Relationship between myocardial energy expenditure and postoperative ejection fraction in patients with severe mitral regurgitation

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Abstract

Objective: This prospective study aimed to investigate the myocardial energy metabolism in severe mitral regurgitation (MR) and explore its effect on postoperative differentiation of ejection fraction (EF).
Methods: A total of 85 patients with severe MR were prospectively enrolled from October 2018 to June 2019. During the study period, a total of 50 patients underwent mitral valve surgery and 49 patients were finally enrolled due to 1 missing data. Left ventricular function, circumferential end-systolic stress (cESS), and myocardial energy expenditure (MEE) were measured by transthoracic echocardiography preoperatively and 3 months after surgery. Patients were divided into 2 groups according to absolute difference of postoperative differentiation of EF.
Results: Nine patients underwent mitral valve repair and 40 underwent prosthetic valve replacement. Patients with reduced EF had higher MEE demonstrated with cESS and MEE. Negative correlation between preoperative EF and N-terminal pro-brain natriuretic peptide (NT-proBNP), cESS, MEEs, and MEEm and positive correlation between preoperative EF and effective regurgitant orifice area were found. Complications occurred in 12 patients during hospitalization. Basal NT-proBNP, left atrium (LA), and cESS were significantly higher in postoperatively decreased EF group. Taking into consideration the covariates of multiple logistic regression analysis, LA and cESS were found to be independent predictors of EF reduction postoperatively.
Conclusion: Higher LA and cESS are independent predictors of postoperative EF reduction. Preoperative high end-systolic stress could predict postoperative EF reduction and hence could be helpful for determining the timing of mitral valve surgery. Although MEE was higher in postoperatively decreased EF group, it did not reach statistical significance. *(Anatol J Cardiol 2020; 24: 254-9)*
Keywords: ejection fraction, end-systolic stress, mitral regurgitation, mitral valve surgery, myocardial energy expenditure

Introduction

Mitral regurgitation (MR) is the most frequent valvular heart disease, and the predominant cause of MR requiring surgical correction is degenerative (1). MR can be classified as either primary (organic) or secondary (functional) based on etiology. Symptomatic chronic severe primary MR is the most common indication for mitral valve surgery. However, surgery is indicated in asymptomatic patients with left ventricular (LV) dysfunction [LV end-systolic diameter (LVESD) ≥45 mm and/or LV ejection fraction (LVEF) ≤60%, class I] and in those with preserved LV function (LVESD <45 mm and LVEF >60%) and atrial fibrillation (AF) secondary to MR, or pulmonary hypertension (systolic pulmonary pressure at rest >50 mm Hg, class IIa) (2).

MR causes LV overload and hypertrophy that may increase cardiac workload contributing to changes in myocardial energy metabolism. Although LVEF may appear normal myocardial dysfunction develops as a result of hypertrophy (3). Invasive methods can be used to detect myocardial energy metabolism, but they are not practical and have not been validated. Myocardial mechanics have been previously assessed using transthoracic echocardiography (TTE), positron emission tomography (PET), and magnetic resonance imaging (MRI). Myocardial energy expenditure (MEE) (4), myocardial blood flow through the coronary sinus (5), and myocardial efficiency can be measured and calculated using TTE. Changes in LV overload, volume, and hypertrophy in severe MR may increase MEE. Therefore, we hypothesized that MEE could correlate with postoperative ejection

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fraction (EF). Consequently, this prospective study aimed to investigate myocardial energy metabolism in severe MR and explore its effect on postoperative differentiation of EF.

Methods

Study population

Patients with severe MR who were scheduled for mitral valve surgery we enrolled in this observational and prospective study. Patients who had mixed valvular heart disease, mitral stenosis, congenital heart disease, severe heart failure (EF ≤30%), renal failure, mechanical prosthetic valve, history of pulmonary embolism, acute coronary syndrome within 3 weeks, history of coronary artery bypass grafting, or hypertrophic obstructive or restrictive cardiomyopathy were excluded from the study. This study protocol was approved by the Local Ethics Committee. We prospectively included 85 patients with severe MR from October 2018 to June 2019. NT-proBNP levels were obtained on the same day of TTE before surgery. During the study period, a total of 50 patients underwent mitral valve surgery. Other patients had an operation in another institution or did not want to undergo surgery. Mitral valve repair or annuloplasty ring was performed in patients when feasible; all remaining patients underwent mitral valve replacement. The surgical operative report was obtained to assess what type of surgery was performed. Patients were assessed during hospitalization for complications such as acute renal failure, prolonged use of inotrope, acute AF, mortality, and prolonged intensive care stay.

Echocardiography

Measurements of LV internal dimension and wall thickness were obtained according to the American Society of Echocardiography recommendations using EPIQ 7 Echocardiography (Philips Healthcare, Andover, MA) by the same echocardiographer (6). Left atrium (LA), LV end-diastolic diameter (LVEDD), and LVESD were recorded as anteroposterior measurements in the parasternal long-axis view. EF was calculated using the modified biplane Simpson method. Preoperative MR severity was determined by color Doppler mapping, MR jet area, ratio of MR jet area to LA area, proximal isovelocity surface area, and vena contracta. Forward stroke volume (SV) was derived from the velocity-time integral of the pulsed Doppler LV outflow tract velocity signal and the LV outflow tract diameter. Continuous-wave Doppler was used to measure the peak pressure gradient of tricuspid regurgitation (TR) using the Bernoulli equation. Pulmonary artery systolic pressure (PAPs) values were obtained by adding the estimated right atrial pressure to peak TR pressure gradient. The global right ventricular systolic function was evaluated by tricuspid annular plane systolic excursion (TAPSE) and tricuspid lateral annular systolic velocity (Tri S). Postoperative echocardiographic examination was performed 3 months after surgery.

Calculation of myocardial energy expenditure

Sarnoff et al. (7) clarified the primary role of the tension applied to the LV throughout systole in determining myocardial O_2 consumption. The tension- time index has been considered to be the most accurate indirect index of myocardial oxygen consumption and MEE (7). LV end-systolic stress is a measure of the systolic tension applied to the myocardium at end-systole that can be calculated noninvasively with echocardiography (8). LV circumferential end-systolic stress (cESS) was extrapolated with TTE at the mid-wall from M-mode tracings, using a formula derived from the cylindric model by Gaasch et al. (9, 10) (Fig. 1).

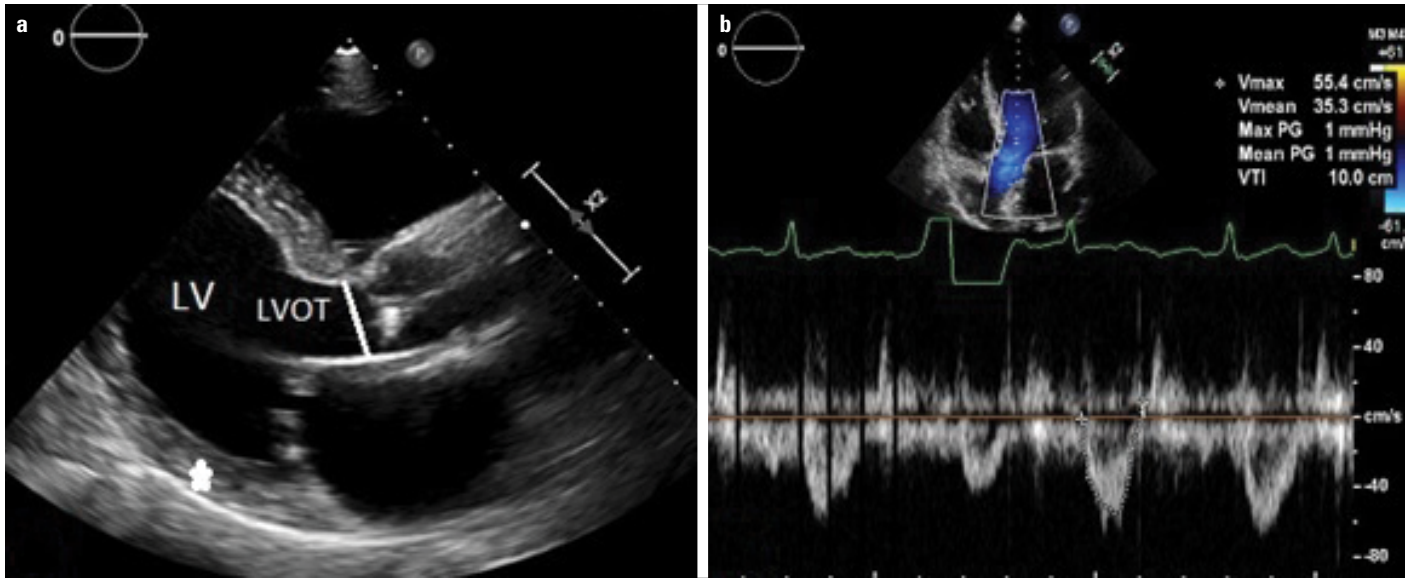

Figure 1. (a) Parasternal long-axis view of transthoracic echocardiography. MEE can be calculated by the formula explained in the text. PWT (marked with asterisk), LV diameters, ejection time, LVOT diameter, LVOT, and VTI are needed for the calculation. (b) Ejection time and LVOT VTI (pulsed Doppler of left ventricular outflow track and trace of velocity time integral) are shown

LV - left ventricle; LVOT - left ventricular outflow tract; MEE - myocardial energy expenditure; PWT - posterior wall thickness; VTI - velocity time integral

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Assuming that cESS is a representative measure of the systolic tension applied to the myocardium during the ejection phase, using Doppler echocardiography to estimate SV (11) and transaortic Doppler flow to the myocardium during LV ejection, MEE per systole was calculated as:

MEEs=cESS (kdyne/cm^2)×ejection time (ET)×SV×4.2×10^{-7}

MEE per minute (MEEm) was calculated as (12):

MEEm=MEE per systole × heart rate

Laboratory data

Blood samples were drawn on the same day of TTE before surgery for N-terminal pro-brain natriuretic peptide (NT-proBNP), biochemistry, and hemogram analysis.

Statistical analysis

The data were presented as mean±SD and median (interquartile range) for continuous variables and as percentage (number of cases) for categorical variables. Normal distribution was tested using Kolmogorov-Smirnov test and confirmed using skewness and kurtosis tests. Logarithmic transformation was performed for some variables due to skewed distribution. Independent samples t-test was used to test the difference between the continuous variables that showed normal distribution between the 2 groups. Mann-Whitney U test was used to compare 2-group non-normally distributed variables. Pearson chi-square, Fisher's exact test, and continuity correction (Yates's correction) test were used to test categorical variables. Percentage change EF was calculated by (EF postoperative–EF preoperative)/EF preoperative x 100 for each patient. The correlation coefficients were presented using Spearman's correlation analysis to determine univariate analyses. We used the independent variables that are significant at the 5% significance level from these univariate analyses as covariates (NT-proBNP, ESS, LA) and preoperative EF that has the most probability to affect postoperative EF according to recent articles in our multiple logistic regression models (13). The results of the models are reported as beta, P values, odd ratios (ORs), and 95% confidence intervals (CIs). P<.05 was considered significant for all tests. SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) was used.

Results

A total of 85 patients (median age, 65 years; 40 males) were enrolled into the study. MR was classified as degenerative mitral valve disease, rheumatic valve, and functional in 36 (42.4%), 21 (24.7%), and 28 (32.9%) patients, respectively. Comorbidities were hypertension in 51 (60%) and DM in 24 (28.2%) patients; 29 patients had AF. Of these 85 patients, 50 had successful mitral valve surgery. Consequently, 49 patients were included in our study due to 1 missing data; 9 patients underwent mitral valve repair, 36 underwent mechanical prosthetic valve replacement, and 4 patients had bioprosthetic valve replacement. Complications occurred in 12 patients during hospitalization. The events were 4 mortality, 5 acute renal failure, 11 prolonged (>48 h) inotropic use, and 9 new AF.

Correlation analysis performed between preoperative EF and some specific variables demonstrated a negative correlation between preoperative EF and NT-proBNP, ESS, MEEs, and MEEm and also positive correlation between preoperative EF and ERO (Table 1). Consequently, patients with reduced EF had higher MEE demonstrated with ESS and MEE.

Table 1. Univariate analysis using Spearman's correlation coefficients between preoperative ejection fraction and some specific variables

	Preop EF	Age	NT-proBNP	LA	LAVI	ERO	ESS	MEEs	MEEm
Preop EF	1.000								
Age	-.166	1.000							
	.129	.							
NT-proBNP	-.461	.325	1.000						
	.000*	.003	.						
LA	-.126	.013	.152	1.000					
	.251	.907	.167	.					
ERO	.277	-.209	-.207	.415	.242	1.000			
	.010*	.055	.059	.000	.025	.			
ESS	-.532	-.130	.166	.241	.154	-.088	1.000		
	.000*	.236	.132	.026	.159	.421	.		
MEEs	-.345	-.173	-.163	-.032	-.121	-.088	.680	1.000	
	.001*	.112	.138	.770	.271	.422	.000	.	
MEEm	-.352	-.245	-.056	.034	-.045	-.114	.739	.908	1.000
	.001*	.024	.611	.759	.680	.297	.000	.000	.

P values reported under correlation coefficients.
*Denotes a significance level of 0.05 or less
EF - ejection fraction; ERO - effective regurgitant orifice; ESS - circumferential end-systolic stress; LA - left atrium; MEEm - myocardial energy expenditure per minute; MEEs - myocardial energy expenditure per systole; NT-proBNP - N-terminal pro-brain natriuretic peptide

Forty-nine patients were divided into 2 groups according to absolute difference of postoperative differentiation of EF. If the absolute decrease is >5%, patients were included in postoperatively decreased EF group (14). Comparison of clinical and laboratory characteristics between patients with decreased and nondecreased postoperative EF is presented in Table 2. In postoperatively decreased EF group, basal NT-proBNP, LA, and ESS were significantly higher. Other demographic and clinical factors were not significantly different between the 2 groups. Although MEEs and MEEm were higher in decreased EF group, it did not reach statistical significance.

On multiple logistic regression analysis, taking into consideration the covariates of univariate regression analysis (preoperative EF, LA, ESS, NT-proBNP), LA (OR, 1.131; 95% CI, 1.016–1.259; p=.025) and cESS (OR, 1.014; 95% CI, 1.000–1.029; p=.047) were found to be independent predictors of postoperative EF reduction (Table 3).

Discussion

Our preliminary prospective study provides findings that higher LA and cESS are independent predictors of postoperative EF reduction. We designed this study with the assumption that MEE would predict postoperative EF reduction. Although it was higher in postoperatively decreased EF group, it did not

Table 2. Comparison of clinical and laboratory characteristics between patients with reduced and nonreduced postoperative ejection fraction

	Postoperatively nonreduced EF (n=25)	Postoperatively decreased EF (n=24)	*P* value
Gender (male) (%)	13 (54.2)	12 (50)	1.0
Diabetes mellitus (%)	5 (20)	9 (37.5)	0.217
Hypertension (%)	17 (68)	11 (45.8)	0.154
Smoking (%)	4 (16)	3 (12.5)	1.0
NYHA class (2<) (%)	10 (40)	15 (62.5)	0.156
Etiology			
RHD	6 (24)	6 (25)	
Degenerative	9 (36)	13 (54.2)	0.305
Functional	10 (40)	5 (20.8)	
Age	59±10	59±16	0.978
BMI	29±5	28±5	0.787
Hgb (g/L)	12.3±1.9	12.7±1.8	0.482
Creatinine (mg/dL)	0.88±0.20	0.85±0.17	0.646
NT-proBNP	483 (95-1314)	1161 (494-2325)	**0.035**
SBP	126±15	127±18	0.743
DBP	75 (70-88)	81 (70-90)	0.107
HR	78±18	85±19	0.208
Preop EF	53 (41-63)	60 (49-65)	0.091
LA (mm)	42±6.5	47±6	**0.007**
ERO	0.45±0.18	0.48±0.18	0.540
SV	61±16	53±15	0.060
ET	286±30	278±27	0.340
TAPSE (mm)	21±3.7	20±3	0.346
PAPs (mm Hg)	39±11	41±14	0.481
cESS (kdyne/cm^2)	209±86	264±61	**0.014**
MEEs (cal/systole)	1.6±0.8	1.69±0.75	0.717
MEEm (cal/min)	114 (73-139)	146 (85-185)	0.187
Total operation time	240 (198-296)	240 (225-300)	0.562
CPBT (min)	118 (107-137)	110 (98-185)	0.762
XCT (min)	78 (64-97)	77 (66-114)	0.658

BMI - body mass index; CPBT - cardiopulmonary bypass time; DBP - diastolic blood pressure; EF - ejection fraction; ET - ejection time; ERO - effective regurgitant orifice; cESS - circumferential end-systolic stress; Hgb - hemoglobin; HR - heart rate; LA - left atrium; MEEm - myocardial energy expenditure per minute; MEEs - myocardial energy expenditure per systole; NT-proBNP - N-terminal pro-brain natriuretic peptide; NYHA - New York Heart Association; PAPs - pulmonary artery systolic pressure; SBP - systolic blood pressure; SV - stroke volume; TAPSE - tricuspid annular plane systolic excursion; XCT - aortic cross-clamping time

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Table 3. Multiple logistic regression analysis for independent predictors of decrease in ejection fraction

	β	OR	P	95% CI
EF basal	0.026	1.027	0.593	0.933-1.130
LA	0.123	1.131	0.025	1.016-1.259
ESS	0.014	1.014	0.047	1.000-1.029
NT- proBNP	0.001	1.001	0.101	1.000-1.001

Hosmer-Lemeshow test, 0.111; Nagelkerke R square, 0.424.
EF - ejection fraction; ESS - end-systolic stress; LA - left atrium; NT-proBNP - N-terminal pro-brain natriuretic peptide

reach statistical significance. In postoperatively decreased EF group, basal NT-proBNP, LA, and cESS were significantly higher. MEE was higher in patients with severe MR who had low EF (<50%) compared with normal EF (≥50%). Moreover, negative correlation between preoperative EF and NT-proBNP, ESS, MEEs, and MEEm and positive correlation between preoperative EF and ERO were found. We based on this study according to a hypothesis that overloaded heart requires more myocardial energy and patients with higher external work may be exposed to further EF reduction and also more cardiovascular events postoperatively.

Starling and Visscher (15) and Bing et al. (16) demonstrated that LV external work was consistent with mean aortic pressure and cardiac output. Sarnoff et al. (7) described the primary role of the systolic stress applied to LV in determining myocardial oxygen consumption or energy expenditure. Considering this, LV work can be calculated from the end-systolic stress multiplied by ET index and SV. LV MEE is higher in systolic dysfunction due to LV enlargement and higher LV mass index (17). LV ET and SV were also lower in more severe LV systolic dysfunction. Notwithstanding reduced ET and SV, MEEm was higher due to more than offset of higher wall stress and heart rate in patients with lower EF. In our study, MEE was higher but not a predictor as cESS, which can be explained by heart rate and ET in its formula.

EF, which indicates myocardial contractility, may be unusually high even in the early course of MR due to the inverse relationship with afterload (18). Preload and afterload increase after correcting MR. High afterload leads to increase in metabolic demand and one may expect that ventricular function and efficiency may reduce. However, the pathophysiology of severe MR is gradual and appears to be reversible early in the disease. With preserved contractility and efficiency, the myocardium is able to maintain forward SV after surgery. If the ventricular injury is irreversible, postoperative reduced EF could certainly be expected. To overcome this phenomenon, surgery should be performed before it is too late, considering LV enlargement and EF. As in our study, calculating end-systolic stress and MEE could be helpful for determining the timing of surgery. There are various techniques to assess MEE noninvasively, but TTE is the easiest and most applicable tool for MEE calculation.

In previous studies, MEE was investigated in different patient populations including those with valvular regurgitation, hypertension, systolic heart failure, syndrome X, and coronary slow flow phenomenon (4, 12, 19-21). According to a study by Çetin et al. (20), MEE was diminished in patients with reduced EF heart failure, and New York Heart Association (NYHA) III–IV patients had lower MEE than both NYHA I–II and control group. ESS was higher than the control group and MEE was an independent predictor of cardiovascular mortality (21). Again Çetin et al. (19, 20) found reduced MEE in coronary slow flow phenomenon and increased MEE in syndrome X. Palmieri et al. (12) described the correlation of MEE with the degree of mitral and aortic regurgitation and demonstrated that an increase in the degree of valvular regurgitation leads to an increase in MEE and decrease in body fat composition. Chow et al. (22) investigated myocardial energetics in patients with severe MR and showed that surgery had a beneficial effect on forward SV and no adverse effects on oxidative metabolism or total work metabolic index.

The major limitation of our study is not to confirm these parameters with invasive procedures or myocardial performance indicators of myocardial scintigraphy like PET or MR. Another limitation is the small sample size, which weakened the statistical power of our results. When measuring MEE, requirement of many measurements using echocardiography increases the probability of mistake. Consequently, further studies are needed to confirm our hypothesis-based study.

Conclusion

In conclusion, patients with mitral valve surgery due to severe MR whose EF reduced postoperatively had higher LA, NT-proBNP, and cESS. Higher LA and cESS were independent predictors of postoperative EF reduction. The idea of preoperative high end-systolic stress could predict postoperative EF decrease and hence could be helpful for determining the timing of mitral valve surgery.

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