings, it remains unproven as the present data is taken from a cross-sectional study that does not allow making longitudinal projections for all stages of MR. Further studies are needed to elucidate the usefulness of MEF to predict outcomes and to determine an optimal cut-off value for MEF that could be used to select patients who could benefit from valve repair or replacement.

### Effects of $\beta$ -blockers and ACE inhibitors on myocardial efficiency in patients with severe mitral regurgitation

$\beta$ -blockers, ACE inhibitors/ARB and mineralocorticoid receptor blockers are only indicated when there is a compelling indication such as heart failure or hypertension.<sup>21)</sup> In the absence of a compelling indication, there is some evidence that  $\beta$ -blockers but not ACE inhibitors could improve LV contractility in severe primary MR, though the data is severely limited and no studies have investigated outcomes.<sup>22)23)</sup> Still, these drugs have positive effects on hemodynamics and myocardial energetics, as  $\beta$ -blockers reduce myocardial O<sub>2</sub> consumption and ACE-inhibitors/ARBs reduce LV afterload and divert blood flow towards aortic valve. Thus, both drugs should theoretically increase MEF in patients with MR and as such, our findings actually indicate a trend towards higher MEF in patients using a combination of both drugs, with a mean MEF of  $0.32 \pm 0.15$  (Table 3). This result lacks statistical significance and obtained from a small subgroup of patients and therefore does not implicate a causal relationship. Nonetheless, in our opinion this latter signal towards improved MEF is encouraging and deserves further research to see whether this would translate into improved outcomes, since available studies have only investigated single drugs rather than a combination approach.

### Feasibility and reliability of calculating myocardial efficiency using echocardiographic methods

MEF is traditionally measured using invasive means, which uses pressure-volume loops to calculate EW and myocardial arterial-venous oxygen difference to determine  $mVO_2$ .<sup>8)24)</sup> Invasive methods are seldom used today since advances in echocardiography and cardiac PET have allowed measurement of individual components of MEF noninvasively. When MEF is measured noninvasively, echocardiography or cardiac MRI is employed to measure EW and cardiac PET is used to measure  $mVO_2$  by determining the transfer rate of radioactive tracer from myocardium to blood, which has been shown as a reliable indicator of  $mVO_2$ .<sup>9)25)</sup> However, this method needs employment of two different modalities and assumes that there is no change in  $mVO_2$  in the interim. Using a single, widely-available and noninvasive modality to measure MEF would clearly be more attractive as it eliminates the need for additional costs, time delays or errors that could be caused by obtaining measurements at different time points and could lead to wider use of MEF as a marker of LV function in clinical practice. As such, there were previous studies that attempted to measure MEF using standalone echocardiographic or cardiac MRI techniques without directly measuring  $mVO_2$  but estimating it through LV wall stress.<sup>26)27)</sup> Others have used surrogate markers such as cardiac power/mass index to estimate MEF, which is conceptually similar to the formula used in the present study but excludes  $mVO_2$  since it could not be directly measured with echocardiography.<sup>28)</sup> Present methodology gives MEF as a percentage using the same formula employed by combined echocardiography/PET studies and allows an indirect comparison of findings between studies. Indeed, we have observed that the mean MEF found for healthy volunteers ( $44 \pm 12\%$ ) in the present study are close to the mean MEF measured using cardiac MRI and PET ( $49 \pm 6\%$ ) by Güçlü et al.,<sup>9)</sup> who have measured MEF in 14 healthy volunteers as a part of their study. That said, present study is only “hypothesis-generating”, is cross-sectional

in design and neither validates nor provides data on agreement between this method and conventional measurement of MEF, and therefore could not be accepted as a valid parameter for clinical use at this time. This is also true for other standalone methods which does not directly measure  $mVO_2$  but estimate it indirectly through equations.<sup>26)27)</sup> Nonetheless, we consider that a noninvasive, “single imaging modality” approach to calculate MEF, either using the methodology described in the present study or with other methods described in the literature, has the potential to bring MEF out of the research realm and make it an alternative and more integrated measure of LV function in the clinical practice.

### Study limitations

Present analysis used data that was collected from a single center and the sample size was limited. The sample size of patients who were actually on  $\beta$ -blockers or ACE inhibitors/ARBs were too small to draw any meaningful conclusions. Also, nearly all patients who were on ACE inhibitors/ARBs were also on  $\beta$ -blockers, so it is not possible to discriminate the effects of individual drugs. Detailed data on drugs, including exact indication or duration of use, were not collected as analyses on medications were done post-hoc to see whether drug use have affected the results and it was not intended as a primary analysis. Finally, since the present study is observational, it is not possible to suggest a causal relationship between medications and observed changes in mechanoenergetics. One important limitation for interpreting the results is that the  $mVO_2$  per gram myocardium was calculated indirectly using the regression formula proposed by Hellerstein and Wegner,<sup>13)</sup> since echocardiography alone is insufficient to calculate or estimate  $mVO_2$ . Nonetheless, this formula uses double product to estimate  $mVO_2$ , which has a close relationship with  $mVO_2$  that is measured using invasive methods and is widely used in clinical practice as a surrogate marker of  $mVO_2$ .<sup>29)</sup> Also, the method as a whole needs further validation and calibration using MEF data that is obtained using conventional methods. A cut-off value to predict overall patient outcomes could not be analyzed due to the design of the study. As such, present study should be considered as an exploratory and “hypothesis generating” analysis that only investigated feasibility of an echocardiography-only method to calculate MEF in patients with severe asymptomatic MR, and therefore further work on this new method is needed before actually considering using it in the clinical practice.

### Conclusions

Patients with severe asymptomatic primary MR and preserved EF have reduced MEF as compared to healthy controls, and the reason for this reduction is primarily related with increased  $mVO_2$ . Reduced MEF precedes the drop in EF and could serve as an early sign of myocardial dysfunction, though further work is needed to see whether it could be clinically useful independent of available parameters. Finally, an echocardiography-only method to calculate LV MEF seems feasible and would increase the utilization of this parameter in clinical practice, but this approach needs further validation.

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