

Original Article



Global Left Ventricular Myocardial Work Efficiency in Patients With Severe Rheumatic Mitral Stenosis and Preserved Left Ventricular Ejection Fraction

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ABSTRACT

BACKGROUND: Assessment of left ventricular (LV) function plays a pivotal role in the management of patients with valvular heart disease, including those caused by rheumatic heart disease. Noninvasive LV pressure-strain loop analysis is emerging as a new echocardiographic method to evaluate global LV systolic function, integrating longitudinal strain by speckle-tracking analysis and noninvasively measured blood pressure to estimate myocardial work. The aim of this study was to characterize global LV myocardial work efficiency in patients with severe rheumatic mitral stenosis (MS) with preserved ejection fraction (EF).

METHODS: We retrospectively included adult patients with severe rheumatic MS with preserved EF (> 50%) and sinus rhythm. Healthy individuals without structural heart disease were included as a control group. Global LV myocardial work efficiency was estimated with a proprietary algorithm from speckle-tracking strain analyses, as well as noninvasive blood pressure measurements.

RESULTS: A total of 45 individuals with isolated severe rheumatic MS with sinus rhythm and 45 healthy individuals were included. In healthy individuals without structural heart disease, the mean global LV myocardial work efficiency was 96% (standard deviation [SD], 2). Compared with healthy individuals, median global LV myocardial work efficiency was significantly worse in MS patients (89%; SD, 4; $p < 0.001$) although the LVEF was similar.

CONCLUSIONS: Individuals with isolated severe rheumatic MS and preserved EF, had global LV myocardial work efficiencies lower than normal controls.

Keywords: Echocardiography; Noninvasive myocardial work; Mitral valve stenosis; Left ventricular function; Rheumatic heart disease

INTRODUCTION

Rheumatic heart disease (RHD) and its complications are significant healthcare problems in middle- and low-income countries due to their very high prevalence and tendency to affect patients at a productive age. Moreover, due to the female predominance of RHD,¹⁾ the maternal mortality rate in countries with a high prevalence of RHD were higher. According to data published by The Global Burden of Disease in 2015, at least 33.4 million people worldwide suffer from RHD.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⁾ This is higher than the worldwide prevalence of tuberculosis in 2018, which affects approximately 10 million people.^{4,5)} RHD differs from other infectious-related conditions due to the structural cardiac changes involved in this condition leading to chronic cardiac disease. In severe cases, these pathological abnormalities cause significant hemodynamic disorders that require surgical or nonsurgical intervention. For patients with rheumatic mitral stenosis (MS), nonsurgical intervention with balloon valvuloplasty proved to be non-inferior to surgery in one survival study.⁶⁾

In daily practice, assessment of left ventricular (LV) systolic function with the LV ejection fraction (EF) remains the standard prognostic marker for patients with valvular heart disease, including that caused by RHD. However, its limitations are well known (i.e., limited reproducibility, load dependency, and certain geometric assumptions).⁷⁾ Speckle-tracking echocardiography-derived LV global longitudinal strain (GLS) has shown additional value over LVEF in predicting prognosis in several cardiac diseases.⁸⁾ However, LV GLS is still a load-dependent parameter.

Noninvasive myocardial work (MW) is a newly identified parameter for measuring LV systolic function derived from LV pressure-strain loop (PSL) analysis incorporating both noninvasive estimated blood pressure and echocardiographic strain data.⁹⁾ Russell et al.^{9,10)} demonstrated that noninvasive LV PSL corresponded well with invasively measured LV PSL, and subsequent studies have confirmed these results.¹¹⁾ However, despite showing great clinical value, there are few data on global LV MW in different cardiac pathologies, in particular heart valve disease. Most patients with rheumatic MS have a preserved LVEF. However, whether this is associated with good MW efficiency has not yet been established. We hypothesize that despite their preserved EF, patients with MS have reduced MW efficiency due to LV underfilling and increased afterload. The aim of this study was to characterize global LV MW efficiency in patients with severe rheumatic MS with preserved LVEF.

METHODS

Study population

We retrospectively included adult patients with symptomatic severe rheumatic MS (mitral valve area less than 1.5 cm²),¹²⁾ preserved LVEF (> 50%), and sinus rhythm who underwent echocardiography examinations at National Cardiovascular Center Harapan Kita, Jakarta, Indonesia 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, intracardiac shunt, atrial fibrillation (during echocardiography examination) and presence of atherosclerotic cardiovascular risk factors. Patients with concomitant mild mitral regurgitation, mild aortic stenosis, or regurgitation were not excluded. In addition, healthy individuals with structurally normal heart, no identifiable atherosclerotic cardiovascular risk factors, and without a history of cardiovascular or cerebrovascular disease were purposively selected from the normal population database in the same hospital as the control subjects to match the baseline characteristics of the MS group (**Figure 1**).

Echocardiographic data acquisition

Transthoracic echocardiographic images were recorded using a Vivid 7, E9, and E95 ultrasound system with M4V or M5S transducers (General Electric Vingmed Ultrasound, Milwaukee, WI, USA) while the patients were 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). Grayscale images were saved at a frame rate of 70 to 90 frames/sec. LV end-diastolic and end-systolic volumes were measured in the apical 2- and 4-chamber views and the LVEF was calculated using the biplane Simpson's method. 2-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.¹³⁾

Quantification of global LV myocardial work efficiency

Global LV MW efficiency was quantified using a noninvasive method that uses echocardiographic strain data as well as brachial blood pressure measurements. This method has been validated in different patient subgroups.^{9,10,14,15)} The strain was measured using 2D speckle-tracking echocardiography by manually tracing the LV endocardial border in the apical 2-, 3-, and 4-chamber views. A noninvasively estimated LV PSL curve was then constructed using the strain and blood pressure,

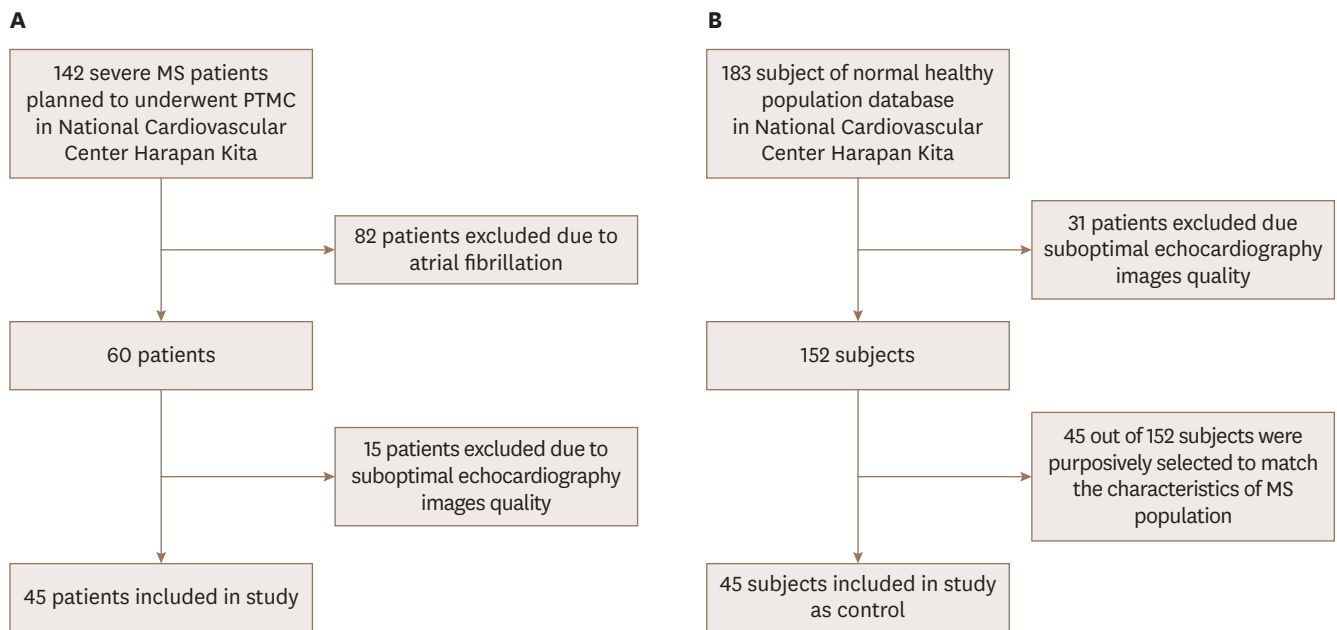


Figure 1. Flow chart of subject inclusion and exclusion criteria. (A) Forty-five patients fulfilled the inclusion criteria for the mitral stenosis group, while other subjects were excluded mostly due to their electrocardiogram showed atrial fibrillation during echocardiographic examination followed by suboptimal echocardiography image quality. (B) Forty-five subjects selected purposively from normal healthy population database in the same hospital. MS: mitral stenosis, PTMC: percutaneous transvenous mitral commissurotomy.

and a normalized reference curve, adjusted according to the duration of the different cardiac cycle phases (defined by the timing of aortic and mitral valve events), was produced. 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. The result, the instantaneous power, 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. Global wasted work (GWW) was defined as work performed during segmental lengthening in systole or during segmental shortening against a closed aortic valve in isovolumic relaxation. Global work efficiency (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.

Statistical analysis

Categorical data are presented as frequencies and percentages. Continuous variables are reported as the mean \pm standard deviation if normally distributed and as the median and interquartile range if nonnormally distributed. Categorical

data were compared with the χ^2 test. Continuous data were compared using Student's t-test if normally distributed or the Mann-Whitney U test or the Kruskal-Wallis test if nonnormally distributed. Correlations of MW efficiency with other echocardiographic parameters were assessed using Pearson's method and Spearman's method for continuous normally distributed and ordinal and continuous nonnormally distributed parameters, respectively. The interobserver and intraobserver variability of GWE was assessed in 22 randomly selected patients, and the intraclass correlation coefficients were calculated. The $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 25.0 (SPSS, Armonk, NY, USA).

RESULTS

Clinical characteristics

A total of 45 individuals with isolated severe rheumatic MS in sinus rhythm (age 39.8 ± 9.8 years) and 45 healthy individuals (age 29.7 ± 11.2 years) were included (**Figure 1**). Patients with MS were predominantly female (73%). Additionally, this group has a significantly lower body surface area and higher resting heart rate compared to the control group. Body mass index, systolic and diastolic blood pressure were similar between isolated MS and control group.

Table 1. Clinical and conventional echocardiographic characteristics

Characteristics	Isolated severe MS (n = 45)	Normal control (n = 45)	p-value
Age (years)	39.8 ± 9.8	29.7 ± 11.2	< 0.001
Male	13 (27)	31 (69)	< 0.001
BSA (m ²)	1.52 ± 0.13	1.71 ± 0.16	< 0.001
BMI (kg/m ²)	22.7 ± 4.2	23.9 ± 3.6	0.129
SBP (mmHg)	120.8 ± 17.9	120.2 ± 12.9	0.888
DBP (mmHg)	75.4 ± 13.6	71.4 ± 13.3	0.161
HR (b.p.m)	81.6 ± 15.4	69.8 ± 11.1	< 0.001
EF (%)	63.1 ± 7.6	62.7 ± 6.2	0.788
LAVi (ml/m ²)	97.1 (55.7–103.4)	27.4 ± 4.5	0.009
Peak E velocity (cm/s)	237 ± 37	90 ± 16	< 0.001
e' septal (cm/s)	5.0 ± 2.0	12.9 ± 2.9	< 0.001
e' lateral (cm/s)	4.9 ± 1.4	16.3 ± 3.4	< 0.001
E/e' average	53 ± 21.2	6 ± 1.4	< 0.001
TR Vmax (m/s)	3.4 ± 0.9	N/A	N/A
Mean MVG (mmHg)	14.3 ± 5.0	N/A	N/A
MVA (cm ²)	0.77 ± 0.24	N/A	N/A
LV GLS (%)	-14.1 ± 3.2	-19.0 ± 1.8	< 0.001

Data are presented as number (%), mean ± standard deviation or median (interquartile range) as appropriate.

BMI: body mass index, BSA: body surface area, DBP: diastolic blood pressure, EF: ejection fraction, HR: heart rate, LAVi: left atrium volume index, LV GLS: left ventricle global longitudinal strain, MS: mitral stenosis, MVA: mitral valve area, MVG: mitral valve gradient, SBP: systolic blood pressure, TR: tricuspid regurgitation.

Conventional echocardiographic characteristics

Clinical and conventional echocardiographic characteristics are summarized in **Table 1**. Patients with MS had larger LA sizes than normal controls. LVEF was similar in both groups. In addition, 84.5% of MS patients had a mitral valve area less than 1.0 cm², and a mean mitral valve gradient greater than 10 mmHg was observed in 78% of patients. Diastolic function parameters (peak E velocity and E/e' average) are significantly abnormal in patients with MS compared to the normal population ($p \leq 0.001$). E/e' average ratio in the MS group was 53 ± 21.2 , significantly higher than the normal control (6 ± 1.4).

2D speckle-tracking data: LV-GLS and myocardial work

Patients with severe isolated MS showed significantly impaired LV-GLS values compared with normal controls ($14.1 \pm 3.2\%$ vs. $19.0 \pm 1.8\%$, respectively). MW parameters are presented in **Figure 2**.

Patients with severe MS showed significantly lower values of GWI ($1,343 \pm 418$ vs. $1,769 \pm 297$ mmHg%, $p \leq 0.001$) and GCW than control subjects ($1,827 \pm 488$ vs. $2,105 \pm 336$ mmHg%, $p = 0.002$) as well as higher values of GWW (205 ± 92 vs. 75 ± 33 mmHg%, $p \leq 0.001$). Compared with that in healthy individuals, the global LV MW efficiency was significantly worse in MS patients ($89 \pm 4\%$ vs $96 \pm 2\%$, $p < 0.001$), although the LVEF was similar (**Table 2**).

Correlation of work efficiency with other parameters

Global work efficiency was not significantly related to LVEF ($p = 0.365$, $R^2 = 0.054$), MS parameters (mean mitral valve gradient: $p = 0.378$, $R^2 = 0.019$; mitral valve area: $p = 0.694$, $R^2 = 0.004$), nor left atrium volume index (LAVi; $p = 0.369$, $R^2 = 0.019$).

Reproducibility

Measurements of GWE showed good intraobserver agreement (intraclass correlation, 0.891; 95% confidence interval [CI], 0.757–0.953; $p < 0.001$) and excellent interobserver agreement (intraclass correlation, 0.913; 95% CI, 0.790–0.964; $p < 0.001$).

DISCUSSION

This is, to our knowledge, the first study analyzing MW in severe rheumatic MS. The main findings of the present study can be summarized as follows: patients with severe rheumatic MS and a preserved LVEF showed impaired values of GLS and global LV MW parameters (GWI, GCW, GWW, and GWE) compared with healthy individuals. Our normal control values of GWW and GWE are similar to a contemporary meta-analysis study of normal ranges of global LV MW indices in adults.¹⁶ We only included individuals with isolated MS without significant lesions in other valves or other structural heart diseases in order to study the effect of MS on LV mechanics and function. **Figure 3** shows a typical example of global LV MW efficiency in a patient with isolated MS and healthy control.

LV systolic function in daily clinical practice is routinely assessed by the EF, which is a prognostic marker in various studies and populations.^{17,19} However, the LVEF is very susceptible to loading conditions and has wide interobserver variability. The GLS by speckle tracking imaging has been increasingly utilized to assess subtle myocardial dysfunction. Although it is an established and well-validated parameter for the assessment of cardiac diseases, it remains limited by its load dependency.²⁰ Suga and Sagawa²¹ developed LV pressure-volume loops that were invasively obtained, providing hemodynamic measures of contractility, elastance, power, and efficiency. The area of the LV pressure-

Table 2. Myocardial work parameters

Parameters	Isolated severe MS (n = 45)	Healthy control (n = 45)	p-value
GWI (mmHg%)	1,343 ± 418	1,769 ± 297	< 0.001
GCW (mmHg%)	1,827 ± 488	2,105 ± 336	0.002
GWW (mmHg%)	205 ± 92	75 ± 33	< 0.001
GWE (%)	89 ± 4	96 ± 2	< 0.001

Data are presented as mean ± standard deviation.

GCW: global constructive work, GWE: global work efficiency, GWI: global work index, GWW: global waste work, MS: mitral stenosis.

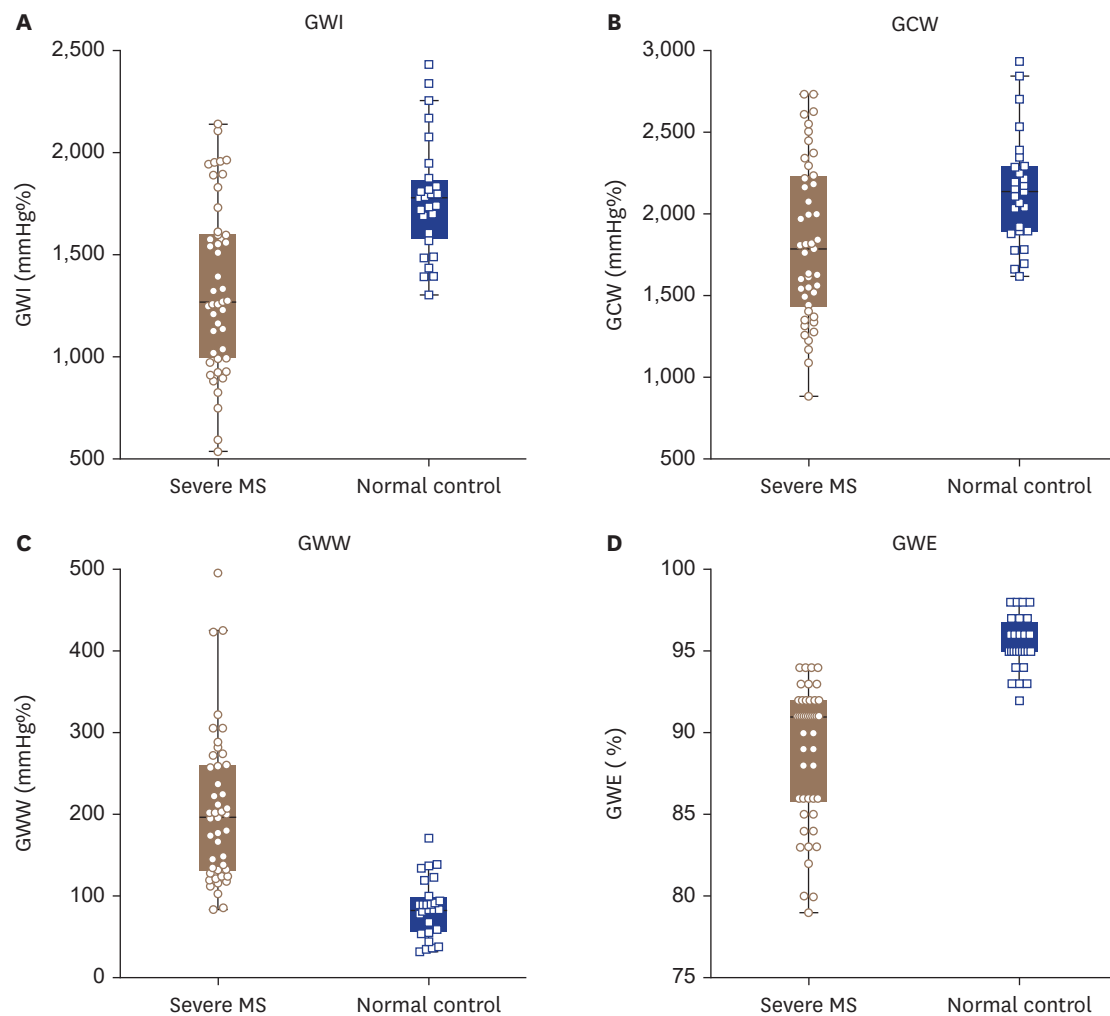


Figure 2. Myocardial work parameters. Graph of mean and standard deviation of the mean across all groups. (A) GWI, (B) GCW, (C) GWW, and (D) GWE. All myocardial work indices in severe MS group are significantly different from normal controls. GCW: global constructive work, GWE: global myocardial work efficiency, GWI: global work index, GWW: global wasted work, MS: mitral stenosis.

volume loop reflects stroke work as well as myocardial oxygen consumption, and it was later confirmed that this concept is valid. According to the same principle, the area of the myocardial force-segment length loop reflects regional MW and oxygen consumption.²¹⁾²²⁾ Because the noninvasive calculation of the myocardial force is challenging, pressure is used as a substitute for force, and the area of the LV pressure-dimension loop is used as an index of regional work.⁹⁾¹⁰⁾

MW, measured using noninvasive PSLs, is a contemporary approach for assessing LV systolic function. It overcomes the load-dependent characteristics of the EF and GLS by integrating afterload into an LV systolic function parameter.⁹⁾¹⁰⁾ In an LV with normal systolic function, increased afterload may lead to decreased global LV strain, which does not necessarily signify impaired contraction. MW gives a rough estimation of the

work that every segment of the LV produces during the cardiac cycle. This work is influenced by the power of the contraction of myocardial fibers, loading of the LV, and wall stress on the LV segments. Loading conditions consist of preload and afterload and have a pivotal role in LV contractility. Indeed, a good correlation has been shown between noninvasively measured LV PSL areas and their invasively measured equivalents, as reported by several studies.⁹⁾¹¹⁾ Russell et al.¹⁰⁾ also reported that the LV pressure-strain loop area corresponded well with the directly measured MW and reflected myocardial metabolism.

The presence of LV systolic dysfunction in patients with MS has been reported previously.²³⁻²⁵⁾ Hemodynamic and myocardial factors have been associated with LV dysfunction in those patients, including a reduction in LV filling, chronic inflammation of the myocardium, scarring of the subvalvular

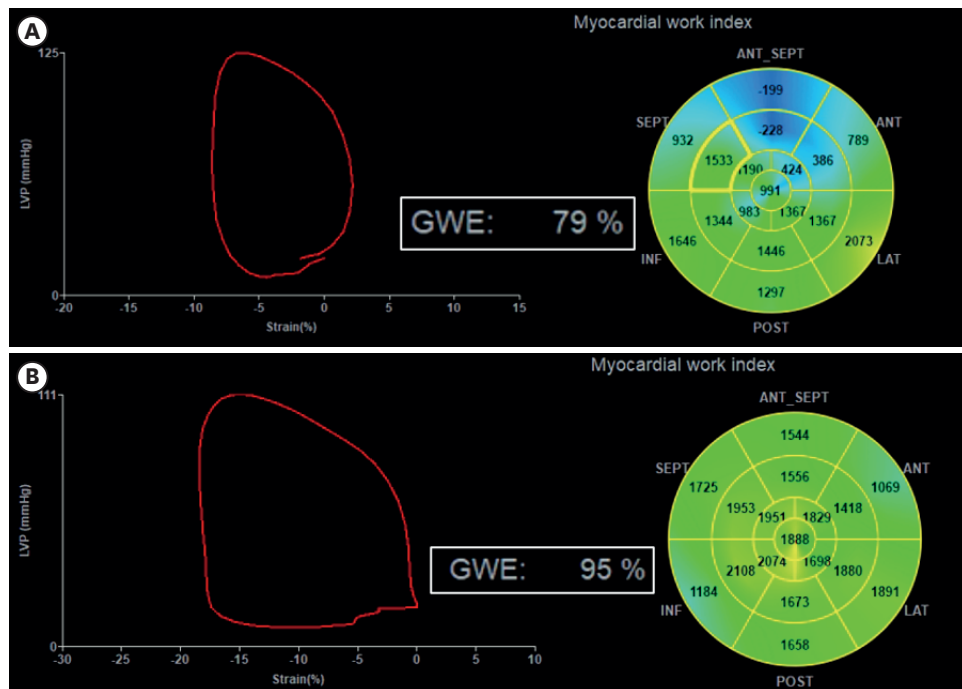


Figure 3. Global LV myocardial work efficiency in a patient with isolated mitral stenosis (A) and a healthy individual (B). Note the progressive reduction in global LV myocardial work from 95% in the healthy individual to 79% in the patient with severe mitral stenosis. GWE: global myocardial work efficiency, LV: left ventricular, LVP: left ventricular pressure.

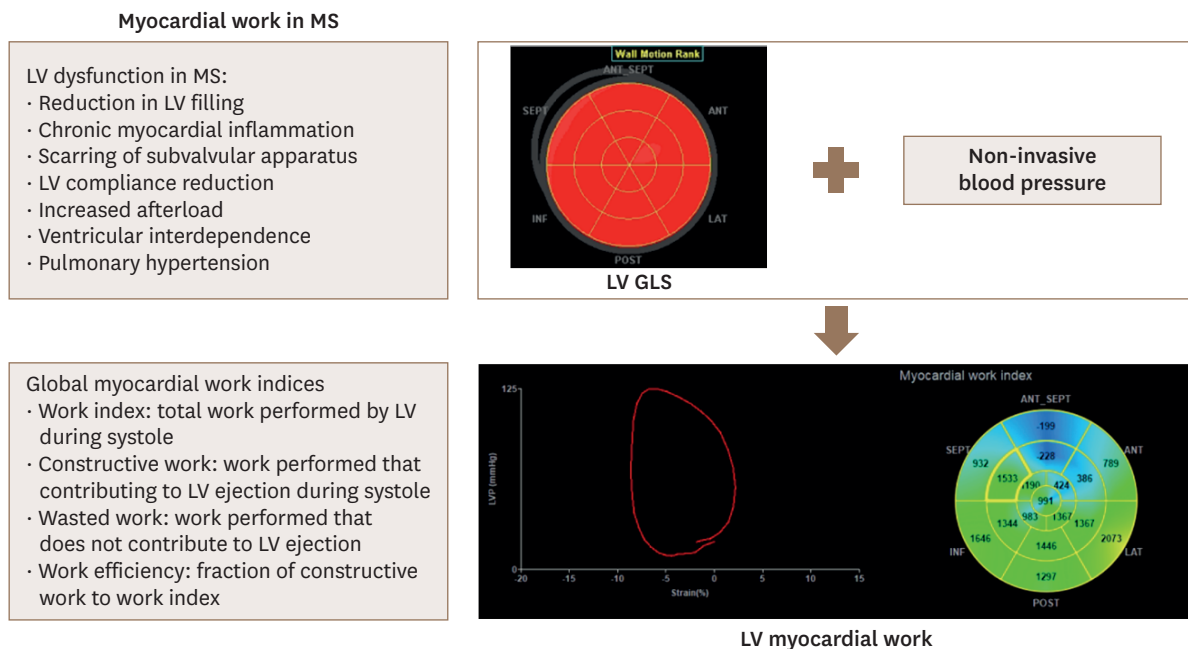


Figure 4. Myocardial work in MS. GLS: global longitudinal strain, LV: left ventricular, MS: mitral stenosis.

apparatus of the mitral valve, LV compliance reduction and diastolic dysfunction, increased afterload, abnormal right-left septal interaction (ventricular interdependence), and pulmonary hypertension (**Figure 4**).²⁶⁾²⁷⁾

Sengupta et al.²⁸⁾ showed that the mitral annular velocities measured by TDI immediately improved after percutaneous mitral balloon valvuloplasty, but not the EF, and this improvement correlated with the changes in MVA. An electron

microscopy study in MS patients by Lee et al.²⁹⁾ showed that regardless of LV function, ultrastructural changes occurred in myocardial cells in all examined specimens, but these impairments were not associated with the severity of the MS. Additionally, patients with LV dysfunction exhibited more extensive loss of myofibrils. These studies suggest that LV dysfunction in MS is dependent on both myocardial and hemodynamic factors.²⁸⁾²⁹⁾ Bilen et al.³⁰⁾ found, in concordance with the findings in the present study, that patients with MS had lower GLS values than healthy controls. Interestingly, there were no significant differences between the mild-moderate and advanced groups when considering the severity of the MS.³⁰⁾ These results suggest that subclinical LV dysfunction depends on myocardial factors rather than hemodynamic factors. Further studies are underway to confirm whether this myocardial fibrosis process can be reversed with anti-inflammatory agents.³¹⁾

Increased afterload has also been proposed as a potential cause of LV dysfunction in MS. Gash et al.³²⁾ stated that the reduction in EF can be explained by high afterload that is not met by an increase in preload due to the decline in mitral valve area in MS. They hypothesized that the high afterload results from inadequate end-systolic wall thickness, which in turn increases wall stress at a normal LV systolic pressure.³²⁾ Wisenbaugh et al.³³⁾ investigated the effect of balloon valvuloplasty on afterload, reporting no significant decrease despite a significant increase in preload. Here, in our study using the new concept of noninvasively measured MW, we further reported 1) the presence of subtle LV dysfunction in patients with severe MS, as shown by a significantly lower LV GLS than that of normal controls despite similar EF and 2) inefficiency of work performed by LV, as shown by significantly higher wasted work and lower constructive work than those of healthy individuals. Hence, the impaired MW in MS patients could be explained by the increased afterload as MW parameters also incorporated afterload in the measurement, in addition to preload.

Hence, subtle LV dysfunction and inefficiency, in addition to other mechanisms of LV dysfunction in MS that have been proposed by other authors, could be explained by the increase in afterload of the LV due to the intrinsic characteristics of MW parameters that take into account deformation and afterload components. We believe that increased afterload has an important role in the observed LV dysfunction and inefficiency unmasked by the preload-independent nature of the MW parameters used in this study. Whether this increased afterload is caused by a hemodynamic response to the low cardiac output or increased circulating vasoactive substances must be confirmed with further studies.

In this pilot study, we currently do not have data that showed additional value or prognostic implications of MW parameters in patients with severe MS compared to established LV systolic function parameters such as EF and GLS. However, these shortening indices (EF and GLS) do not reflect MW or oxygen demand. On the other hand, non-invasive MW measurement as performed in this study was reported to correspond well with invasive measurements and with directly measured MW and it reflected myocardial metabolism.¹⁰⁾ Also, studies in ischemic heart disease and nonobstructive hypertrophic cardiomyopathy showed that MW was associated with a worse long-term outcome.³⁴⁾³⁵⁾

This study also showed that patients with MS had significantly abnormal diastolic function parameters (peak E velocity, E/e' average ratio, and LAVi) compared to the normal control. However, the interpretation of this finding is challenging. Increased peak E velocity in MS patient may be caused by stenotic mitral valve, while reduced motion of basal LV segments due to tethering of stenotic mitral valve may results in reduced septal and lateral e'. Furthermore, dilatation of LA in patients with significant MS was predominantly caused by stenotic valve. Differentiating whether these abnormal diastolic function parameters were caused by LV diastolic dysfunction or by the stenotic mitral valve is challenging, no specific methods are currently available. As a result, evaluation of diastolic function in patients with significant MS was not routinely performed in daily practice.

The application of MV parameters in addition to GLS in the routine evaluation of patients with MS might improve our understanding of cardiac function in these patients at both the global and segmental levels, overcoming the load dependency of other echocardiographic parameters by incorporating afterload. This is particularly relevant in patients with MS, as afterload might change with medication and improvement of preload due to the commissurotomy procedure. However, future research is needed before applying MW parameters to patient management.

This study is subject to the inherent limitations of a single-center, retrospective analysis. The inclusion of only patients with severe MS might limit the generalizability of our results to the complete spectrum of MS, which also consists of mild and moderate severity. Furthermore, the exclusion of significant coronary artery disease that may cause a decrease in the GWE value was performed with history taking and electrocardiography findings. We exclude subjects with the presence of cardiovascular risk factors, history of coronary artery disease, and stroke. Presence of coronary artery disease However, in most subjects, this exclusion was based on clinical history. Moreover, we

purposely tried to match the age and gender between the 2 groups, however, due to limitations to our normal population database, there were still significant differences of age and gender proportion between groups. However, our control group has GWW and GWE parameters that are similar to the reference values in a meta-analysis study.¹⁶⁾

In conclusion, individuals with isolated severe rheumatic MS and preserved LVEF had global LV MW efficiencies lower than those of normal controls. The echocardiographic evaluation of LV mechanical efficiency is a promising tool for the evaluation of LV function in valvular heart disease.

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Rudiktyo E; Formal analysis: Rudiktyo E; Investigation: Rudiktyo E; Methodology: Rudiktyo E; Supervision: Soesanto AM, Cramer MJ, Siswanto BB, Doeveandans PA; Writing - original draft: Rudiktyo E, Yonas E; Writing - review & editing: Soesanto AM, Cramer MJ, Yonas E, Teske AJ, Siswanto BB, Doeveandans PA.

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