# Prognostic implications of left ventricular myocardial work indices in patients with secondary mitral regurgitation

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Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

# Prognostic Implications of Left Ventricular Myocardial Work Indices in Patients With Secondary Mitral Regurgitation

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**BACKGROUND:** Assessment of left ventricular (LV) function in patients with secondary mitral regurgitation (SMR) remains challenging but is an important parameter for risk stratification. The association of LV myocardial work components (work index [GWI], constructive [GCW] and wasted [GWW] work, and work efficiency) derived from pressure-strain loops obtained with speckle tracking echocardiography, and all-cause mortality in patients with SMR was investigated.

**METHODS:** LV myocardial GWI, GCW, GWW, and global work efficiency were measured with speckle tracking strain echocardiography in 373 patients (72% men, median age 68 years) with various grades of SMR. All-cause mortality was the primary end point.

**RESULTS:** Mild SMR was observed in 143 patients, 128 had moderate SMR, and 102 had severe SMR. Patients with severe SMR had the largest LV volumes and the worst LV ejection fraction and LV global longitudinal strain. In patients with severe SMR, LV GWI and GCW were more impaired (500 mm Hg% versus 680 mm Hg% $P$=0.024 and 678 mm Hg% versus 851 mm Hg% $P$=0.006, respectively), while GWW was lower (130 mm Hg% versus 260 mm Hg% $P$<0.001, respectively) and global work efficiency was significantly higher (82% versus 76%, $P$=0.001) compared with patients with mild SMR. After a median follow-up of 56 months, 161 patients died. LV GWI≤500 mm Hg%, LV GCW≤750 mm Hg%, and LV GWW<300 mm Hg% were independently associated with excess mortality.

**CONCLUSIONS:** Patients with severe SMR had the worst LV GWI and LV GCW but better LV GWW and global work efficiency reflecting the unloading of the LV in the low-pressure left atrial chamber. These parameters were independently associated with worse long-term survival in patients with SMR.

**Key Words:** echocardiography ■ mitral regurgitation ■ mortality ■ prognosis ■ survival

See Editorial by Lavall and Stöbe



Secondary mitral regurgitation (SMR) is frequently observed in patients with heart failure and is associated with high morbidity and mortality.[1] Guideline-directed medical therapy, cardiac resynchronization therapy, and transcatheter or surgical mitral valve repair or replacement are potential therapies that can improve the outcome of patients with severe SMR.[2] However, the heterogenous etiologies and pathophysiology of heart failure that lead to SMR have challenged randomized controlled trials testing medical and device therapy versus surgical mitral valve intervention. Mitral transcatheter therapies have demonstrated their safety and efficacy in registries.[3] The MITRA-FR trial (Percutaneous Repair With the MitraClip Device for Severe functional/Secondary Mitral Regurgitation)[4] and the COAPT trial (Cardiovascular Outcomes Assessment

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For Sources of Funding and Disclosures, see page 902.

*Circulation: Cardiovascular Imaging* is available at www.ahajournals.org/journal/circimaging

## CLINICAL PERSPECTIVE

Assessment of left ventricular (LV) function in patients with secondary mitral regurgitation remains challenging and is key to select the patients who may benefit from surgical intervention. Current measurements of LV ejection fraction and LV global longitudinal strain do not take into account the afterload conditions of the patients with secondary mitral regurgitation and mainly assess the function of the LV myocardium during the ejection phase without taking into consideration the direction of the blood flow. Novel noninvasive measurements of pressure-strain loops provide a thorough characterization of the LV performance throughout the entire cardiac cycle and myocardial work parameters can be calculated. In 373 patients with heart failure and various grades of secondary mitral regurgitation, patients with severe secondary mitral regurgitation had more impaired LV myocardial work index, constructive work, lower global wasted work, and higher global work efficiency, in comparison to patients with mild mitral regurgitation. LV global work index ≤500 mm Hg%, LV global constructive work ≤750 mm Hg%, and LV global wasted work <300 mm Hg% were independently associated with excess mortality. Whether these new parameters can select better the patients who will benefit from mitral valve interventions needs to be elucidated in larger studies.

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **COAPT trial** | Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy of Heart Failure Patients With Functional Mitral Regurgitation |
| **GCW** | global constructive work |
| **GLS** | global longitudinal strain |
| **GWE** | global work efficiency |
| **GWI** | global work index |
| **GWW** | global wasted work |
| **IQR** | interquartile range |
| **LV** | left ventricular |
| **LVEF** | left ventricular ejection fraction |
| **MITRA-FR trial** | Percutaneous Repair With the MitraClip Device for Severe functional/Secondary Mitral Regurgitation |
| **SMR** | secondary mitral regurgitation |

of the MitraClip Percutaneous Therapy of Heart Failure Patients With Functional Mitral Regurgitation)[5] have provided conflicting results. Although the MITRA-FR trial did not show survival benefit of the MitraClip device as compared to guideline-directed medical therapy, the COAPT trial showed significant improvements in the rate of the composite end point of heart failure hospitalization and all-cause mortality as compared to guideline-directed medical therapy. Differences in left ventricular (LV) volumes and mitral regurgitation severity of the study populations might partially explain the conflicting results. Yet, the LV ejection fraction (LVEF) was similar in the 2 studies. It is acknowledged that although echocardiographic assessment of LVEF is a useful tool for risk stratification, its accuracy in characterizing LV contractility in patients with severe SMR is poor.[6] LVEF reflects volume change but does not take in account the flow direction, resulting in overestimation of LV systolic function. Two-dimensional LV global longitudinal strain (LV GLS) proved to be more sensitive for abnormal myocardial mechanics than LVEF and was associated with all-cause mortality in patients with significant SMR, whereas LVEF was not.[7] However, LV GLS does not integrate afterload, a substantial contributor to the severity of SMR. The assessment of LV myocardial work parameters with speckle tracking strain echocardiography incorporates blood pressure measurements, as an estimation of the LV afterload, which might provide additional information on LV performance in patients with SMR. This method has been validated in patients with heart failure and was associated with outcomes.[8] However, the clinical application of this novel methodology and its prognostic implications in patients with SMR have not been evaluated. Accordingly, the aim of our study was to investigate myocardial work in patients with various grades of SMR and its association with survival.

# METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Study Population

Patients with various grades of SMR were identified from the departmental echocardiographic database. Patients were referred for transthoracic echocardiography between 2003 and 2018. Patients in atrial fibrillation with previous mitral valve intervention or who had concomitant moderate or severe aortic valve disease were excluded. In addition, patients with echocardiographic data not feasible for speckle tracking analysis and patients without blood pressure measurements at the time of echocardiography were excluded (Figure 1). Demographic and clinical data were collected from the electronic patient files (EPD-vision, Leiden University Medical Center, Leiden, the Netherlands). Ischemic heart failure was defined by the presence of coronary artery disease. Heart failure symptoms, associated comorbidities, and medical therapy were collected. For retrospective analysis of clinically acquired data, the institutional review board waived the need for written patient informed consent. All data used for this study were acquired for clinical purposes and handled anonymously.

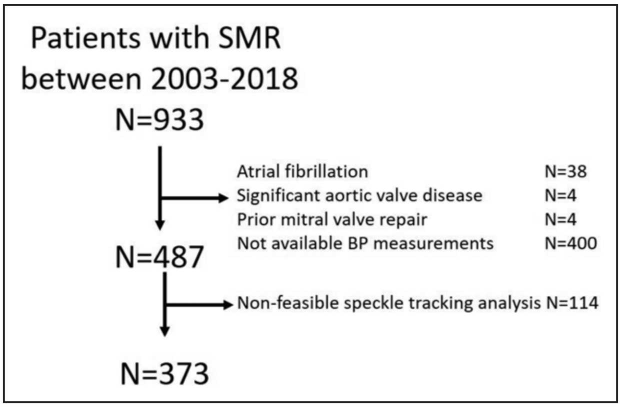


**Figure 1. Study population.**
BP indicates blood pressure; and SMR, secondary mitral regurgitation.

## Echocardiographic Data Acquisition and Analysis

Transthoracic echocardiographic images were recorded using Vivid 7, E9 or E95 ultrasound systems (General Electric Vingmed Ultrasound, Horten, Norway) with patients at rest, in the left lateral decubitus position. ECG-triggered echocardiographic data were acquired with 3.5 MHz or M5S transducers and digitally stored in cine-loop format for offline analysis with EchoPac (EchoPac 203, General Electric Vingmed Ultrasound, Horten, Norway). LV end-diastolic and end-systolic volumes were measured from the apical 2- and 4-chamber views, and the LVEF was calculated using the biplane Simpson's method.[9] Mitral regurgitation quantification was performed according to contemporary guidelines.[10] Based on an integrative approach that includes qualitative, semiquantitative, and quantitative measures, the study population was divided into 3 groups: patients with mild SMR, moderate SMR, and severe SMR.

## Quantification of Myocardial Work

Global LV myocardial work was measured as previously described.[11] Using vendor-specific software (EchoPac 203, General Electric Vingmed Ultrasound, Horten, Norway), LV GLS was measured from the apical 4-, 3-, and 2-chamber views. The timing of aortic and mitral valve opening and closure was set to define the isovolumic contraction and relaxation, the LV ejection, and filling intervals. These were defined based on 2-dimensional parasternal or apical long-axis views to simultaneously visualize the mitral and aortic valves. Next, the noninvasive blood pressure measurements were modeled onto a reference curve derived from a population averaged to form a LV pressure curve.[12] The normalized, noninvasive LV pressure curve was then integrated with strain data according to the valve events, resulting in a noninvasive LV pressure-strain loop. The area enclosed in the pressure-strain loop represents the global work index (GWI). Global constructive work (GCW) is defined as myocardial work performed during the shortening of a myocardial segment in systole and during lengthening in isovolumic relaxation (thus effectively contributing to the ejection or relaxation). Global wasted work (GWW) is defined as work performed during lengthening in systole or during shortening against a closed aortic valve in isovolumic relaxation (thus, ineffective contribution to the LV ejection or relaxation; Figure 2). Finally, global work efficiency (GWE) is calculated as the ratio of GCW, divided by the sum of GCW and GWW and expressed as a percentage (representing a global measure of the net effective contribution to the LV ejection and relaxation).

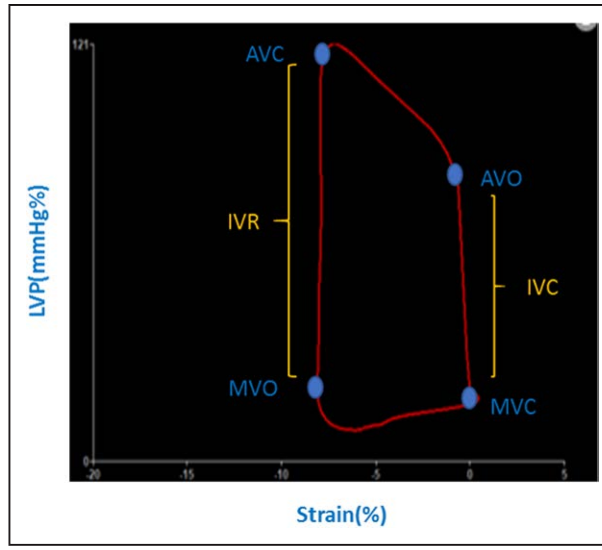


**Figure 2. Pressure-strain loop.**
Integrating the noninvasive measurement of the arterial blood pressure, longitudinal strain, and the timings of opening and closure of the mitral and aortic valve, the left ventricle pressure (LVP)-strain loop is built. The 4 phases of the cardiac cycle are presented: the isovolumic contraction (IVC), the ejection phase (from the aortic valve opening [AVO] to closure [AVC]), the isovolumic relaxation (IVR) and the filling of the left ventricle (from the opening of the mitral valve [MVO] to its closure [MVC]).

## Follow-Up

Patients were followed-up for the occurrence of all-cause mortality (primary end point). The mortality data were collected via the departmental cardiology information system (EPD-vision, Leiden University Medical Center, Leiden, The Netherlands), which is linked to the governmental registry database.

## Statistical Analysis

Categorical data are presented as frequencies and percentages. Continuous variables are reported as mean±SD if normally distributed and as median and interquartile range (IQR) if not normally distributed. Categorical data were compared with the $\chi^2$ test, followed by post hoc analysis of subgroups. Continuous data were compared using the Student *t* test if normally distributed or the Mann-Whitney *U* test and the Kruskal-Wallis test if not normally distributed. The survival analysis was performed according to the Kaplan-Meier test, and the log-rank test was used to compare groups. Univariable and multivariable Cox regression analyses were used to evaluate the association of clinical and echocardiographic parameters with all-cause mortality. Variables that showed a *P* value of <0.10 in the univariable analysis were selected as covariates in the multivariable Cox regression models. The proportional-hazards assumption was confirmed using statistics and graphs on the basis of the Schoenfeld residuals. The goodness of fit of the multivariable Cox regression models was evaluated by calculating the C statistics. Statistical analyses were performed using the SPSS version 25.0 (SPSS, Armonk, NY). The association between myocardial work parameters and the hazard of all-cause mortality was assessed with spline curve analysis, and the 95% CIs were overlaid. This analysis was performed in R environment (R Foundation for Statistical Computing).

# RESULTS

## Patient Population

A total of 373 patients were included (72% men, median age 68 years [IQR, 60–74]). A total of 143 patients had mild SMR, whereas 128 had moderate SMR and 102 had severe SMR. Ischemic cardiomyopathy was present in 60% of patients and 68% had New York Heart Association functional class III-IV symptoms. Patients with severe SMR were older, were more symptomatic, had a worse renal function, and more often received cardiac resynchronization therapy and diuretic treatment as compared to patients with mild SMR (Table 1).

## Echocardiographic and LV Myocardial Work Characteristics

Patients with moderate and severe SMR had significantly larger LV volumes, and the LVEF was lower as compared to patients with mild SMR (Table 2). In addition, LV GLS was more impaired in patients with severe and moderate SMR as compared to patients with mild SMR. Quantitative analysis of the severity of SMR was feasible in the majority of patients with moderate (59% feasibility) and severe (79% feasibility) SMR: the median effective regurgitant orifice area was 15.3 mm$^2$ (IQR, 11.3–21.8 mm$^2$) and the regurgitant volume 22 mL (IQR, 16.3–29 mL) for patients with moderate SMR, and 20 mm$^2$ (15.3–27.8 mm$^2$) and 32 mL (21.5–43 mL), respectively, in patients with severe SMR.

In terms of myocardial work indices, patients with moderate and severe SMR had the most impaired values of GWI and GCW, whereas GWW values were most preserved (Table 2 and Figure 3). As a result, patients with moderate and severe SMR had better GWE than patients with mild SMR (Table 2).

## Survival Analysis

During a median follow-up of 56 months (IQR, 30–82), 161 patients died. The hazard change for all-cause mortality across the range of GWI, GCW, GWW, and GWE was assessed with a spline curve (Figure 4). There was an increased risk of mortality, as shown by the rise of hazard ratio for LV GWI≤500 mm Hg%, LV GCW≤750

**Table 1. Clinical Characteristics**

| | Overall population (n=373) | Mild MR (n=143) | Moderate MR (n=128) | Severe MR (n=102) | *P* value |
|---|---|---|---|---|---|
| Age, y | 68 [60–74] | 66 [59–72]* | 67 [60–73] | 70 [62–76]† | 0.033 |
| Male, n (%) | 269 (72.1) | 110 (76.9) | 91 (71.1) | 68 (66.7) | 0.200 |
| BSA, m$^2$ | 1.93±0.21 | 1.95±0.18 | 1.92±0.23 | 1.89±0.22 | 0.133 |
| Ischemic cause | 223 (59.8) | 85 (59.4) | 73 (57) | 65 (63.7) | 0.586 |
| GFR, mL/min per 1.73 m$^2$ | 64.4 [49.4–81.9] | 66.8 [55.8–88.7]* | 67.2 [52.1–82.8]* | 54.5 [42.0–72.1]† | <0.001 |
| NYHA class | | | | | |
| I, n (%) | 27 (7.2) | 10(7) | 11 (8.6) | 6 (5.9) | 0.725 |
| II, n (%) | 93 (24.9) | 44 (30.8)* | 34 (26.6) | 15 (14.7)† | 0.014 |
| III, n (%) | 223 (59.8) | 81 (56.6) | 78 (60.9) | 64 (62.7) | 0.598 |
| IV, n (%) | 30 (8) | 8 (5.6)* | 5 (3.9)* | 17 (16.7)† | 0.001 |
| Diabetes, n (%) | 98 (26.3) | 31 (21.7) | 32 (25) | 35 (34.3) | 0.079 |
| CABG, n (%) | 68 (80.2) | 23 (16.1) | 24 (18.8) | 21 (20.6) | 0.655 |
| LBBB, n (%) | 132 (35) | 64 (45)* | 43 (34) | 25 (25)† | 0.004 |
| Non-BBB, n (%) | 141 (38) | 43 (30)* | 55 (43)† | 43 (42) | 0.052 |
| Paced QRS, n (%) | 100 (27) | 36 (25) | 30 (23) | 34 (33) | 0.207 |
| QRS duration, ms | 152 [125–173] | 154 [126–176]* | 152 [120–172] | 146 [125–172]† | 0.572 |
| CRT, n (%) | 21 (5.6) | 3 (2.1)* | 8 (6.3) | 10 (9.8)† | 0.033 |
| β-blockers, n (%) | 280 (75.1) | 108 (75.5) | 98 (76.6) | 74 (72.5) | 0.773 |
| ACE inhibitor/ARB, n (%) | 311 (83.4) | 124 (86.7) | 108 (84.4) | 79 (77.5) | 0.148 |
| Diuretics, n (%) | 305 (81.8) | 108 (75.5)* | 107 (83.6) | 90 (88.2)† | 0.032 |
| Digoxin, n (%) | 45 (12.1) | 14 (9.8) | 12 (9.4) | 19 (18.6) | 0.058 |

Data are presented as mean±SD if normally distributed or median (25th–75th percentile) if not normally distributed. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BBB, bundle branch block; BSA, body surface area; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; LBBB, left bundle branch block; MR, mitral regurgitation; and NYHA, New York Heart Association.

**P*<0.05 vs †.

**Table 2. Echocardiographic and Myocardial Work Indices**

| | Mild MR (n=143) | Moderate MR (n=128) | Severe MR (n=102) | *P* value |
|---|---|---|---|---|
| SBP, mm Hg | 117±17 | 123±21* | 115±22† | 0.017 |
| DBP, mm Hg | 70 [63 to 76] | 73 [63 to 80]* | 66 [60 to 74]† | 0.004 |
| LVEF (%) | 30 [25 to 34]* | 26 [19 to 33]† | 26 [21 to 33] | 0.010 |
| LVEDV, mL | 171 [133 to 226]* | 196 [158 to 255]† | 196 [156 to 263]† | 0.001 |
| LVESV, m | 121 [90 to 160]* | 147 [109 to 189]† | 149 [107 to 197]† | 0.001 |
| GLS (%) | −7.4 [−10 to −5.6]* | −6.7 [−8.9 to −4.1]† | −6.0 [−8 to −4]† | <0.001 |
| GWI, mm Hg% | 680 [450 to 916]* | 578 [335 to 821] | 500 [338 to 768]† | 0.024 |
| GCW, mm Hg% | 851 [638 to 1122]* | 749 [486 to 1083]† | 678 [466 to 945]† | 0.001 |
| GWW, mm Hg% | 260 [161 to 346]* | 182 [103 to 291]† | 130 [87 to 222]‡ | <0.001 |
| GWE (%) | 76 [67 to 84]* | 81 [70 to 87] | 82 [76 to 88]† | 0.001 |

Data are presented as mean±SD if normally distributed or median (25th–75th percentile) if not normally distributed. DBP indicates diastolic blood pressure; GCW, global constructive work; GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index; GWW, global wasted work; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; and SBP, systolic blood pressure.

*$P$<0.05 vs †.

‡$P$<0.05 vs * and †.

mm Hg% (less effective contribution to LV ejection and relaxation), and for LV GWW<300 mm Hg% (less ineffective contribution to LV ejection and relaxation). In contrast, there was no association between LV GWE (net effective contribution to LV ejection and relaxation) and all-cause mortality.

When the population was divided according to a cutoff value of LV GWI≤500 mm Hg% versus >500 mm Hg%, the cumulative survival rates at 1, 2, and 5 years follow-up were significantly better for patients with LV GWI>500 mm Hg% (95%, 90%, and 74% versus 87%, 82%, and 56%, respectively; $P$=0.001;

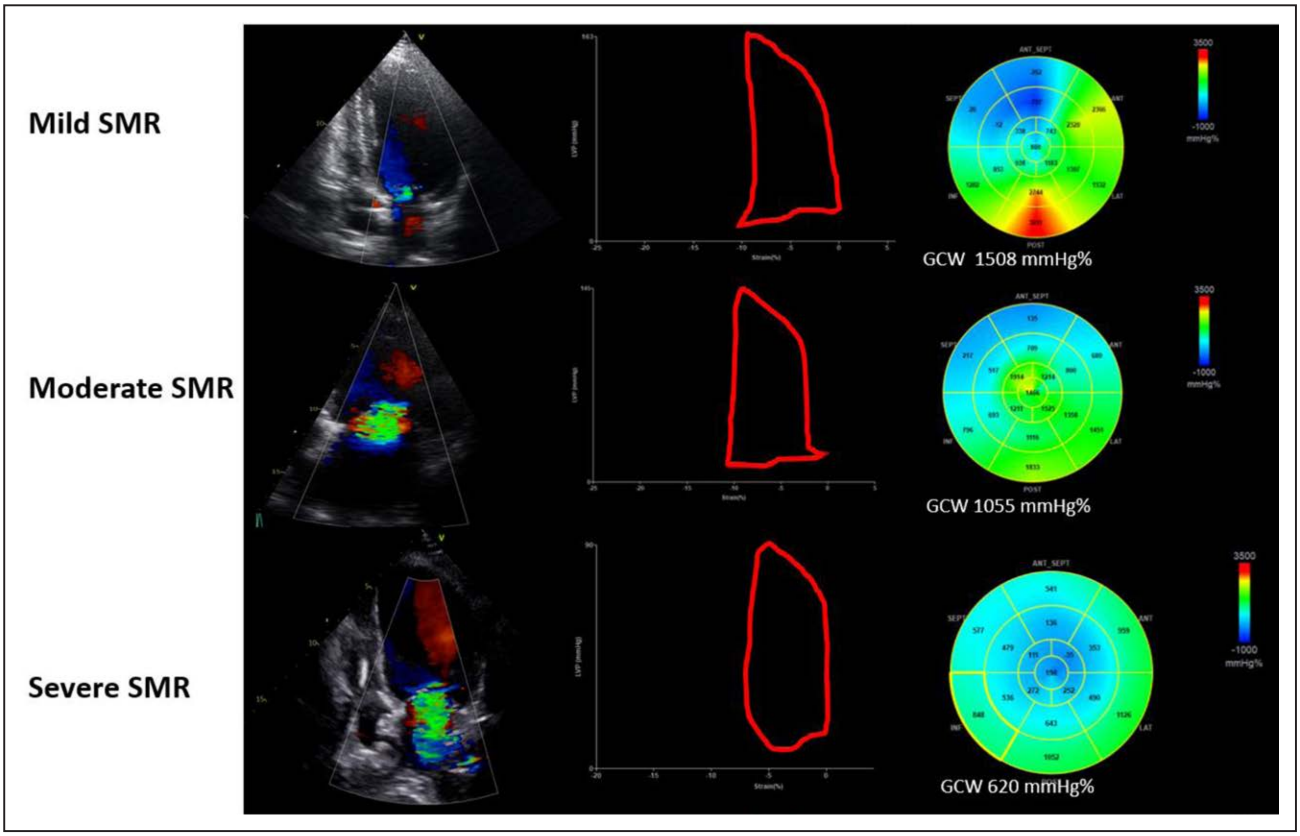


**Figure 3. Assessment of myocardial work in patients with secondary mitral regurgitation (SMR).**
The panels show a mid-systolic frame of the apical 4-chamber view with color Doppler on the mitral valve to illustrate the regurgitant jet of SMR, the pressure-strain loop reflecting the global myocardial work index, and the bull's eye plot with the value of myocardial global constructive work (GCW). Note the reduction in the area enclosed in the pressure-strain loop and in GCW along with the increase in severity of SMR.

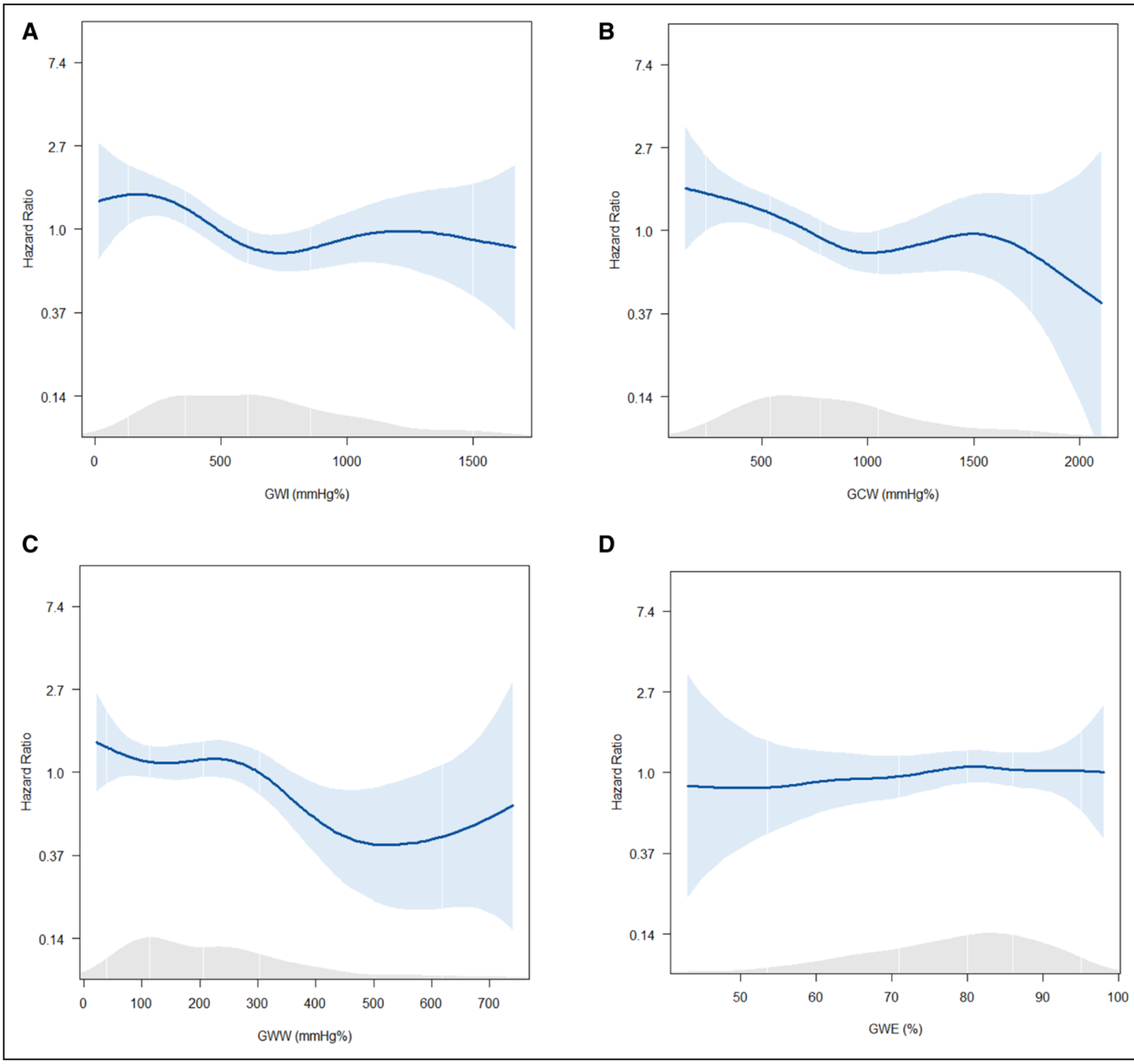


**Figure 4. Association between myocardial work indices and all-cause mortality.**

The figures show the hazard ratio for all-cause mortality (blue line with the 95% CI in light-blue) across a range of left ventricular global work index (LV GWI, **A**), global constructive work (GCW, **B**), global wasted work (GWW, **C**), and global work efficiency (GWE, **D**). **A** demonstrates that values of GWI≤500 mm Hg% were associated with a higher risk of mortality. **B** shows that values of GCW≤750 mm Hg% were associated with a higher risk of mortality. **C** shows that values of GWW<300 mm Hg% were associated with a higher risk of mortality. **D** shows that the risk of mortality did not change across different values of GWE. The gray density plot below each figure illustrates the distribution of the population according to the different myocardial work indices.



Figure 5A). Similarly, patients with LV GCW>750 mm Hg% (more preserved) had better 1-, 2-, and 5-year survival rates as compared to patients with LV GCW≤750 mm Hg% (more impaired): 95%, 90%, and 75% versus 89%, 83%, and 57%, respectively; *P*=0.001; Figure 5B. When the population was divided according to the cutoff value of LV GWW≥300 mm Hg% (more impaired) versus <300 mm Hg% (more preserved), the cumulative survival rates at 1, 2, and 5 years follow-up were significantly better for patients with LV GWW≥300 mm Hg% as compared to their counterparts (98%, 97%, and 83% versus 91%, 83%, and 61%, respectively; *P*=0.001; Figure 5C).

On univariable Cox regression analysis, age, renal function, the use of diuretics, moderate and severe SMR, LV GLS, LV GWI≤500 mm Hg%, LV GCW≤750 mm Hg%, and LV GWW<300 mm Hg% were significantly associated with all-cause mortality (Table 3). To avoid multicollinearity, LV GCW and LV GWW were entered one multivariable model and LV GWI in another separate model. After adjusting for potential confounders in the multivariable analysis, LV GCW≤750 mm Hg% and LV

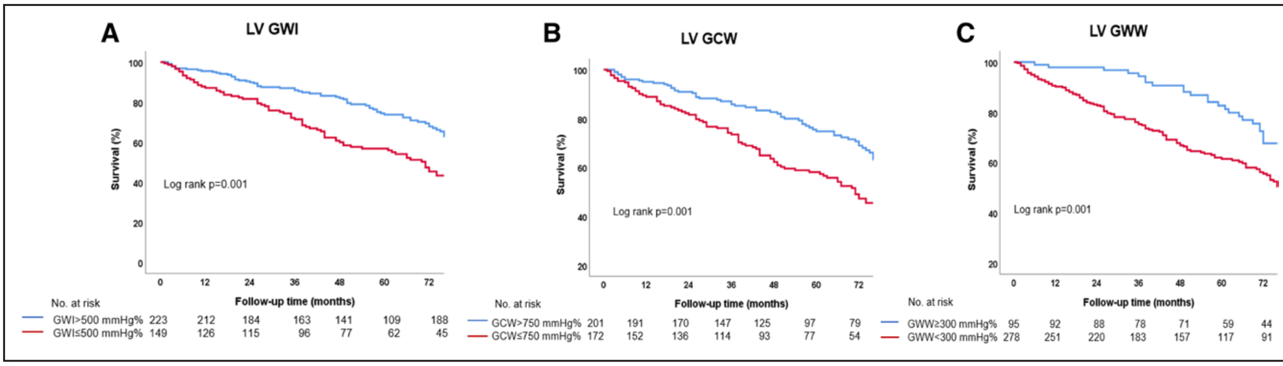


**Figure 5. Survival analysis.**
Kaplan-Meier curves for left ventricular global work index (LV GWI, **A**), LV global constructive work (GCW, **B**), and LV global wasted work (GWW, **C**) with the population divided according to cutoff values obtained with the spline curves.

GWW<300 mm Hg% (Table 4, model A) and LV GWI≤500 mm Hg% (Table 4, model B) remained independently associated with all-cause mortality. The C statistics of multivariable Cox regression model A was 0.733 (95% CI, 0.682–0.784, *P*<0.001), whereas the C statistics of model B was 0.720 (95% CI, 0.668–0.772, *P*<0.001), indicating a good prognostic utility of the models.

## DISCUSSION

This study demonstrates that LV MW parameters correlate with the different grades of SMR. The LV GWI and GCW became more impaired as the SMR degree worsened. In contrast, the LV GWW was less impaired with a worse degree of SMR, suggesting potential benefit on myocardial energetics caused by emptying of the LV into a low-pressure chamber, that is, the left atrium. Moreover, LV MW indices showed a significant association with prognosis as impaired LV GWI and GCW and lower LV GWW were independently associated with all-cause mortality.

**Table 3. Univariable Cox Regression Analyses of All-Cause Mortality**

| | Univariable | *P* value |
|---|---|---|
| Age, per y | 1.037 (1.020–1.055) | <0.001 |
| SBP, per mm Hg | 0.999 (0.991–1.007) | 0.797 |
| DBP, per mm Hg | 0.995 (0.981–1.008) | 0.440 |
| GFR, per mL/min per 1.73 m$^2$ | 0.971 (0.963–0.979) | <0.001 |
| CRT, yes | 1.382 (0.728–2.623) | 0.323 |
| NYHA class IV, yes | 1.473 (0.878–2.470) | 0.142 |
| Use of diuretics, yes | 2.316 (1.400–3.829) | 0.001 |
| LVEF, per each 1% increment | 0.989 (0.971–1.008) | 0.254 |
| GLS, per each 1% increment (more positive value) | 1.091 (1.034–1.151) | 0.001 |
| LVEDV, per 1 mL | 1.001 (0.999–1.004) | 0.201 |
| LVESV, per 1 mL | 1.002 (0.999–1.004) | 0.214 |
| Moderate/severe MR | 1.418 (1.000–2.012) | 0.050 |
| GWI≤500 mm Hg% | 1.713 (1.256–2.335) | 0.001 |
| GCW≤750 mm Hg% | 1.652 (1.208–2.226) | 0.002 |
| GWW<300 mm Hg% | 1.963 (1.305–2.953) | 0.001 |
| GWE, per each 1% | 1.616 (0.398–6.565) | 0.502 |

CRT indicates cardiac resynchronization therapy; DBP, diastolic blood pressure; GCW, global constructive work; GFR, glomerular filtration rate; GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index; GWW, global wasted work; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; and SBP, systolic blood pressure.

### Evaluation of LV Performance in Patients With SMR

Surgical mitral valve repair (preferably) or replacement in patients with significant SMR may relieve symptoms and induce LV reverse remodeling, but its beneficial effect on survival has not been consistently demonstrated.[13,14] Accordingly, current guidelines consider surgical mitral valve intervention concomitant to coronary artery bypass grafting. The survival benefit of transcatheter edge-to-edge repair with the MitraClip device (Abbott Vascular, Menlo, CA) has been demonstrated in the randomized clinical trial COAPT[5] and accordingly, the recent American guidelines consider this alternative as a reasonable treatment for symptomatic patients on guideline-directed medical therapy with severe SMR and appropriate mitral valve anatomy, LV function, and dimensions.[15] LVEF is an important factor in the decision-making of patients with severe SMR.[2] However, it has been shown that in patients with chronic volume overload, the LVEF may not accurately reflect true LV function.[16] LVEF calculates the differences between LV end-diastolic and end-systolic volumes but does not take into account the direction of the blood flow, which, in SMR is directed to a low-pressure left atrium and does not contribute to forward stroke volume. In SMR, LVEF could not identify the patients who would benefit from MitraClip since this functional parameter was similar in the MITRA-AF and COAPT trials, despite contrasting results.

**Table 4. Multivariable Cox Regression Analyses of All-Cause Mortality**

| | Model A | | Model B | |
|---|---|---|---|---|
| | Multivariable | *P* value | Multivariable | *P* value |
| Age, per y | 1.023 (1.004–1.043) | 0.017 | 1.022 (1.003–1.042) | 0.021 |
| GFR, per mL/min per 1.73 m² | 0.976 (0.968–0.985) | <0.001 | 0.978 (0.969–0.987) | <0.001 |
| Diuretics, yes | 1.574 (0.939–2.638) | 0.085 | 1.576 (0.939–2.646) | 0.085 |
| Moderate/severe MR | 0.920 (0.636–1.329) | 0.656 | 1.072 (0.750–1.531) | 0.703 |
| GCW≤750 mm Hg% | 1.495 (1.074–2.081) | 0.017 | … | |
| GWW<300 mm Hg% | 2.011 (1.317–3.071) | 0.001 | … | |
| GWI≤500 mm Hg% | … | | 1.591 (1.148–2.204) | 0.005 |

GCW indicates global constructive work; GFR, glomerular filtration rate; GWI, global work index; GWW, global wasted work; and MR, mitral regurgitation.

LV GLS is a more sensitive method for the assessment of LV function.[17] In patients with dilated cardiomyopathy, LV GLS had better ability to detect more profound impairment in systolic LV function than LVEF among patients with severe SMR.[18] Moreover, impaired LV GLS was independently associated with an increased risk for all-cause mortality in patients with SMR, whereas LVEF was not.[7] One of the limitations of LV GLS is that this parameter does not take into consideration the LV afterload (which is an important factor influencing the severity of SMR). In contrast, LV myocardial work parameters do combine blood pressure (as a measure of LV afterload) with the LV GLS. The values of LV myocardial work parameters in individuals without cardiovascular disease have been reported.[19] The subanalysis of the Normal Reference Ranges for Echocardiography study reported the reference values of LV myocardial work[20] which were significantly better for GWI, GCW, and GWE, and the median GWW was significantly lower as compared to the values reported in the present study. Other groups have evaluated the contractility of the LV, in patients with SMR, based on noninvasive pressure-volume curves obtained with echocardiography.[21] The area enclosed in the pressure-volume curve represents the total stroke work. In 46 patients with moderate and severe mitral regurgitation (70% with SMR), Lavall et al[22] reported a total stroke work of 54 466±2241 mm Hg×mL.

Between patients with moderate and severe SMR, there were no differences in LVEF and LV GLS, while LV GWW was significantly more impaired in patients with severe SMR as compared to patients with moderate SMR. In addition, an interesting finding is a fact that LV GWW is less in patients with severe SMR as compared to patients with mild and moderate SMR. This suggests that the pump function of the LV is facilitated by emptying the blood volume into the low-pressure left atrium. This may explain why LVEF could be falsely preserved compared with LV GLS. In the present study, patients with moderate and severe SMR, LV GLS was significantly more impaired as compared to patients with mild SMR. These results confirm the findings of the study by Kamperidis et al,[18] where all patients were matched for LVEF, and those with significant SMR had worse LV GLS as compared to patients without SMR.

## Prognostic Implications of LV MW Parameters in Patients With SMR

The present article provides new data in terms of prognostic associations of LV myocardial work parameters in patients with SMR. Patients with GWI≤500 mm Hg% and GCW≤750 mm Hg%, indicating reduced LV function, had a worse prognosis while LVEF was not associated with all-cause mortality. Wang et al[23] showed similar findings in patients with heart failure and reduced LVEF and reported that an LV GWI<750 mm Hg% was associated with 3-fold higher risk of all-cause mortality and heart failure hospitalization. Furthermore, patients with GWW˂300 mm Hg% (less energy wasted) had a worse prognosis as compared to patients with GWW≥300 mm Hg%. This apparent paradox could be explained by the emptying of the LV into a low-pressure chamber (the left atrium) suggesting that the LV cannot generate enough work to pump the blood volume into a higher pressure chamber (the aorta).

## Clinical Implications

Assessment of the severity of SMR and LV systolic function remains challenging: the severity of the SMR is influenced by loading conditions and closing forces (LV systolic function) and LV systolic function is influenced as well by loading conditions. Assessment of myocardial work with speckle tracking echocardiography can take into consideration the loading conditions since LV GLS will be influenced in part by the magnitude of myocardial lengthening (LV end-diastolic volume) at the beginning of the systole (representing the preload of the LV) and the computation of the systolic blood pressure and the timings of the aortic and mitral valve closure will determine the afterload and the timings of the cardiac cycle respectively which provide a more comprehensive assessment of the LV performance. Selection of the patients with SMR who may benefit from intervention is crucial, and assessment of LV systolic function is one of the factors that influence prognosis. Taking into account the preload, afterload, and the timing of the events that the cardiac cycle comprises is a more comprehensive approach to assess LV performance than measurements such as LVEF of LV GLS.

## Study Limitations

This is a retrospective, single-center study. In addition, patients with atrial fibrillation or without blood pressure measurements or echocardiographic data feasible for speckle tracking analysis were excluded, potentially introducing a selection bias. Furthermore, the current software to calculate the LV myocardial work is available from only one ultrasound vendor, and the results may not be applicable when using other vendors. All-cause mortality was the end point chosen since the cause of death was not systematically ascertained.

## Conclusions

Patients with severe SMR had the worst LV GWI and LV GCW but better LV GWW and GWE reflecting the unloading of the LV in the low-pressure left atrial chamber. These parameters were independently associated with worse long-term survival in patients with SMR.

## ARTICLE INFORMATION

Received November 3, 2020; accepted July 11, 2021.

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### Sources of Funding

The Department of Cardiology of the Leiden University Medical Center received research grants from Abbott Vascular, GE Healthcare, Bioventrix, Bayer, Ionis, Medtronic, Biotronik, Boston Scientific, GE Healthcare, and Edwards Lifesciences. Dr Yedidya received a fellowship grant from Rabin Medical Center, Israel. Dr Lustosa received funding from the European Society of Cardiology (ESC Research Grant R-2018-17759).

### Disclosures

Dr Delgado received speaker fees from Abbott Vascular, Edwards Lifesciences, GE Healthcare, MSD, Novartis, and Medtronic. Drs Ajmone Marsan and Bax received speaker fees from Abbott Vascular. The other authors report no conflicts.

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