Left Ventricle Myocardial Work Correlated with Functional Capacity in Severe Rheumatic Mitral Stenosis with Preserved Left Ventricular Ejection Fraction

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Abstract

Background and Aims: Functional capacity is reduced in mitral stenosis (MS) patients. Previous studies showed a correlation between left atrial strain and functional capacity in this population. However, currently, no left ventricle (LV) echocardiographic parameters were associated with functional capacity in patients with MS. Noninvasive LV pressure-strain loop analysis is a new echocardiographic method for evaluating LV function, integrating longitudinal strain from speckle-tracking analysis and noninvasively measured blood pressure to estimate myocardial work (MW) that overcomes the preload-dependent characteristics conventional parameters by integrating afterload. This study aimed to evaluate the association between MW and functional capacity measured using exercise tests in patients with severe MS and preserved LV ejection fraction (LVEF). **Methods:** Adult patients with symptomatic severe rheumatic MS (mitral valve area <1.5 cm^2), and preserved LVEF (>50%) and sinus rhythm who underwent echocardiography and exercise stress test in our hospital from 2019 to 2021 were included. Exclusion criteria were suboptimal image quality for myocardial deformation analysis, significant mitral regurgitation or aortic valve lesions, coronary artery disease, intracardiac shunt, and atrial fibrillation. Standard echocardiographic parameters were measured, and all MW parameters were included. Exercise treadmill testing was performed using the modified Bruce protocol. **Results:** A total of 33 individuals with isolated severe rheumatic MS in sinus rhythm (age 39.8 ± 9.8 years) were included in the study. Patients with severe isolated MS showed significantly impaired LV-global longitudinal strain values compared to normal reference values. Furthermore, patients with severe MS showed significantly lower values of global work index, global constructive work, and efficiency compared to normal values and higher wasted work. Global work efficiency was significantly correlated to the duration of exercise ($P = 0.025$, Pearson's $r = 0.389$). **Conclusions:** In stable patients with isolated severe mitral stenosis, MW efficiency significantly correlated with functional capacity measured objectively through exercise testing.

Keywords: Functional class, mitral stenosis, myocardial work

Introduction

The incidence of mitral stenosis (MS) due to rheumatic heart disease (RHD) has decreased in developed countries; however, MS still results in significant morbidity and mortality worldwide. According to the data published by The Global Burden of Disease in 2019, at least 40.50 million people worldwide suffer from RHD, an increase from 33.40 million in 2015.[1,2] Previous studies in Asia have estimated a current RHD burden of 10.8–15.9 million patients, accounting for 356,000–524,000 deaths per year.[3] With the current high global burden of RHD, disparity occurs between the number of patients and the capacity of the health infrastructure to deal with the high number of cases, which results in patients presenting at a later and more advanced stage of disease, assessment of LV function

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and mechanics using strain measurements has the potential to determine an early course of treatment for these patients.

Left ventricle (LV) mechanics are impaired in patients with MS, while LV ejection fraction (LVEF) remains intact. We have previously shown an impairment in LV global longitudinal strain (GLS).[4] The predictive value of LV longitudinal strain in various cardiovascular diseases, including in patients with valvular disease, has been confirmed in several studies.[5,6] The influence of increased afterload on longitudinal strain reduction was previously established, which might lead to misinterpretation of the true contractile function of the myocardium and can lead to ambiguous conclusions regarding decreased myocardial function.[7] The load-dependent limitation of strain might be improved by measuring myocardial work (MW), which corrects for this by using both longitudinal strain and afterload.[8] MW parameters were previously determined during cardiac catheterization.[9] However, this method is an invasive and not practical method for routine clinical assessment. Subsequently, measurement of echocardiography-derived MW parameters was established and validated by Russell *et al*.[10,11]

Our recent study showed that severe MS had a significant impact on MW in terms of increased global wasted work (GWW) and reduced global work efficiency (GWE).[12] This can be explained by the fact that MW takes into account not only LV longitudinal mechanics but also arterial blood pressure and timing of valvular events, which altogether provide pressure-strain loops (PSLs) that can estimate LV performance in a noninvasive manner.

Functional capacity is commonly reduced in MS patients; however, very few studies explore the association of echocardiographic parameters and functional capacity in MS patients.[13,14] However, the relationship between MW parameters and functional capacity is unknown. We hypothesize that echocardiographic-derived MW correlates to functional capacity in MS patients. In this study, we aimed to evaluate echocardiography-derived MW in patients with severe isolated MS, as well as the association between MW and functional capacity measured using exercise tests in these patients.

Methods

Study population

This study was part of an MS study conducted at the National Cardiovascular Center Harapan Kita, Jakarta, Indonesia. We retrospectively included adult patients with symptomatic severe rheumatic MS (mitral valve area <1.5 cm^2),[15] and preserved LVEF (>50%) and sinus rhythm who underwent both echocardiography examination and treadmill stress testing in our hospital from January 2019 to September 2021. Exclusion criteria were suboptimal image quality for myocardial deformation analysis, significant mitral regurgitation or aortic valve lesions, coronary artery disease (CAD), intracardiac shunt, and atrial fibrillation (AF) (during echocardiography or stress testing). Exercise treadmill testing was performed on the same day with echocardiographic examination. Ethical clearance for this study was issued by the Institutional Review Board of the National Cardiovascular Center Harapan Kita. Letter No. LB.02.01/VII/469/KEP 070 / 2020.

Echocardiographic data acquisition

Transthoracic echocardiographic images were recorded using a Vivid 7, E9, or E95 ultrasound system with M4V or M5S transducers (General Electric Vingmed Ultrasound, Milwaukee, Wisconsin, USA) with patients at rest in the left lateral decubitus position. Electrocardiogram-triggered echocardiographic data were acquired and digitally stored in cine-loop format for offline analysis with EchoPac (EchoPac 204, General Electric Vingmed Ultrasound, USA). Grayscale images were saved at a frame rate of 70–90 frames/s. LV end-diastolic and end-systolic volumes were measured in the apical two- and four-chamber views and the LVEF was calculated using the biplane Simpson's method. Two-dimensional (2D) and Doppler echocardiographic measurements were performed in accordance with the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[16]

Quantification of global LV myocardial work

MW was quantified using a noninvasive method based on echocardiographic strain data as well as brachial blood pressure measurements. This method has been validated in different patient subgroups.[8,10,11,17] The strain was measured using 2D speckle-tracking echocardiography by manually tracing the LV endocardial border in the apical two-, three-, and four-chamber views. A noninvasively estimated LV PSL curve was then constructed using the strain and blood pressure, and a normalized reference curve was adjusted according to the duration of the different cardiac cycle phases (defined by the timing of aortic and mitral valve events by visual assessment). MW was subsequently computed segmentally by differentiation of the strain values over time, giving the segmental shortening rate, which was then multiplied by the instantaneous LV pressure. Instantaneous power (the result) was integrated over time to yield the segmental (as well as the global) LV MW values as a function of time. During the LV ejection period, defined as the period between mitral valve closure and mitral valve opening, the total work within the area of the LV PSL represented the global work index (GWI). Global constructive work (GCW) was defined as work performed during segmental shortening in systole or during lengthening in isovolumic relaxation. GWW was defined as work performed during segmental lengthening in systole or work performed during segmental shortening against a closed aortic valve in isovolumic relaxation. At the same time, GWE was calculated as the sum of constructive work in all LV segments, divided by the sum of constructive and wasted work in all LV segments, expressed as a percentage.

Exercise test

Exercise treadmill testing was performed on the same day with echocardiographic examination using the modified Bruce

protocol. Patients were encouraged to exercise if possible and achieving target heart rate alone was not used as a justification for terminating exercise. Testing was symptom limited and was terminated if patients reported limiting symptoms of dyspnea, fatigue, and chest pain or for medical reasons, including ischemic ST-segment changes, abnormal blood pressure response to exercise, or ventricular ectopy.

Statistical analysis

Categorical data are presented as frequencies and percentages. Continuous variables are reported as mean ± standard deviation (SD) if normally distributed and as the median and interquartile range if nonnormally distributed. Calculations for univariate mean ± SD and median (minimum-maximum) were performed using SPSS. Categorical data were compared with the Chi-squared test, and continuous data were compared using the Student's *t*-test if normally distributed or the Mann–Whitney *U*-test or the Kruskal–Wallis test if nonnormally distributed. Correlations of GWE with other echocardiographic parameters and functional capacity were assessed using Pearson's method and Spearman's method for continuous normally distributed and ordinal and continuous nonnormally distributed parameters, respectively. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 25.0 (SPSS, Armonk, NY, USA).

Results

There were 142 severe MS patients planned to undergo percutaneous transluminal mitral commissurotomy during the study period. However, 109 patients were excluded due to AF, suboptimal image quality, or due to a cancelation of their exercise test due to various reasons. A total of 33 individuals with isolated severe rheumatic MS in sinus rhythm (age 39.8 ± 9.8 years) were included in the study [Figure 1].

Demographic and conventional echocardiographic characteristics

Demographic and conventional echocardiographic characteristics are summarized in Table 1. Patients with MS in our study were predominantly female (84%), and had good right ventricular contractility.

Two-dimensional speckle-tracking data: LV-global longitudinal strain and myocardial work

Patients with severe isolated MS showed significantly impaired LV-GLS values as compared with reference values. MW parameters are presented in Table 2. Patients with severe MS showed significantly lower values of GWI, GCW, and efficiency and higher GWW compared to reference values.

Correlation of myocardial work parameters with functional capacity

We observe a statistically significant correlation between GWE and exercise duration [$P = 0.025$, Pearson's $r = 0.389$, Figure 2]. No significant correlation were observed between other MW indices (GWI, GCW, and GWW) with exercise duration.

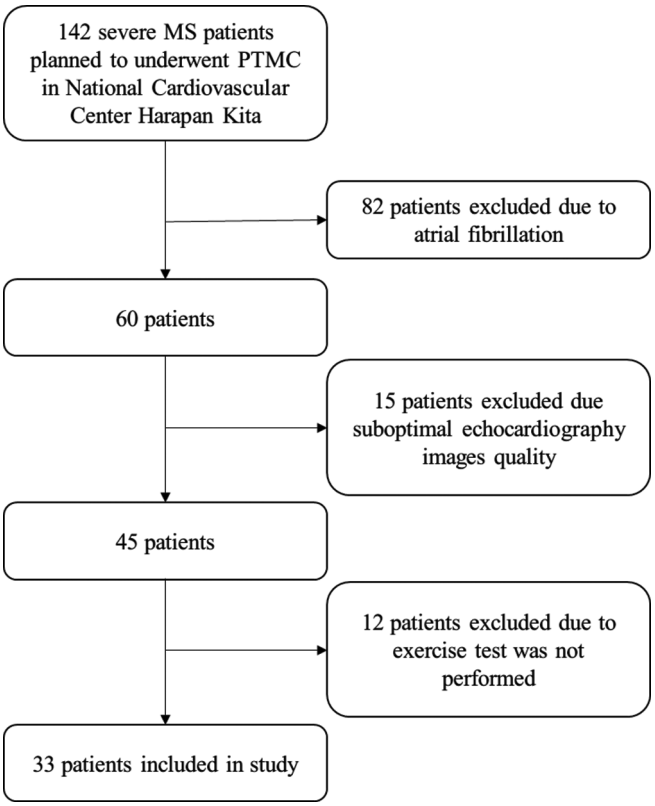

Figure 1: Patient inclusion flowchart. PTMC = Percutaneous transluminal mitral commissurotomy

Table 1: Demographic and conventional echocardiographic characteristics

	n=33
Female	84%
Age (years)	39.8±9.8
SBP (mmHg)	119±18
DBP (mmHg)	73±11
BSA (m^2)	1.5±0.1
BMI (kg/m^2)	22.1±4.2
LAVi (mL/m^2)	67 (52–101)
LV EDD (mm)	42±8
LV ESD (mm)	27±6
LVEF (%)	63±7
TAPSE (mm)	22±5
MVA planimetry (cm^2)	0.8±0.2
Mean MVG (mmHg)	13.8±5.1

Data are presented as *n* (%), mean±SD, or median (IQR) as appropriate. BSA=Body surface area, BMI=Body mass index, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, HR=Heart rate, LAVi=Left atrium volume index, MVA=Mitral valve area, MVG=Mitral valve gradient, LV=Left ventricle, TAPSE=Tricuspid annular plane systolic excursion, SD=Standard deviation, IQR=Interquartile range, EDD=End-diastolic diameter, ESD=End-systolic dimension, LVEF=LV ejection fraction

Discussion

This is the first study that explores the association of MW in severe rheumatic MS patients with functional capacity measured objectively through an exercise stress test. The main

Table 2: LV - global longitudinal strain and myocardial work efficiency

	Isolated severe MS ($n=33$)	Reference values (JASE and EACVI-NORRE study)[18,19]
V-GLS (%)	−14.4±3.5	−21.3±2.0
GWI (mmHg%)	1350±422	1896±308
GCW (mmHg%)	1833±506	2232±331
GWW (mmHg%)	196 (134–248)	78 (53–122)
GWE (mmHg%)	90 (84–92)	96 (94–97)

GWI and GCW presented as mean±SD while GWW and GWE presented as median (IQR). GWW=Global waste work, GWI=Global work index, GCW=Global constructive work, GWE=Global work efficiency, IQR=Interquartile range, MS=Mitral stenosis, SD=Standard deviation, EACVI-NORRE=European Association of Cardiovascular Imaging-normal reference ranges for echocardiography

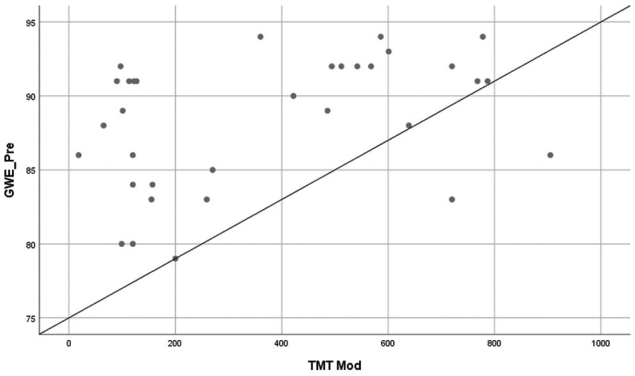

Figure 2: Correlation between global work efficiency (GWE) and exercise duration. Pearson's correlation coefficient (*r*). Statistically significant correlation between GWE and exercise duration were observed ($P = 0.025$; $P = 0.389$). GWE = Global work efficiency

findings of the present study can be summarized as follows: (1) Patients with severe rheumatic MS showed impaired values of GLS and global LV MW parameters (GWI, GCW, GWW, and GWE) compared to normal references values and (2) in patients with isolated severe MS, GWE significantly correlated with functional capacity measured objectively with exercise test.

Few studies show significant associations between echocardiographic parameters and functional capacity in a patient with MS.[13,14] This is the first study that shows a significant relationship between LV parameters represented as LV myocardial function based on LV MW with functional capacity. Previous studies did not show a significant relationship between conventional LV parameters (ejection fraction or LV-GLS) with functional capacity. The study by Chien *et al*. showed that atrial deformation parameters, speckle tracking echocardiography-derived LA strain (LAS), and peak positive filling strain rate (LASRr) during the LA reservoir phase, are independently correlated with heart failure symptoms.[14] However, their study uses a subjective assessment of functional capacity (NYHA functional class). The study by Osman Amin *et al*. also reported that LA deformation (LAS and LASRr) was significantly correlated with heart failure symptoms (NYHA Classes III and IV) in patients with MS.[13] None of these studies performed echocardiographic strain measurements of the left ventricle, correlation with functional capacity were performed using only atrial strain and deformation data.

MW measurement incorporates blood pressure into the equation and consequently provides incremental information to LVEF and LV longitudinal strain that is sensitive to LV afterload. Russell *et al*. reported that increased afterload induces a reduction of longitudinal strain, which is not associated with decreased contractility but with a change in afterload.[10,11]

The inclusion of blood pressure parameters in MW assessment is crucial due to impaired strain parameters in hypertensive patients. Changes in strain parameters, particularly longitudinal strain, can even be observed in prehypertensive and mask hypertension patients.[10,20-22] Assessment of strain echocardiography can identify early and subtle changes of LV mechanics in hypertensive patients.[23] Examination of left ventricular MW and strain parameters using echocardiography has the advantages of being rapid, noninvasive, and sensitive in detecting early changes of left ventricular dynamics, and it can be done in an outpatient setting. This examination is also potentially widely available using current echocardiographic machines.

Furthermore, the PSL area reflects myocardial metabolic demand (myocardial glucose metabolism measured by positron emission tomography) and oxygen consumption, which showed that the MW method provided insight into myocardial energetics.[10] These studies showed that MW was independently associated with metabolism in the heart. This may explain why GWE was significantly correlated with functional capacity in this study. An illustrative example of the measurement of MW in patients with severe MS and normal individuals is shown in Figure 3.

Echocardiographic evaluation of MW has several important advantages over invasive measurements obtained during heart catheterization. This is a noninvasive, potentially widely available, and rapid method that is not related to any complication for the patient. MW was reported to be a more sensitive marker of myocardial impairment than longitudinal strain and, therefore, could be used in the evaluation of LV function in MS patients.

Functional capacity is a complex parameter that is determined by various factors, not only by cardiac (echocardiographic) parameters but also by demographic and psychological factors, and the function of the other organs.[24,25] In patients with MS, the stenotic mitral valve leaflet causes an impairment of left ventricular filling that may be followed by reduced stroke volume and reduced perfusion to multiple organs, which ultimately may cause reduced functional capacity. Furthermore, the presence of AF and pulmonary hypertension commonly found in RHD patients may also have a negative impact on functional capacity.[26] In RHD MS patients, stenotic

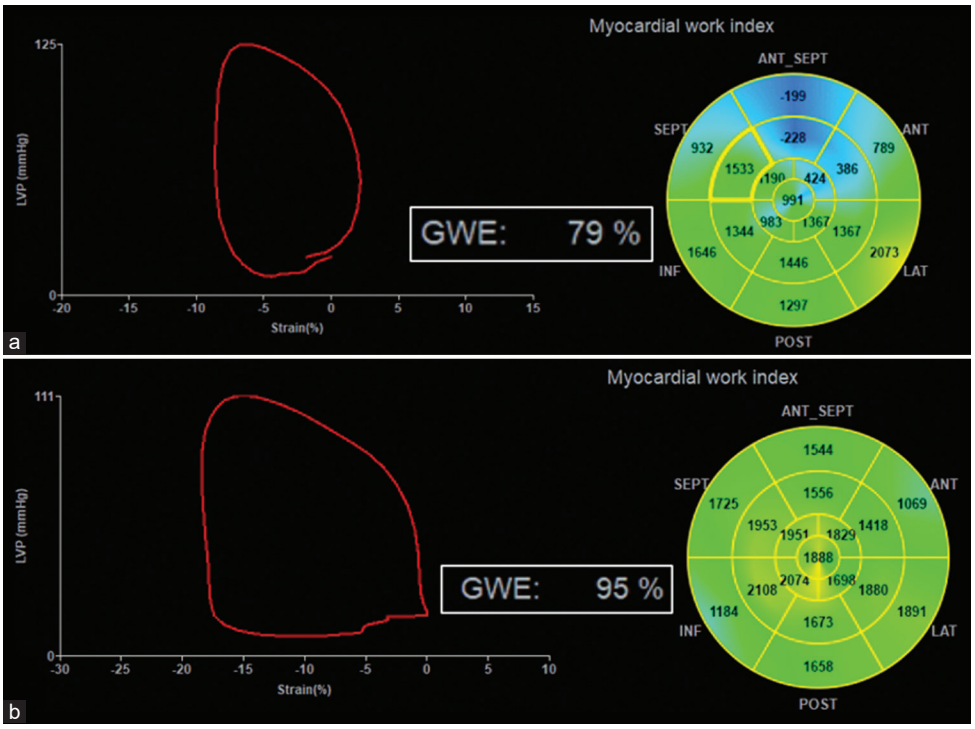

Figure 3: Global LV myocardial work efficiency in a patient with isolated mitral stenosis (a) and a healthy individual, (b) Note the progressive reduction in global LV myocardial work from 95% in healthy individuals to 79% in a patient with severe mitral stenosis. GWE = Global work efficiency

mitral valves will cause impaired LV filling and an increase in LA pressure. This, in turn, will cause impaired LV filling, atrial enlargement, and pulmonary hypertension. Atrial enlargement will pose as a substrate of AF occurrence, which will diminish cardiac output even further and affect the functional class of patients.[27] Evaluation of functional capacity is very important in patients with valvular heart disease, including rheumatic MS, to determine the timing of intervention or to evaluate the results of treatment.[15]

However, in most cases, evaluation is based on the subjective assessment using NYHA functional capacity, which is prone to inherent limitations of self-reporting symptoms, especially unreliable in patients with low economical or educational status. On the other hand, the application of objective-based assessment using various exercise tests is not widely practiced in daily clinical settings due to the potential of events during exercise testing in this population or due to a lack of adequate resources. We showed that the exercise test in stable MS patients was safe with adequate screening and monitoring; no significant adverse effect or need for hospitalization related to stress test was observed. Hence, measurement of MW on top of subjective assessment to predict functional capacity may be performed if objective assessment is not feasible.

Study limitations

This study is subject to the inherent limitations of a single-center retrospective analysis. The inclusion of only patients with severe MS and in sinus rhythm might limit the generalizability of our results to all MS patients that also include mild and moderate MS severity. Furthermore, the exclusion of significant CAD that may cause a decrease in GWE value was performed only with history taking and electrocardiography results. However, our patient cohort was young (mean age <40 years) which makes the likelihood of CAD low.

Clinical implications

Exercise testing in stable severe MS patients is safe with adequate screening and monitoring. Measurement of MW as an add-on of subjective assessment to predict functional capacity may be performed if objective assessment is not feasible. Examination of left ventricular MW and strain parameters using echocardiography has the advantages of being rapid, noninvasive, sensitive in detecting early changes of left ventricular dynamics, and can be done in an outpatient setting. This examination is also potentially widely available using current echocardiographic machines.

Conclusions

In stable patients with isolated severe MS, patients with severe isolated MS showed significantly impaired LV-GLS values compared to normal reference values. Lower values of GWI, GCW, and efficiency were also observed. GWE is correlated with functional capacity measured objectively with exercise testing.

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Conflicts of interest

There are no conflicts of interest.

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