Noninvasive left ventricular myocardial work in patients with chronic aortic regurgitation and preserved left ventricular ejection fraction

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Noninvasive Left Ventricular Myocardial Work in Patients with Chronic Aortic Regurgitation and Preserved Left Ventricular Ejection Fraction

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Background: Left ventricular (LV) global longitudinal strain (GLS) has been proposed as a sensitive marker of myocardial damage in patients with chronic severe aortic regurgitation (AR) and preserved LV ejection fraction (LVEF). However, LV GLS does not take into account the afterload. Noninvasive LV myocardial work is a novel parameter of LV myocardial performance, which integrates measurements of myocardial deformation and noninvasive blood pressure (afterload). The aims of this study were (1) to assess noninvasive LV myocardial work in patients with chronic AR and preserved LVEF and its correlation with other echocardiographic parameters, (2) to evaluate changes of LV myocardial work after aortic valve replacement or repair (AVR), and (3) to assess the relationship between LV myocardial work and postoperative LV reverse remodeling.

Methods: Fifty-seven patients (53 ± 16 years; 67% men) with moderate or severe chronic AR and preserved LVEF treated by AVR were included. Noninvasive LV myocardial work indices were measured at baseline and postoperatively (between 2 and 12 months after surgery) and compared with previously reported normal reference ranges.

Results: Based on normal reference values, patients with chronic AR and preserved LVEF had preserved or increased values of LV global work index (GWI; 82% and 18%, respectively) and LV global constructive work (GCW; 74% and 25%, respectively) and preserved LV global work efficiency (GWE). Left ventricular GWI and GCW showed a positive correlation with markers of AR severity and parameters of LV systolic function. Left ventricular GWI, GCW, and GWE decreased after AVR ($P < .001$), without changes in LV global wasted work ($P = .28$). The postoperative impairment of LV GWI, observed in 28% of patients, was closely associated with reduced LV reverse remodeling.

Conclusions: Noninvasive myocardial work may allow better understanding of myocardial function and energetics than afterload-dependent echocardiographic parameters in chronic AR with preserved LVEF. (J Am Soc Echocardiogr 2022;35:703-11.)

Keywords: Aortic regurgitation, Myocardial work, LV remodeling, Aortic valve surgery, Speckle-tracking echocardiography

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Abbreviations

AR = Aortic regurgitation

AVR = Aortic valve replacement or repair

BSA = Body surface area

EROA = Effective regurgitant orifice area

GLS = Global longitudinal strain

GCW = Global constructive work

GWE = Global work efficiency

GWI = Global work index

GWW = Global wasted work

ICC = Intraclass correlation coefficient

LV = Left ventricular, ventricle

LVEDV = Left ventricular end-diastolic volume

LVEF = Left ventricular ejection fraction

LVESV = Left ventricular end-systolic volume

RVol = Regurgitant volume

Chronic severe aortic regurgitation (AR) causes significant left ventricular (LV) volume and pressure overload, which leads to progressive eccentric hypertrophy and LV dilatation. These are compensatory mechanisms that can normalize LV wall stress and preserve LV systolic function for a long time before symptoms develop. However, several studies have demonstrated that measures of LV deformation such as LV global longitudinal strain (GLS) may reveal subclinical LV systolic dysfunction at earlier stages, before the onset of symptoms and while LV ejection fraction (LVEF) is still preserved.[1-3] The impairment of LV GLS in patients with chronic severe AR and preserved LVEF has been associated with adverse outcomes.[1-3] Nevertheless, similar to LVEF, LV GLS is influenced by loading conditions, particularly by the afterload. This may be a relevant limitation in patients with chronic severe AR, as the afterload may consistently change with medication use and after aortic valve replacement or repair (AVR).

Noninvasive assessment of LV myocardial work with speckle-tracking echocardiography takes into account LV deformation and LV afterload, allowing a more comprehensive measure of LV myocardial performance and providing an estimate of LV myocardial energetics.[4] The application of noninvasive myocardial work in the evaluation of patients with chronic severe AR may shed light on how myocardial mechanics and energetics adapt to preserve LV systolic function and may provide further insight into the process of LV reverse remodeling after AVR. Of note, this novel parameter has never been studied in patients with chronic AR and preserved LVEF. Therefore, the aims of our study were (1) to assess noninvasive LV myocardial work in patients with chronic moderate or severe AR and preserved LVEF and its correlation with parameters of LV remodeling and AR severity, (2) to evaluate the changes in LV mechanics and myocardial work after AVR, and (3) to assess the potential relationship between myocardial work and postoperative LV reverse remodeling.

METHODS

Study Population and Data Collection

Patients with chronic moderate or severe AR and preserved LVEF (≥50%) who underwent surgical AVR at the Leiden University Medical Center between January 2002 and December 2019 were retrospectively evaluated. Patients with echocardiographic data available at baseline and within 1 year after surgery (between 2 and 12 months) were selected. Exclusion criteria were mixed aortic valve disease, concomitant moderate or severe mitral regurgitation, acute endocarditis, and aortic dissection. Patients were also excluded when speckle-tracking echocardiography analysis was not feasible or when noninvasive blood pressure measurements were not available at the time of the baseline or follow-up echocardiogram (Figure 1).

The decision to operate was based on consensus between cardiologists and cardiothoracic surgeons after a thorough discussion regarding risks and benefits with the patients.

Additionally, age- and sex- matched healthy individuals with structurally and functionally normal hearts ($n = 57$) were selected from an echocardiographic database to form the control group.

Demographics and clinical data were collected from the departmental electronic medical record (EPD-vision; Leiden University Medical Center, Leiden, the Netherlands). As this study concerned a retrospective analysis of clinically acquired data, the institutional review board of the Leiden University Medical Center waived the need for written patient informed consent.

Echocardiographic Analysis

Comprehensive transthoracic echocardiograms were acquired using a commercially available system (VIVID 7, E9 and E95, GE-Vingmed, Horten, Norway) equipped with the MS5 and 4Vc-D 4D matrix cardiac probes. Two-dimensional, color, spectral continuous- and pulsed-wave Doppler images were obtained from the

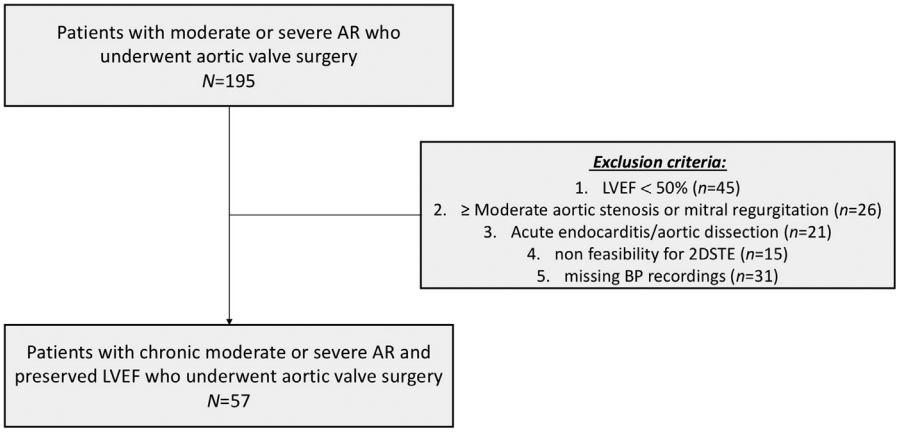

Figure 1 Flow chart of the study with inclusion and exclusion criteria. *BP*, Blood pressure; *2DSTE*, two-dimensional speckle-tracking echocardiography.

HIGHLIGHTS

- LV myocardial work was studied in patients with chronic AR and preserved LVEF.
- LV GWI and GCW positively correlate with AR severity.
- Aortic valve surgery results in a decrease of LV GWI, LV GCW, and LV GWE.
- Postoperative impaired LV GWI is associated with adverse LV reverse remodeling.
- LV myocardial work indices may provide further insights on LV function in chronic AR.

parasternal, apical, and subcostal views. All images were digitally stored for offline analyses, which were performed by an experienced operator (M.C.M.) blinded to the patients' clinical characteristics.

The LV linear dimensions were measured on the parasternal long-axis window, and the LV mass was calculated according to the Devereux formula and indexed for body surface area (BSA).[5] From the apical two- and four-chamber views, the LV end-diastolic and end-systolic volumes (LVEDV and LVESV, respectively) were measured and indexed for BSA and LVEF was calculated using the biplane Simpson's method.[6] The left atrial volume was measured from the apical two- and four-chamber views using the biplane Simpson's method and indexed for BSA.[5] In addition, images from the apical four- and two-chamber and long-axis views zoomed on the LV were acquired with a frame rate of ≥40 frames/sec to assess LV GLS by speckle-tracking echocardiography. LV GLS was calculated as the average of peak systolic longitudinal strain values of the 17 LV segments.[5] The values of LV GLS are reported in absolute values.

For grading the severity of AR, color Doppler images of the aortic valve were acquired with optimized gain and Nyquist scale (50 to 60 cm/sec). From the zoomed color Doppler parasternal long-axis view of the AR jet, the vena contracta was identified as the narrowest portion of the regurgitant jet that occurred at, or just downstream from, the regurgitant orifice.[6] The ratio of the jet width to the LV outflow tract was also measured in the parasternal long-axis view.[6] Finally, the proximal isovelocity surface area method was used for calculation of the effective regurgitant orifice area (EROA) and the regurgitant volume (RVol).[6]

Quantification of LV Myocardial Work

Quantification of LV myocardial work was performed using a commercially available software package (EchoPAC, ver. 203; GE Medical Systems, Horten, Norway). As described elsewhere,[4] myocardial work indices are calculated from pressure-strain loop areas, which are constructed from noninvasive estimation of peak LV pressure using patient brachial cuff blood pressure recordings (which assumes that peak systolic LV pressure is equal to peak arterial pressure) combined with speckle-tracking echocardiographic strain data. After calculating LV GLS and introducing the values of blood pressure measurements, the opening and closing time points of the aortic and mitral valve were identified from the apical five- or three-chamber views. An LV pressure strain curve was then constructed from LV GLS data of the entire cardiac cycle, and the isovolumic relaxation and contraction, ejection, and filling phases were defined by timing the aortic and mitral valve opening and closing. Cardiac work was calculated as a function of time throughout the cardiac cycle, and four parameters of LV myocardial work were calculated by the software:

Table 1 Baseline characteristics of the study population

Variables	Population (n = 57)
Clinical and demographic characteristics	
Sex, male	38 (67)
Age, years	53 ± 16
BMI, kg/m^2	25.5 ± 4.0
Hypertension	28 (49)
Diabetes	2 (4)
Dyslipidemia	12 (21)
Active smoker	15 (26)
Coronary artery disease	7 (12)
Chronic obstructive pulmonary disease	8 (14)
New York Heart Association class I-II/III-IV	44 (77)/13 (23)
Medications	
Beta-blockers	24 (42)
ACE-inhibitors or AT-receptor antagonists	36 (63)
Loop diuretics	17 (30)
Mineralocorticoid receptor antagonists	3 (5)
Statins	11 (19)
Aspirin	12 (21)
Anticoagulants	12 (21)
Echocardiographic characteristics	
LVEDD, mm	56 ± 8
LVM index, g/m^2	143 ± 40
LVEDV index, mL/m^2	79.6 (59.4-104.2)
LVESV index, mL/m^2	29.2 (24.3-41.7)
LVEF, %	59.7 ± 4.4
LV GLS, %	18.4 ± 3.0
LAV index, mL/m^2	33.9 ± 12.3
Bicuspid or unicuspid morphology	24 (42)
EROA, cm^2	31 ± 10
RVol, mL	66 ± 24
AVMG, mm Hg	9 ± 5
AVPG, mm Hg	16 ± 7
Procedural characteristics	
Valve type	
Biological	30 (53)
Mechanical	11 (19)
Aortic valve repair	16 (28)
Concomitant CABG	7 (12)

Data are presented as n (%), mean ± SD, or median (interquartile range). *ACE*, Angiotensin-converting enzyme; *AT*, angiotensin; *AVMG*, aortic valve mean gradient; *AVPG*, aortic valve peak gradient; *BMI*, body mass index; *CABG*, coronary artery bypass grafting; *LAV*, left atrial volume; *LVEDD*, LV end-diastolic diameter; *LVM*, LV mass.

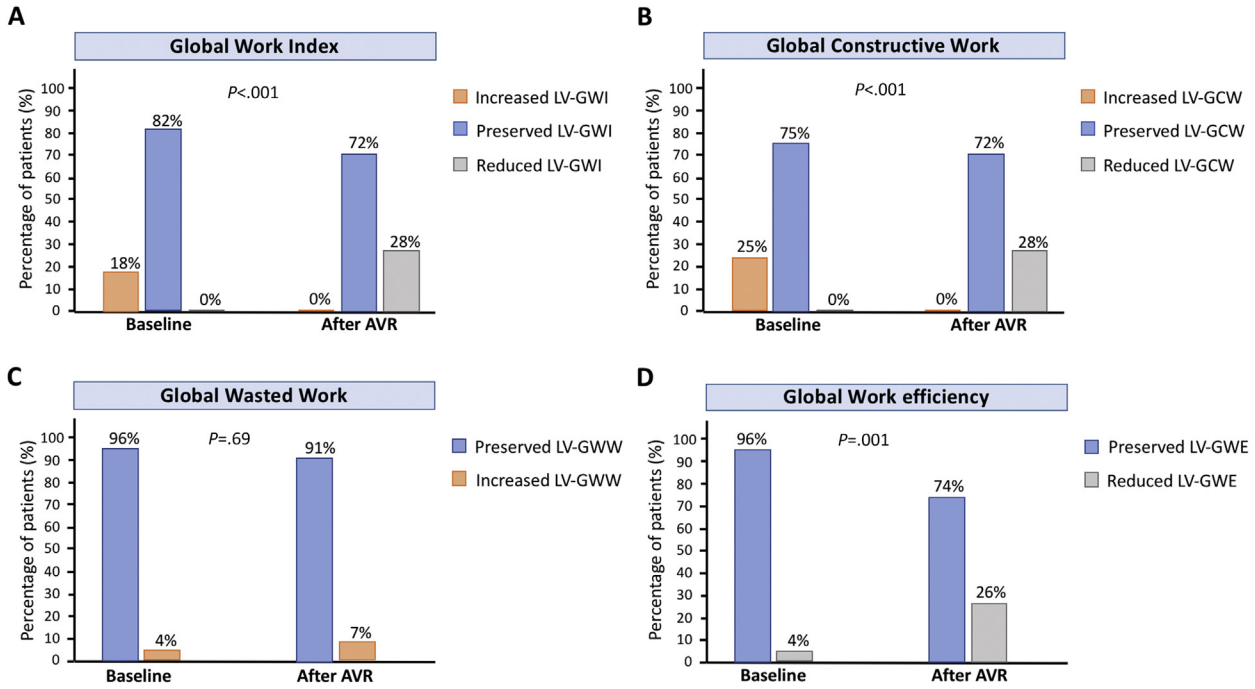

Figure 2 Percentages of patients with or without preserved myocardial work indices at baseline and after aortic valve surgery, based on normal references ranges. **(A)** Normal range of LV GWI, 1,270-2,428 mm Hg% (men) and 1,310-2,538 mm Hg% (women). **(B)** Normal range of LV GCW, 1,650-2,807 mm Hg% (men) and 1,543-2,924 mm Hg% (women). **(C)** Highest expected value of LV GWW, 238 mm Hg% (men) and 239 mm Hg% (women). **(D)** Lower expected value of LV GWE, 90% (men) and 91% (women).[8]

1. LV global work index (GWI, mm Hg%): defined as total work within the area of the LV pressure-strain loop, calculated from mitral valve closure to opening.
2. LV global constructive work (GCW, mm Hg%): defined as work performed during shortening in systole or during lengthening in isovolumic relaxation.
3. LV global wasted work (GWW, mm Hg%): defined as work performed during lengthening in systole or during shortening against a closed aortic valve in isovolumic relaxation.
4. LV global work efficiency (GWE, %): calculated as LV GCW divided by the sum of LV GCW and LV GWW and expressed as a percentage.

The values of LV GLS and myocardial work indices, calculated at baseline and postoperatively, were compared with previously reported sex-specific reference ranges.[7,8] The study population was then divided between patients with or without reduced values of LV GWI after AVR, and the differences were assessed. Subsequently, patients with preserved LV GWI after AVR were further divided according to the presence of postoperative impairment of LV GLS and the three groups were compared. As supplementary analysis, the values of myocardial work indices, calculated at baseline and postoperatively, were compared with those obtained in age- and gender-matched healthy control individuals.

Statistical Analysis

Normally distributed continuous variables are presented as mean ± SD, whereas nonnormally distributed data are presented as median and interquartile range. Categorical variables are expressed as frequencies and percentages. Correlations between myocardial work indices and traditional echocardiographic parameters were tested using the Pearson's or Spearman's correlation coefficient, as appropriate. Changes in clinical and echocardiographic variables between baseline and post-AVR were assessed by the paired Student's *t* test (for normally distributed continuous variables), Wilcoxon test (for nonnormally distributed continuous variables and ordinal variables), and McNemar's test (for dichotomous variables). Comparison between patients with or without postoperative impairment of LV GWI was performed by the unpaired Student's *t* test (for normally distributed continuous variables), Mann-Whitney *U* test (for nonnormally distributed continuous variables), and χ^2 test or the Fisher's exact test, as appropriate (for categorical variables). Similarly, the analyses were repeated for comparison of patients and healthy controls. One-way analysis of variance with Bonferroni post hoc tests was used to compare three groups, defined according to the presence of LV GLS and LV GWI impairment, when continuous variables were normally distributed. Alternatively, the Kruskal-Wallis test was performed when continuous variables were not normally distributed. To further investigate the probability of LV reverse remodeling (defined as LVEDV reduction > 20% and LVESV reduction > 15%),[9] according to the values of LV GWI, a spline curve analysis was performed. In addition, receiver operator curve analysis was used to define a threshold value of LV GWI associated with LV reverse remodeling. Fifteen random patients were selected for the evaluation of intra- and interobserver variability of myocardial work indices using intraclass correlation coefficients (ICCs). Excellent agreement was defined by an ICC > 0.9, whereas good agreement was defined by a value between 0.75 and 0.90. All tests were two-sided, and *P* values < .05 were considered statistically significant. Data analysis was performed using SPSS version 25.0 (SPSS, Chicago, IL) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

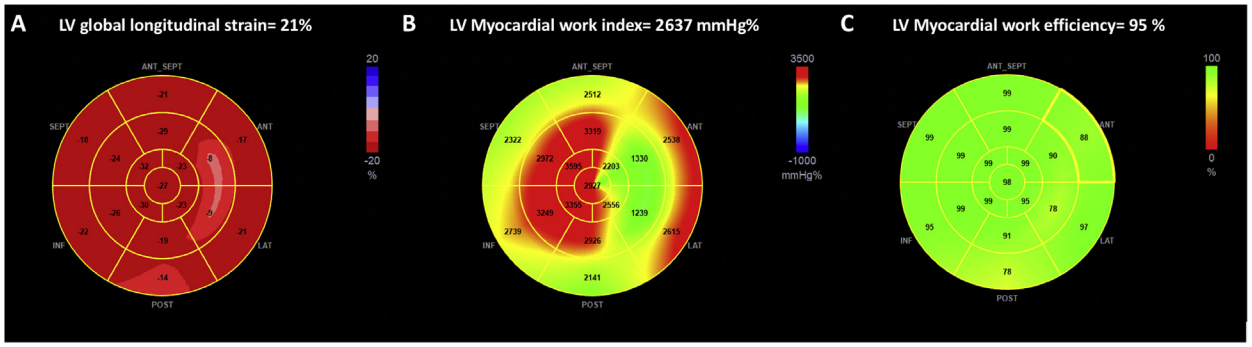

Figure 3 Example of increased LV GWI in severe chronic AR and preserved LVEF. Left ventricular GLS is normal (21%) **(A)**, and blood pressure is mildly elevated (149/70 mm Hg). Left ventricular GWI is significantly increased (2,637 mm Hg%), with a predominantly *red-shaded* bull's-eye **(B)**, while LV GWE is unaffected (95%) **(C)**.

RESULTS

Study Population

This retrospective study included 57 patients (67% men; mean age of 53 ± 16 years) with chronic moderate or severe AR and preserved LVEF who underwent surgical AVR. The baseline clinical, echocardiographic, and procedural characteristics of the study population are shown in Table 1. A summary of surgical indications and outcomes is provided in Supplemental Table 1.

LV Myocardial Work Indices at Baseline

Based on the comparison with reported reference ranges,[7] 47 (82%) patients had preserved values of LV GWI at baseline, while 10 (18%) patients showed increased values of LV GWI (Figures 2 and 3). Similarly, LV GCW was increased in 14 (25%) patients, whereas it was normal in the remaining 43 (75%) patients. Increased values of LV GWW and impaired values of LV GWE were found in only two (4%) patients. Despite being within the normal ranges in the vast majority of patients, LV GWW and LV GWE were still significantly worse than those observed in age- and gender-matched healthy controls (both $P < .001$; Supplemental Table 2). Conversely, there were no significant differences in LV GWI values between the two groups ($P = .13$), while there was a trend for higher values of LV GCW in patients with chronic AR ($P = .05$; Supplemental Table 2). Left ventricular GLS was impaired in 18 (32%) patients (<16.7% in men and <17.8% in women)[8] and was significantly worse than the values observed in healthy controls ($P = .03$).

LV GWI and GCW showed a good correlation with LV GLS ($r = 0.66$, $P < .001$ and $r = 0.70$, $P < .001$, respectively) and a moderate correlation with LVEF ($r = 0.40$, $P = .002$ and $r = 0.39$, $P = .003$, respectively). Additionally, LV GWI and GCW had a moderate positive correlation with markers of AR severity: jet width/LV outflow tract ratio ($r = 0.30$, $P = .02$ and $r = 0.30$, $P = .02$, respectively), EROA ($r = 0.32$, $P = .02$ and $r = 0.32$, $P = .02$, respectively), and RVol ($r = 0.38$, $P = .006$ and $r = 0.37$, $P = .008$, respectively) but not with vena contracta ($r = 0.11$, $P = .41$ and $r = 0.10$, $P = .46$, respectively). LV GWE had a good correlation with LV GLS ($r = 0.57$, $P < .001$) and a moderate correlation with LVEF ($r = 0.32$, $P = .01$). No significant relations were found between myocardial work indices and LV volumes or LV mass index. Additionally, there were no differences in baseline myocardial work indices between patients with or without history of hypertension.

Table 2 Changes in clinical and echocardiographic variables between baseline and post-AVR

Variables	Baseline	Post-AVR	*P* value
SBP, mm Hg	142 ± 19	130 ± 16	<.001
DBP, mm Hg	69 ± 15	76 ± 12	.003
MBP, mm Hg	93 ± 14	94 ± 12	.72
LVM index, g/m^2	143 ± 40	115 ± 29	<.001
LVEDV index, mL/m^2	79.6 (59.4-104.2)	53.4 (44.8-64.2)	<.001
LVESV index, mL/m^2	29.2 (24.3-41.7)	21.5 (18.0-27.4)	<.001
LAV index, mL/m^2	33.9 ± 12.3	29.3 ± 10.2	.01
LVEF, %	59.7 ± 4.4	58.1 ± 6.5	.06
LV GLS, %	18.4 ± 3.0	15.2 ± 2.8	<.001
LV GWI, mm Hg%	2,084 ± 483	1,519 ± 363	<.001
LV GCW, mm Hg%	2,482 ± 525	1,797 ± 390	<.001
LV GWW, mm Hg%	116 ± 61	129 ± 78	.29
LV GWE, %	94.4 ± 2.6	91.6 ± 4.4	<.001

Data are presented as mean ± SD or median (interquartile range). *DBP*, Diastolic blood pressure; *LAV*, left atrial volume; *LVM*, LV mass; *MBP*, mean blood pressure; *SBP*, systolic blood pressure.

The ICCs for the intraobserver variability of LV myocardial work indices were 0.98 for LV GWI, 0.98 for GCW, 0.92 for GWW, and 0.90 for GWE, demonstrating excellent agreement (Supplemental Table 3). The ICCs for the interobserver variability were 0.98 for LV GWI and 0.99 for GCW, indicating excellent agreement, whereas the ICCs for GWW and GWE were 0.84 and 0.87, respectively, indicating good agreement.

Changes in Blood Pressure, LV Mechanics, and Myocardial Work after Aortic Valve Surgery

The median time between AVR and the postoperative echocardiogram was 3 months (2-7 months). Changes in clinical and echocardiographic parameters between baseline and post-AVR are shown in Table 2. A significant decrease in LV GWI, GCW, and GWE was observed, while LV GWW remained unchanged.

Based on normal references values,[7,8] 41 (72%) patients had normal values of LV GWI and GCW after AVR, whereas 16 (28%) patients had impaired LV GWI and LV GCW (Figure 2). Moreover 15 (26%) patients had reduced values of LV GWE. Interestingly, only

Table 3 Comparison between patients with and without postoperative impairment of LV GWI

Variables	Post-AVR preserved LV GWI (*n* = 41)	Post-AVR impaired LV GWI (*n* = 16)	*P* value
Baseline characteristics			
Sex, male	27 (66)	11 (69)	.84
Age, years	54 ± 15	51 ± 17	.41
Hypertension	23 (56)	5 (31)	.09
Diabetes	2 (5)	0 (0.0)	.37
Coronary artery disease	4 (10)	3 (19)	.35
New York Heart Association class I-II/III-IV	33 (80)/8 (20)	11 (69)/5 (31)	.34
SBP, mm Hg	143 ± 19	141 ± 21	.62
DBP, mm Hg	72 ± 15	68 ± 15	.37
LVEDV index, mL/m^2	82.6 (61.0-110.0)	70.5 (58.5-85.0)	.11
LVESV index, mL/m^2	32.0 (24.4-44.4)	28.7 (23.2-35.1)	.30
LVEF, %	60.0 ± 4.4	58.8 ± 4.4	.33
LV GLS, %	19.2 ± 3.1	16.6 ± 2.4	.005
LVM index, g/m^2	144 ± 36	143 ± 42	.91
LAV index, mL/m^2	35.7 ± 13.1	32.0 ± 11.2	.33
EROA, cm^2	32 ± 10	29 ± 8	.28
AVMG, mm Hg	8 ± 4	10 ± 6	.35
LV GWI, mm Hg%	2,188 ± 424	1,819 ± 534	.008
LV GCW, mm Hg%	2,590 ± 467	2,204 ± 575	.01
LV GWW, mm Hg%	113 ± 63	124 ± 57	.54
LV GWE, %	94.7 ± 2.4	93.4 ± 2.8	.10
Post-AVR characteristics			
SBP, mm Hg	133 ± 14	122 ± 17	.01
DBP, mm Hg	77 ± 12	73 ± 12	.20
LVEDV index, mL/m^2	54.7 (43.8-64.2)	50.5 (45.6-65.9)	.52
LVESV index, mL/m^2	21.1 (16.9-26.3)	24.2 (20.9-33.2)	.04
LVEF, %	60.1 ± 5.9	53.0 ± 4.8	<.001
LV GLS, %	16.3 ± 2.1	12.0 ± 1.6	<.001
Post-AVR remodeling			
% Reduction of LVEDV	32.7 (27.4-44.3)	18.4 (13.2-32.8)	.001
Reduction LVEDV >20%	37 (90)	8 (50)	.001
% Reduction of LVESV	32.0 (20.4-45.6)	14.5 (0-28.8)	<.001
Reduction LVESV >15%	36 (88)	8 (50)	.002
Reduction of LV GLS, %	2.7 ± 3.0	4.5 ± 3.0	.04

Data are presented as *n* (%), mean ± SD, or median (interquartile range). *AVMG*, Aortic valve mean gradient; *DBP*, diastolic blood pressure; *LAV*, left atrial volume; *LVM*, LV mass; *MBP*, mean blood pressure; *SBP*, systolic blood pressure.

16 (28%) patients had preserved values of LV GLS after AVR. Postoperative values of LV GLS and myocardial work indices were significantly impaired compared with those obtained in healthy controls (Supplemental Table 2).

The Interplay between LV Myocardial Work and LV Remodeling

The differences between patients with or without impairment of LV GWI after AVR are presented in Table 3. Patients with reduced LV GWI after AVR had lower values of LV GLS, GWI, and GCW at baseline compared with those patients with preserved LV GWI. Moreover, the postoperative impairment of LV GWI was associated with a lesser reduction in LVEDV and LVESV after surgery and a more pronounced impairment in LV GLS.

To further characterize the changes in LV GWI, which could be related to changes in GLS or in blood pressure, three groups were compared (Table 4 and Figure 4): patients with postoperative preserved LV GLS and GWI (defined as group I), patients with reduced LV GLS with preserved LV GWI (defined as group II), and patients with impaired LV GLS and GWI (defined as group III). Patients in group III had lower values of LVEF and LV GWE postoperatively compared with the other groups. Conversely, patients in group II had preserved LVEF and LV GWE and had higher values of systolic blood pressure. Moreover, patients in groups I and II exhibited increased LV reverse remodeling compared with patients in group III.

The association between postoperative LV GWI and LV reverse remodeling was further assessed using spline curve and receiver operator curve analysis (Supplemental Figure 1). The receiver operator curve analysis identified a threshold value of 1,285 mm Hg% for LV GWI as a predictor of LV reverse remodeling (area under the curve, 0.790; 95% CI, 0.651-0.929; $P = .001$) with a sensitivity of 88% and specificity of 72%. Of interest, this threshold value corresponded approximately to the previously reported lower limit of normality of LV GWI.[7]

Notably, patients with increased values of LV GWI or GCW at baseline showed similar reduction in LV volumes postoperatively but a greater impairment in LV GLS compared with patients with preserved values of LV GWI or LV GCW (Supplemental Table 4).

DISCUSSION

The main findings of this retrospective study are summarized as follows: (1) patients with chronic moderate or severe AR and preserved LVEF had preserved or increased LV GWI and LV GCW, preserved LV GWE, but moderately impaired LV GLS; (2) LV GWI and GCW showed a positive correlation with markers of AR severity and parameters of LV systolic function; (3) LV GWI, GCW, and GWE decreased significantly early after AVR, without changes in LV GWW; (4) a considerable percentage of patients (28%) showed a postoperative impairment of LV GWI, which was strongly associated with reduced LV reverse remodeling.

The definition of the appropriate surgical timing in patients with chronic severe AR is crucial to achieve the recovery or preservation of LV systolic function and to improve long-term survival. Current guidelines recommend surgery in symptomatic patients or, in the case of asymptomatic patients, when there is LV dysfunction (LVEF < 50%) or significant LV dilatation.[10] Despite these indications, decisions about the timing of cardiac surgery remain challenging, because an increase in mortality has been reported before reaching the currently recommended surgical thresholds.[3,11-13] As a result, several studies have focused on identifying more sensitive markers, including LV GLS, that may unmask subclinical LV dysfunction at earlier stages, provide incremental risk stratification, and help in the decision-making process.[1-3] The impairment of LV GLS in chronic

Table 4 Comparison according to the postoperative impairment of LV GLS and LV GWI

Variables	Group I (*n* = 16)	Group II (*n* = 25)	Group III (*n* = 16)	*P* value
Post-AVR characteristics				
SBP, mm Hg	130 ± 16	135 ± 14	122 ± 17*	.03
DBP, mm Hg	75 ± 12	79 ± 12	73 ± 12	.27
LVEDV index, mL/m^2	50.3 (43.7-59.0)	56.2 (43.7-69.1)	50.5 (45.6-65.9)	.49
LVESV index, mL/m^2	18.9 (16.2-22.2)	21.6 (17.8-28.6)	24.2 (20.9-33.2)†	.03
LVEF, %	61.9 ± 5.2	59.0 ± 6.1	52.9 ± 4.8*†	<.001
LV GLS, %	18.4 ± 1.6	15.2 ± 1.5†	12.0 ± 1.6*†	<.001
LV GWI, mm Hg%	1,769 ± 241	1,650 ± 255	1,066 ± 130*†	<.001
LV GCW, mm Hg%	2,077 ± 312	1,902 ± 276	1,355 ± 197*†	<.001
LV GWW, mm Hg%	99 ± 70	122 ± 61	171 ± 94†	.02
LV GWE, %	94.4 ± 3.4	92.4 ± 3.2	87.7 ± 4.3*†	<.001
Post-AVR remodeling				
% Reduction of LVEDV	32.9 (29.2-39.9)	32.7 (26.8-45.5)	18.4 (13.2-32.9)*†	.005
% Reduction of LVESV	30.7 (23.6-44.8)	34.8 (16.7-48.3)	14.5 (0-28.9)*†	.002
Reduction of LV GLS, %	1.7 ± 2.2	3.3 ± 3.3	4.5 ± 3.0†	.03

Data are presented as mean ± SD or median (interquartile range). Comparison between patients with preserved LV GLS and GWI (group I), patients with impaired LV GLS and preserved GWI (group II), and patients with impaired LV GLS and GWI (group III). *DBP*, Diastolic blood pressure; *MBP*, mean blood pressure; *SBP*, systolic blood pressure.
*P < .05 vs group II.
†P < .05 vs group I.

severe AR has been correlated with adverse outcomes following AVR.[1-3,13] However, even when only patients with preserved LVEF are considered, LV GLS values showed marked heterogeneity,[14] probably reflecting the significant influence of loading conditions (particularly the afterload) on LV GLS. Of importance, the load dependency of LV GLS may represent a relevant limitation in patients with chronic severe AR, as afterload may vary with medication use, geometric changes, and, particularly, the relief of volume and pressure overload after AVR.

Myocardial work has been introduced as a novel parameter of LV performance that takes into account LV deformation and LV afterload.[4] Moreover, it demonstrated a robust correlation with myocardial glucose utilization assessed with positron emission tomography.[4] The application of noninvasive LV myocardial work in patients with chronic severe AR and preserved LVEF may improve our understanding of LV performance and energetics, as well as of postoperative LV reverse remodeling, overcoming the load dependency of other echocardiographic parameters (LVEF and LV GLS).

LV Myocardial Work Indices in Chronic Severe AR

Patients with chronic moderate or severe AR and preserved LVEF were characterized by preserved or increased values of LV GWI and LV GCW and preserved values of LV GWW and LV GWE in the vast majority of cases (96%), based on reported references ranges.[7] Nevertheless, a slight but statistically significant difference in LV GWW and LV GWE was detected between patients with chronic AR and age- and gender-matched healthy controls.

From a pathophysiological view, the progressive volume and pressure overload in chronic severe AR results from an increased stroke volume, which induces a rise in systolic blood pressure. Increased systolic blood pressure, together with increased LVEDV due to the high preload, leads to a significant elevation of LV wall stress (afterload). In this context, increased LV GWI and GCW may reflect the compensatory mechanisms that match the increased arterial afterload, allowing the preservation of LVEF, at the price of an elevated myocardial oxygen consumption. Furthermore, the positive correlation of LV GWI and GCW with markers of AR severity suggests an interplay between AR progression and the increase of LV GWI and GCW, which may function until the impairment of myocardial contractile reserve occurs. Indeed, chronically increased cardiac loading conditions lead to progressive myocardial fibrosis with increased LV stiffness and eventually cardiac failure. Interestingly, similar findings have been reported by Chan *et al.*[15] in uncontrolled hypertension, which represents a different model of increased LV wall stress, caused by a pure pressure overload. The authors showed that patients with moderate-to-severe hypertension had higher values of LV GWI compared with control subjects, with preserved LV GWE due to the proportional increase in GCW and GWW. Of note, myocardial work parameters were not associated with vena contracta width, a semiquantitative parameter of AR severity that is less influenced by loading conditions.[16]

As expected, LV GWI, GCW, and GWE were also significantly correlated with parameters of LV systolic performance (LVEF and LV GLS). Conversely, no significant correlation was found between myocardial work indices and LV volumes or LV mass indexed to BSA. This is possibly related to the variability in LV remodeling responses and the inclusion of only patients with preserved LVEF. Moreover, even if an increase in contractile mass could theoretically produce higher positive work, a reduction of myocardial work indices has been reported in patients with pathological myocardial hypertrophy, including hypertrophic cardiomyopathy.[17]

Changes in Blood Pressure, LV Mechanics, and Myocardial Work after Aortic Valve Surgery

The relief of volume and pressure overload after AVR leads to a decrease in systolic blood pressure, LV GLS, and, consequently, LV

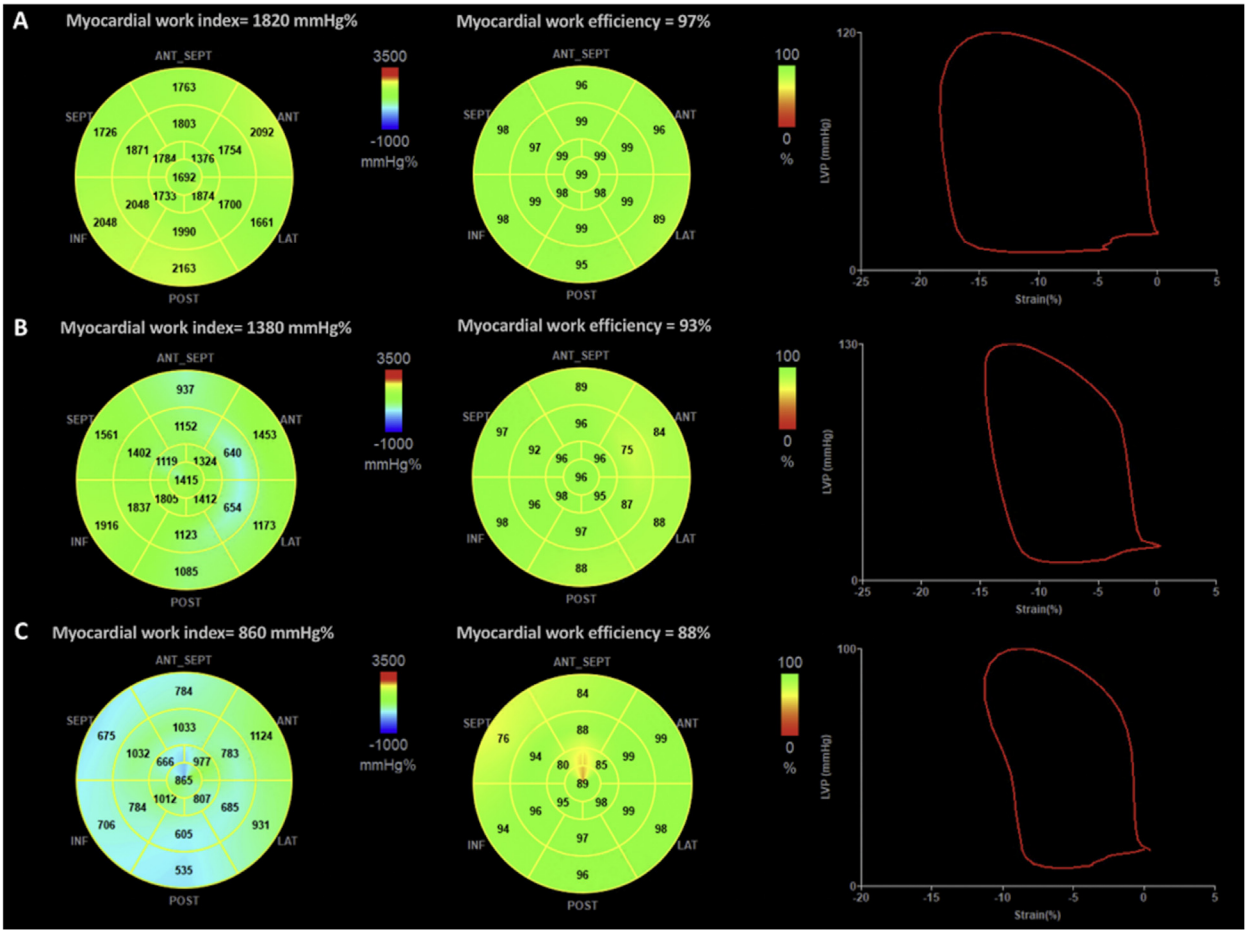

Figure 4 Examples of myocardial work indices after aortic valve surgery. Preserved segmental values of LV GWI and LV GWE are presented in *green*, while reduced segmental values are presented in *yellow*. Examples of patients with postoperative preserved LV GLS and LV GWI **(A)**, reduced LV GLS and preserved LV GWI **(B)**, and impaired LV GLS and LV GWI **(C)** are provided. Of note, LV GWE is preserved in the first two cases **(A, B)** but reduced in the third patient **(C)**. *LVP*, LV pressure.

GWI. Previous studies have reported worsening of LV GLS in patients with chronic severe AR early after AVR.[13,18] The postoperative unloading of the LV leads to a decrease in chamber dimensions and, according to the Frank-Starling law, less stretch of the myocardial fibers, which explains the reduction in LV GLS. Additionally, in our study, a reduction of LV GCW was observed after AVR, without significant changes of LV GWW, leading to a decrease of LV GWE. Left ventricular GCW represents the positive work, that is, the work contributing to LV ejection. Similar to LV GWI, LV GCW was reduced after the postoperative unloading of the LV. On the other hand, LV GWW estimates the amount of paradoxical myocardial lengthening or shortening that does not contribute to the LV filling during diastole and LV ejection during systole. The absence of postoperative changes in LV GWW may reflect the balanced effects played by the decreased wall stress and new-onset septal dyssynchrony after AVR.

The Interplay between LV Myocardial Work and LV Reverse Remodeling

The impairment of LV GLS after AVR was much more prevalent than the impairment of LV GWI (72% vs 28%). However, patients with impaired LV GLS and preserved LV GWI showed a good LV contractile performance, with preserved values of LVEF and LV GWE and, notably, higher systolic blood pressure. These findings might suggest that, at least in some of these patients, LV GLS is falsely reduced, because of the higher LV systolic pressure.

The sustained impairment of LV GLS within 1 year after AVR, in addition to LV GLS worsening of at least 5% from baseline, has been correlated with lower survival in patients with asymptomatic chronic severe AR and preserved LVEF.[13] However, the postoperative impairment of LV GLS (defined as values <19%) was highly prevalent also in this cohort (70% of patients), suggesting that conventional cutoff values of LV GLS may be suboptimal thresholds for postsurgical risk stratification.

Moreover, in our study, the postsurgical impairment of LV GWI demonstrated a stronger association with less pronounced LV reverse remodeling (compared with the impairment of LV GLS) and was also accompanied by a larger reduction in LV GLS from baseline. Left ventricular reverse remodeling responses are heterogeneous and not fully explained by the preoperative hemodynamics. Notably, adverse LV reverse remodeling after AVR has been associated with higher long-term mortality.[19,20] The adverse LV functional recovery in patients with impaired LV GWI could be explained by more advanced structural remodeling with an increased extent of myocardial fibrosis. The presence of myocardial fibrosis in patients with severe AR has been

correlated with a smaller improvement in LV function and poorer survival after AVR.[21] Moreover, it has been reported that the formation of interstitial fibrosis may not regress after surgery,[22] highlighting the importance of redefining the optimal time of intervention, before irreversible damage of the myocardium may occur.

Study Limitations

This is a retrospective, single-center study, conducted with a small sample size. Our data suggest that noninvasive assessment of LV myocardial work may be useful in the echocardiographic evaluation of chronic AR but did not demonstrate superiority over LV GLS for risk stratification or prediction of clinical outcomes. Larger studies are needed to further evaluate these novel parameters and establish prognostic implications in chronic AR. Finally, considering the significant advances in surgical techniques and strategies of myocardial protection, the wide period of patient inclusion (from 2002 to 2019) represents an additional limitation of the present study.

CONCLUSION

Patients with chronic moderate or severe AR and preserved LVEF showed preserved or increased LV GWI and LV GCW and preserved LV GWE, despite the moderate impairment of LV GLS. Aortic valve replacement or repair results in a significant decrease of myocardial work indices, with the exception of LV GWW, which did not change. The postoperative impairment of LV GWI, observed in 28% of the patients, was closely associated with worse LV reverse remodeling and could be related to a greater extent of myocardial fibrosis.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2022.01.008.

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Supplemental Table 1 Surgical indications and outcomes

	Population (n = 57)
Indications for AVR	
Severe AR	46 (80.7)
Significant aortic root dilation	5 (8.8)
Moderate AR in patients with heart failure symptoms and high N-terminal-pro hormone BNP, not explained by other causes	2 (3.5)
Chronic aortic endocarditis with evidence of progressive valve dysfunction	2 (3.5)
Moderate AR in patients with progressive LV dilation not explained by other causes	2 (3.5)
Postoperative outcomes	
Trivial-mild AR	55 (96.5)
Moderate AR	2 (3.5)*

Data are presented as n (%).
*Residual moderate AR was observed in two patients with preoperative severe AR treated by AVR.

Supplemental Table 2 Comparison of LV myocardial work indices in patients with chronic AR, calculated at baseline and postoperatively, with age- and gender-matched healthy controls

Variable	Patients with chronic AR (n = 57)		Controls (n = 57)	P value*	P value†
	Baseline	Postoperatively			
Sex, male, n (%)	38 (67)	—	38 (67)	1.00	—
Age, years	53 ± 16	—	53 ± 15	.90	—
SBP, mm Hg	142 ± 19	130 ± 16	129 ± 19	<.001	.64
DBP, mm Hg	69 ± 15	76 ± 12	79 ± 11	<.001	.16
MBP, mm Hg	93 ± 14	94 ± 12	96 ± 13	.36	.48
LV GLS, %	18.4 ± 3.0	15.2 ± 2.8	19.5 ± 2.1	.03	<.001
LV GWI, mm Hg%	2,084 ± 483	1,519 ± 363	1,956 ± 427	.13	<.001
LV GCW, mm Hg%	2,482 ± 525	1,797 ± 390	2,293 ± 497	.05	<.001
LV GWW, mm Hg%	116 ± 61	129 ± 78	79 ± 44	<.001	<.001
LV GWE, %	94.4 ± 2.6	91.6 ± 4.4	95.8 ± 1.5	<.001	<.001

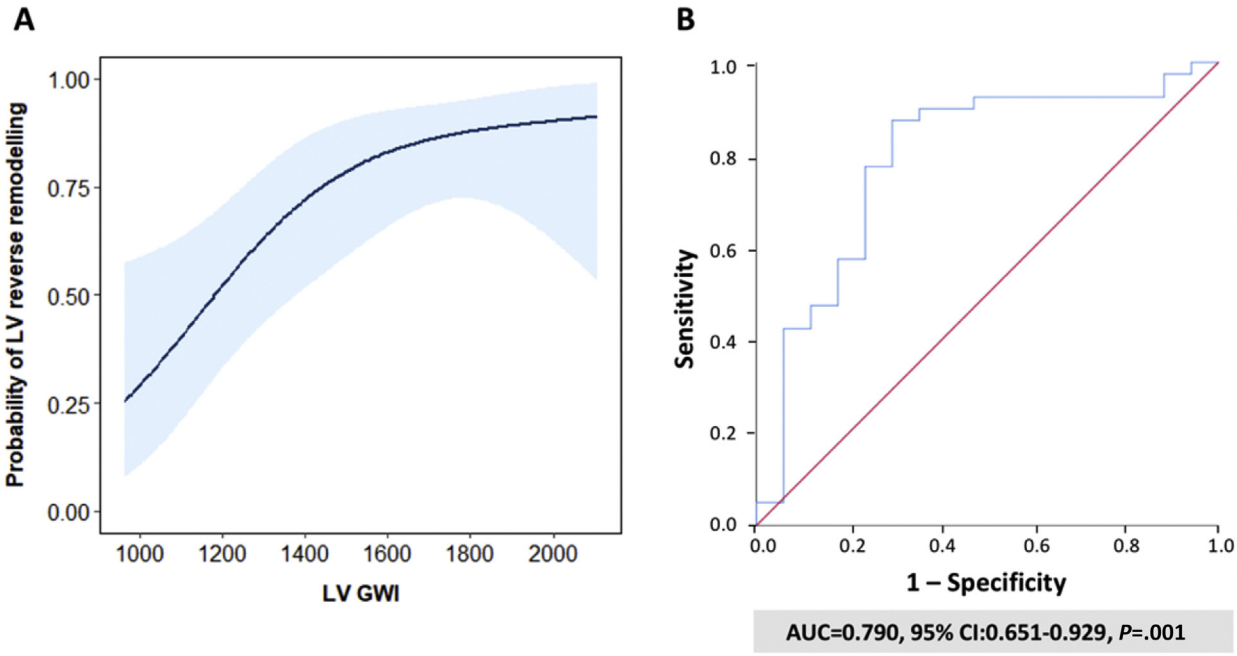
Data are presented mean ± SD unless otherwise indicated.
DBP, Diastolic blood pressure; *MBP*, mean blood pressure; *SBP*, systolic blood pressure.
*P value of the comparison between patients with chronic AR, at baseline, and healthy controls.
†P value of the comparison between patients with chronic AR, postoperatively, and healthy controls.

Supplemental Table 3 Intraobserver and interobserver correlation coefficients for baseline myocardial work indices

	Intraclass correlation (95% CI)
Intraobserver variability	
LV GWI, mm Hg%	0.98 (0.94-0.99)
LV GCW, mm Hg%	0.98 (0.96-1.00)
LV GWW, mm Hg%	0.92 (0.77-0.97)
LV GWE, %	0.90 (0.71-0.97)
Interobserver variability	
LV GWI, mm Hg%	0.98 (0.94-0.99)
LV GCW, mm Hg%	0.99 (0.96-1.00)
LV GWW, mm Hg%	0.84 (0.54-0.95)
LV GWE, %	0.87 (0.45-0.96)

Supplemental Table 4 Post-AVR remodeling in patients with or without preserved myocardial work indices at baseline

	Comparison according to the baseline LV GWI		
	Increased LV GWI (*n* = 10)	Preserved LV GWI (*n* = 47)	*P* value
% Reduction of LVEDV	30.1 (24.4-45.0)	32.5 (22.8-37.2)	.95
% Reduction of LVESV	26.7 (6.1-44.7)	29.0 (16.0-41.4)	.63
Reduction of LV GLS, %	5.1 ± 2.4	2.8 ± 3.1	.03
	Comparison according to the baseline LV GCW		
	Increased LV GCW (*n* = 14)	Preserved LV GCW (*n* = 43)	*P* value
% Reduction of LVEDV	30.7 (27.4-44.9)	32.5 (20.1-37.2)	.61
% Reduction of LVESV	27.7 (17.9-40.6)	29.0 (15.0-44.6)	.88
Reduction of LV GLS, %	5.0 ± 2.4	2.6 ± 3.1	.01



Supplemental Figure 1 Association between postoperative LV myocardial work index and LV reverse remodeling by spline curve and receiver operator curve analysis. **(A)** Probability of LV reverse remodeling (defined as LVEDV reduction > 20% and LVESV reduction > 15%) according to postoperative values of LV GWI, using spline curve analysis. After an initial plateau region until 1,500 mm Hg%, there was a steep linear decrease in the probability of LV reverse remodeling with lower values of LV GWI. **(B)** Receiver operator curve analysis for LV reverse remodeling according to the postoperative values of LV GWI. A cutoff value of 1,285 mm Hg% for LV GWI was associated with LV reverse remodeling, with a sensitivity of 88% and specificity of 72%. *AUC*, Area under curve.