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Left Ventricular Myocardial Work in Patients with Severe Aortic Stenosis

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Background: Left ventricular myocardial work (LVMW) is a novel method to assess left ventricular (LV) function using pressure-strain loops that takes into consideration LV afterload. The estimation of LV afterload in patients with severe aortic stenosis (AS) may be challenging, and no study so far has investigated LVMW in this setting. The aim of this study was to develop a method to calculate LVMW in patients with severe AS and to analyze its relationship with heart failure symptoms.

Methods: Indices of LVMW were calculated in 120 patients with severe AS who underwent transcatheter aortic valve replacement and invasive LV and aortic pressure measurements. LV systolic pressure was also derived by adding the mean aortic valve gradient to the aortic systolic pressure. LV global longitudinal strain and echocardiography-derived LV systolic pressure were then incorporated to construct pressure-strain loops of the left ventricle.

Results: An excellent correlation was observed between LVMW indices calculated using the invasive and echocardiography-derived LV systolic pressure. Patients in New York Heart Association functional class III or IV (n = 97 [73%]) had lower LV global longitudinal strain, LV global work index, LV global constructive work, and right ventricular free wall strain compared with those in New York Heart Association functional class I or II. In contrast to LV global longitudinal strain, LV global work index (odds ratio per 100 mm Hg% increase, 0.91; 95% CI, 0.85–0.98; P = .012) and LV global constructive work showed independent associations with New York Heart Association functional class III or IV heart failure symptoms.

Conclusions: The calculation of echocardiography-based LVMW indices is feasible in patients with severe AS. In particular, LV global work index and global constructive work showed independent associations with heart failure symptoms and may provide additional information on myocardial remodeling and function in patients with severe AS. (J Am Soc Echocardiogr 2021;34:257-66.)

Keywords: Aortic stenosis, Left ventricle, Myocardial work

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Aortic valve stenosis (AS) is the most common valvular heart disease worldwide and is characterized by progressive thickening, fibrosis, and calcification of the aortic valve that reduces leaflet motion and valve area.[1,2] The consequent increase in left ventricular (LV) afterload leads to a hypertrophic response to normalize LV wall tension and cardiac output. Although compensatory, LV remodeling has unfavorable consequences and leads to a decrease in LV performance, the development of symptoms and adverse clinical outcomes.[2,3] American and European guidelines recommend surgical or transcatheter aortic valve replacement (AVR) in patients with severe AS who present with symptoms or in asymptomatic patients with reduced LV ejection fractions (LVEFs; <50%).[4,5] However, both the presence of symptoms related to severe AS and impaired LVEF already represent a late stage of the disease, when irreversible LV damage may have occurred and outcomes after AVR may be less favorable.[6,7]

The systolic performance of the left ventricle in patients with AS is commonly evaluated by measuring parameters of myocardial fiber shortening such as LVEF and LV global longitudinal strain (GLS). However, these indices do not take into account the afterload, which differs with AS severity and peripheral vascular resistance, and they do not reflect LV myocardial work or oxygen demand.[8] Recently,

Abbreviations

AS = Aortic valve stenosis

AVR = Aortic valve replacement

GCW = Global constructive work

GLS = Global longitudinal strain

GWE = Global work efficiency

GWI = Global work index

GWW = Global wasted work

HF = Heart failure

ICC = Intraclass correlation coefficient

LV = Left ventricular

LVEF = Left ventricular ejection fraction

NYHA = New York Heart Association

RV = Right ventricular

TAVR = Transcatheter aortic valve replacement

Russell *et al.*[8,9] developed a novel method to noninvasively assess LV myocardial work, which correlated well with invasively assessed myocardial performance and oxygen consumption. According to this method, LV myocardial work can be estimated by incorporating blood pressure recordings and echocardiographic strain data to derive a pressure-strain loop. This technique makes it possible to quantify the total work of the left ventricle during a cardiac cycle (i.e., global work index [GWI]); furthermore, it provides (1) global constructive work (GCW), which represents the work that is functional to LV relaxation during diastole and contraction during systole; (2) the amount of LV dyssynchrony or paradoxical myocardial lengthening or shortening that does not occur in the appropriate cardiac phase (i.e., global wasted work [GWW]); and to derive from these parameters the (3) LV global work efficiency (GWE), which is a global estimation of LV performance. However, in patients with severe AS, noninvasively measured systolic blood pressure does not reflect LV pressure, as the calcific aortic valve poses an obstruction to LV outflow; therefore, noninvasive LV myocardial work has never been characterized in this condition. Accordingly, the aim of the present study was to develop an echocardiography-based method to evaluate LV myocardial work in patients with severe AS undergoing transcatheter AVR (TAVR) and to investigate the association between echocardiography-derived myocardial work indices and the presence of heart failure (HF) symptoms.

METHODS

Study Population

Patients with severe AS who underwent TAVR between February 2016 and August 2018 were selected. Those who underwent transthoracic echocardiography within 48 hours before invasive aortic and LV pressure measurements during TAVR were included (6.7% of the echocardiographic examinations were performed the same day, 90.8% the day before, and 2.5% 2 days before TAVR). Patient demographics and clinical data were collected from the departmental electronic medical record (EPD-vision; Leiden University Medical Center, Leiden, the Netherlands). As this study involved the retrospective analysis of clinically acquired data, the institutional review board of the Leiden University Medical Center waived the need for written patient informed consent.

Invasive LV and Aortic Pressure Measurements

Left heart catheterization was performed before TAVR via retrograde access from the femoral artery, where an 8-Fr sheath was placed. A 6-Fr Amplatz L2 catheter (Cordis Corporation, Milpitas, CA) was used to obtain LV pressure measurements, while aortic pressure was simultaneously measured through the side port of the femoral sheath. Transducers were calibrated with zero level set at the midaxillary line, and systolic and diastolic pressures were recorded (Figure 1).

Echocardiographic Data Acquisition and Measurements

Comprehensive transthoracic echocardiography was performed using a Vivid E9 or E95 ultrasound system (GE Vingmed Ultrasound, Horten, Norway) with patients at rest in the left lateral decubitus position. Electrocardiographically triggered echocardiographic data were acquired with M5S transducers and digitally stored in cine-loop format for offline analysis with a dedicated software (EchoPAC version 203; GE Vingmed Ultrasound). Parasternal, apical, and subcostal views were used to acquire two-dimensional, color, pulsed-wave, and continuous-wave Doppler data according to current recommendations.[10] AS severity was quantified by measuring the maximum velocity through the aortic valve using continuous-wave Doppler, and the simplified Bernoulli equation was used to derive the peak transaortic pressure gradient from the maximum velocity.[11,12] The mean pressure gradient across the aortic valve was estimated by averaging the instantaneous gradients over the ejection period.[11,12] The LV outflow tract diameter was measured from a zoomed parasternal long-axis view proximal to the aortic valve.[11,12] The velocity-time integral was measured on the pulsed-wave Doppler recordings of the LV outflow tract acquired from the LV apical three- or five-chamber view with the sample volume located below the aortic valve and was used to calculate the stroke volume.[11,12] Subsequently, aortic valve area was derived using the continuity equation and indexed to body surface area.[11,12] An aortic valve area index < 0.6 cm^2/m^2 was used to identify severe AS. Stroke volume index and the mean pressure gradient across the aortic valve were used to identify the following hemodynamic categories of AS[4]: high-gradient AS (mean gradient $\geq$ 40 mm Hg); low-flow, low-gradient AS (stroke volume index $\leq$ 35 mL/m^2 and mean gradient $<$ 40 mm Hg); and normal-flow, low-gradient AS (stroke volume index $>$ 35 ml/m^2 and mean gradient $<$ 40 mm Hg). LV volumes were estimated using the biplane Simpson method, and LVEF was calculated as recommended.[10] LV mass was derived using the standard linear two-dimensional approach.[10] LV diastolic function was assessed by measuring the peak early (E) and late (A) diastolic velocities on transmitral flow pulsed-wave recordings, septal and lateral e′ were measured in the apical four-chamber view on tissue Doppler imaging, and average E/e′ ratio was calculated.[13] Concomitant valvular heart diseases were identified and graded as recommended.[4,5,11,12] Pulmonary artery systolic pressure was calculated from the tricuspid regurgitation jet peak velocity applying the modified Bernoulli equation and adding mean right atrial pressure, estimated on the basis of the diameter and collapsibility of the inferior vena cava.[14]

The apical two-, three- and four-chamber views were used to derive LV GLS.[15,16] The endocardial border was traced at an end-systolic frame, and a region of interest was automatically defined by the software and manually adapted to include the entire myocardial thickness. Right ventricular (RV) systolic function was characterized by measuring tricuspid annular plane systolic excursion[14] and RV free wall strain from an RV-focused apical four-chamber view.[16]

HIGHLIGHTS

- LV myocardial work can be derived with echocardiography in patients with severe AS.
- LV myocardial work indices may provide further insights on LV function in severe AS.
- LV myocardial work indices independently correlate with HF symptoms in severe AS.

Quantification of LV Myocardial Work

Global LV myocardial work indices were derived using proprietary software (EchoPAC version 203) that integrates LV strain measurements with blood pressure recordings.[8] LV systolic pressure was estimated on echocardiography by adding the mean aortic transvalvular gradient to the aortic systolic pressure. The mean pressure gradient was preferred over the peak gradient for the following reasons. Considering the pressure recovery phenomenon[17] and the time difference between the pressure peak in the aorta and in the left ventricle[18] (while Doppler echocardiography measures instantaneous pressure gradient across the aortic valve), adding peak pressure gradient to the aortic systolic pressure would tend to overestimate LV systolic pressure compared with adding mean pressure gradient. In accordance with this hypothesis, in our cohort the estimation of LV systolic pressure adding the mean pressure gradient showed higher agreement with the invasive measurement (intraclass correlation coefficient [ICC], 0.846; 95% CI, 0.781–0.891; $P < .001$) compared with adding the peak pressure gradient (ICC, 0.772; 95% CI, 0.397–0.892; $P < .001$), which also led to a significant overestimation of LV systolic pressure by Bland-Altman analysis (Supplemental Figure 1). LV systolic pressure, estimated both invasively and on echocardiography (by adding the mean pressure gradient to the aortic systolic pressure), and aortic diastolic pressure were entered into the software (Figure 1). The apical three-chamber view and the pulsed-wave Doppler recordings were used to manually identify aortic and mitral valve openings and closures. Measurements of LV strain and the previously defined pressures were then synchronized by cardiac cycle timings (determined by aortic and mitral valve events) to produce pressure-strain loops of the left ventricle. The patient-specific LV pressure curve was then estimated by measuring the time of valvular events by echocardiography and adjusting a standard LV pressure curve[8] to the pressures entered into the software and the duration of LV isovolumic contraction, ejection, and isovolumic relaxation. The software then constructed a global noninvasive LV pressure-strain curve combining LV GLS data of the entire cardiac cycle and the estimated LV instantaneous pressure. Cardiac work was calculated as a function of time throughout the cardiac cycle, and four parameters of LV myocardial work were derived by the software:

1. LV GWI (mm Hg%): the area within the global LV pressure-strain loop, calculated from mitral valve closure to opening. This index gives a comprehensive estimation of LV diastolic and systolic work.
2. LV GCW (mm Hg%): the constructive work contributing to shortening during systole and lengthening during isovolumic relaxation. This index represents the work that is functional to LV contraction during systole and relaxation during diastole.
3. LV GWW (mm Hg%): the wasted work contributing to lengthening during systole and shortening during isovolumic relaxation. This parameter provides an estimation of the amount of LV dyssynchrony or paradoxical myocardial lengthening or shortening that does not contribute to the filling of the left ventricle during diastole and LV ejection during systole.
4. LV GWE (%): LV GCW divided by the sum of LV GCW and LV GWW. This index indicates the percentage of total LV work that is useful to LV contraction and relaxation during systole and diastole, respectively, providing a comprehensive estimation of LV performance.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, NY) and in R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria). Adherence to normality was visually assessed by comparing histograms of the sample data with a normal probability curve. Continuous variables are presented as mean ± SD in the case of normal distribution and as median (interquartile range) in the case of non-normal distribution. Categorical variables are expressed as absolute frequencies and percentages. ICCs were used to investigate the agreement between LV myocardial work indices estimated with invasively measured versus echocardiography-derived LV systolic pressures. Differences between patients presenting in New York Heart Association (NYHA) functional class I or II and those in NYHA functional class III or IV were analyzed using the unpaired Student's t test for continuous variables with normal distributions, the Mann-Whitney U test for continuous variables not normally distributed, and the Pearson χ^2 test for categorical variables. Multiple comparisons were performed using Bonferroni correction. To investigate the associations between echocardiographic and clinical features and NYHA functional class III or IV HF symptoms, uni- and multivariate logistic regression analyses were performed. Potential confounders with significant P values in the univariate analysis were included in the multivariate logistic regression analysis. The goodness of fit of the multivariate logistic regression models was evaluated by calculating C statistics. To further characterize the associations between LV myocardial work indices and the probability of presenting with NYHA functional class III or IV HF symptoms, a spline curve was fitted. Fifteen random individuals were selected for the evaluation of intra- and interobserver agreement using ICCs and Bland-Altman analysis. The second observer was blinded to the measurements of the first observer for interobserver measurements. Excellent agreement was defined by an ICC > 0.75, whereas strong agreement was defined by a value between 0.60 and 0.74. All tests were two sided, and P values < .05 were considered statistically significant.

RESULTS

LV Myocardial Work Measurements in Severe AS

The ICC for LV myocardial work indices calculated with invasive versus echocardiography-derived LV systolic pressures showed excellent agreement (Supplemental Table 1). The ICCs for intraobserver variability of echocardiography-derived LV myocardial work indices were 0.95 for LV GWI, 0.97 for GCW, 0.80 for GWW, and 0.79

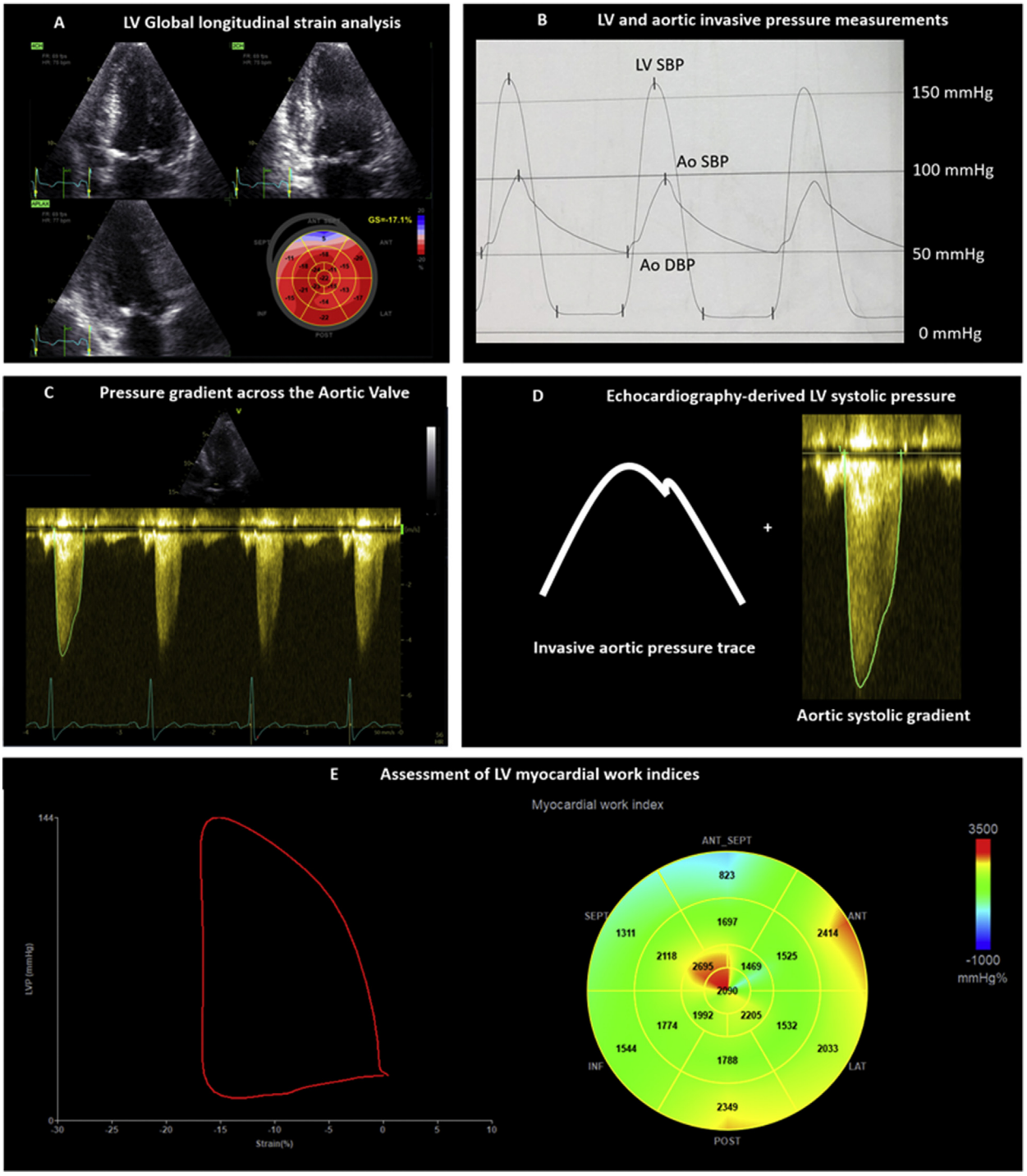

Figure 1 LV myocardial work assessment in patients with severe AS. **(A)** Measurement of LV GLS. **(B)** Invasive measurements of LV and aortic (Ao) blood pressures. The mean pressure gradient across the aortic valve **(C)** was added to Ao systolic blood pressure (SBP) to derive the echocardiographic estimation of LV SBP **(D)**. Echocardiography-derived LV SBP and Ao diastolic blood pressure (DBP) were entered into the software and combined with LV GLS to derive LV pressure-strain loops *(red loop)* and global myocardial work indices **(E)**.

Table 1 Clinical characteristics of the study population and according to HF symptoms

Variable	Overall (*N* = 120)	NYHA functional class I or II (*n* = 33)	NYHA functional class III or IV (*n* = 87)	*P*
Age, y	85 (80–89)	84 (79–88)	85 (80–89)	.529
Sex, male	62 (52)	20 (61)	42 (48)	.227
AF	24 (20)	4 (12)	20 (23)	.184
Heart rate, beats/min	71 ± 12	71 ± 13	71 ± 12	.913
Hb, mmol/L	7.7 ± 1.0	7.4 ± 1.1	7.8 ± 1.0	.067
Creatinine, μmol/L	89 (73–116)	90 (72–115)	88 (73–117)	.828
Hypertension	95 (79)	29 (88)	66 (76)	.148
Diabetes mellitus	34 (28)	11 (33)	23 (26)	.454
Dyslipidemia	60 (50)	18 (55)	42 (48)	.540
Previous MI	14 (12)	4 (12)	10 (12)	.924
COPD	21 (18)	6 (18)	15 (17)	.904
Diuretics	77 (64)	18 (55)	59 (68)	.176

AF, Atrial fibrillation; *COPD*, chronic obstructive pulmonary disease; *Hb*, hemoglobin, *MI*, myocardial infarction.
Data are expressed as median (interquartile range), number (percentage), or mean ± SD.

for GWE, demonstrating excellent agreement (Supplemental Table 2). While the ICCs for interobserver variability were 0.97 for LV GWI and 0.98 for GCW, indicating excellent agreement, the ICCs for GWW and GWE were 0.66 and 0.62, respectively, indicating strong agreement. The Bland-Altman analysis for assessing the intra- and interobserver variability of the aforementioned LV myocardial work indices is displayed in Supplemental Figure 2.

Patient Characteristics

A total of 120 patients with severe AS were included (Supplemental Figure 3). The clinical characteristics of the overall population and according to the presence of HF symptoms are illustrated in Table 1. Overall, the median age was 85 years (interquartile range, 80–89 years), 52% were men, and 64% received diuretics. Thirty-three patients (27.5%) presented with NYHA functional class I or II HF symptoms, whereas 87 patients (72.5%) reported NYHA functional class III or IV HF symptoms. Patients with NYHA functional class III or IV HF symptoms had similar age, comorbidities, and cardiovascular risk factors compared with those with NYHA functional class I or II HF symptoms.

Echocardiographic characteristics are shown in Table 2. A total of 82 patients (68%) presented with high-gradient AS; 29 (24%) with low-flow, low-gradient AS; and nine (8%) with normal-flow, low-gradient AS. Overall, mean LV volumes were within normal limits, mean LV GLS was impaired, and average E/e′ ratio was increased (>14) in 81% of the patients. Mean pulmonary artery systolic pressure was at the upper limit of normality, and mean RV systolic function (both estimated with tricuspid annular plane systolic excursion and RV free wall strain) was preserved. In the per-group analysis, patients with NYHA functional class III or IV HF symptoms had significantly lower LV GLS and RV free wall strain compared with patients with NYHA functional class I or II HF symptoms.

Echocardiography-derived LV myocardial work indices are illustrated in Table 3. Overall, compared with values reported in healthy subjects,[19] mean LV GWI (normal range, 1,292–2,505 mm Hg%), GCW (normal range, 1,582–2,881 mm Hg%), and LV GWW (normal range, <226 mm Hg%) were within the normal limits, while mean GWE (normal range, >90%) was reduced, indicating less efficient myocardial mechanics in the setting of severely increased LV afterload. In the per-group analysis, patients with NYHA functional class III or IV HF symptoms had lower LV GWI and GCW, whereas GWW was similar and GWE showed a trend toward being lower compared with patients with NYHA functional class I or II HF symptoms. Interestingly, LV GWI and GCW were higher in patients with high-gradient AS compared with those with low-flow, low-gradient AS (Supplemental Table 3).

Relationship Between Patient Characteristics and HF Symptoms

The univariate logistic regression analysis showed an association between NYHA functional class III or IV HF symptoms and the following parameters (Table 4): LV GLS, RV free wall strain, and echocardiography-derived LV GWI, GCW, and GWE. For collinearity reasons, several bivariate logistic regression models with one parameter of LV function and RV free wall strain were built. After correcting for RV free wall strain, although LV GLS was not independently associated with NYHA functional class III or IV HF symptoms (Table 5), echocardiography-derived LV GWI (adjusted odds ratio per 100 mm Hg% increase, 0.91; 95% CI, 0.85–0.98; $P = .012$) and GCW (adjusted odds ratio per 100 mm Hg% increase, 0.94; 95% CI, 0.89–1.00; $P = .042$) retained independent associations with HF symptoms; in particular, the model including LV GWI yielded the highest increment in the C statistic. A spline curve analysis was performed to further characterize the association between echocardiography-derived LV myocardial work indices and NYHA functional class III or IV HF symptoms. Figure 2 demonstrates that lower values of LV GWI and LV GCW were associated with an increased probability of presenting with NYHA functional class III or IV HF symptoms.

DISCUSSION

The main findings of the present study can be summarized as follows: in patients with severe AS, the measurement of LV myocardial work

Table 2 Echocardiographic characteristics of the overall population and according to HF symptoms

Variable	Overall (*N* = 120)	NYHA functional class I or II (*n* = 33)	NYHA functional class III or IV (*n* = 87)	*P*
LVEDV, mL/m^2	58 ± 20	54 ± 16	60 ± 22	.119
LVEF, %	55 (44–63)	58 (50–63)	53 (42–62)	.098
LV GLS, %	−13 ± 4	−14 ± 3	−13 ± 4	.023
LV SVi, mL/m^2	37 ± 11	40 ± 11	36 ± 12	.158
LV mass index, g/m^2	126 ± 38	130 ± 32	125 ± 41	.459
LAVi, mL/m^2	45 ± 19	47 ± 19	45 ± 19	.642
Mean E/e′ ratio > 14	93 (81)	22 (71)	71 (86)	.074
MR moderate or greater	21 (18)	5 (16)	16 (18)	.726
AV mean gradient, mm Hg	48 ± 16	52 ± 15	47 ± 16	.107
AVA index, cm^2/m^2	0.40 ± 0.09	0.40 ± 0.10	0.39 ± 0.09	.852
AR moderate or greater	16 (13)	5 (15)	11 (13)	.718
RVOT, mm	30 ± 5	29 ± 5	30 ± 6	.204
TAPSE, mm	18 ± 5	19 ± 5	18 ± 5	.246
RV FW strain	−22 ± 7	−24 ± 5	−21 ± 7	.019
TR moderate or greater	29 (24)	9 (27)	20 (23)	.624
PASP, mm Hg	34 ± 10	32 ± 7	34 ± 11	.216
RAVi, mL/m^2	29 (18 –41)	29 (19–36)	30 (18–41)	.793
Hemodynamic classification of AS				
High-gradient AS	82 (68)	28 (85)	54 (62)	.056
Low-flow, low-gradient AS	29 (24)	4 (12)	25 (29)	
Normal-flow, low-gradient AS	9 (8)	1 (3)	8 (9)	

AR, Aortic regurgitation; *AV*, aortic valve; *AVA*, aortic valve area; *FW*, free wall; *LAVi*, left atrial volume index; *LVEDV*, LV end-diastolic volume; *MR*, mitral regurgitation; *PASP*, pulmonary artery systolic pressure; *RAVi*, right atrial volume index; *RVOT*, RV outflow tract; *SVi*, stroke volume index; *TAPSE*, tricuspid annular plane systolic excursion; *TR*, tricuspid regurgitation.
Data are expressed as mean ± SD, median (interquartile range), or number (percentage).

Table 3 LV myocardial work indices for the overall population and according to HF symptoms

Variable	Overall (*N* = 120)	NYHA functional class I or II (*n* = 33)	NYHA functional class III or IV (*n* = 87)	*P*
Invasive LV SBP, mm Hg	152 (135–175)	161 (148–187)	150 (129–166)	.014
Echocardiography-derived LV SBP, mm Hg	146 (130–173)	161 (134–191)	144 (129–167)	.032
Aortic DBP, mm Hg	51 (42–59)	52 (44–61)	50 (41–58)	.146
GWI, mm Hg%	1,543 ± 645	1,851 ± 723	1,427 ± 576	.001
GCW, mm Hg%	1,889 ± 757	2,177 ± 851	1,776 ± 691	.009
GWW, mm Hg%	167 (102–256)	152 (114–193)	171 (92–268)	.605
GWE, %	90 (85–93)	91 (88–93)	89 (84–93)	.084

DBP, Diastolic blood pressure; *SBP*, systolic blood pressure.
Data are expressed as median (interquartile range) or mean ± SD.

Table 4 Univariate logistic regression to identify the determinants of HF symptoms (NYHA functional class III or IV)

Variable	Univariate analysis	
	OR (95% CI)	*P*
Age	1.015 (0.957–1.076)	.630
Sex, male	0.607 (0.269–1.371)	.229
AF	2.164 (0.679–6.894)	.192
Hb	1.452 (0.970–2.173)	.070
Creatinine	1.000 (0.994–1.007)	.909
Previous MI	0.942 (0.274–3.240)	.924
COPD	0.938 (0.330–2.666)	.904
LVEDV	1.018 (0.995–1.040)	.121
LVEF	0.968 (0.933–1.004)	.084
LV GLS	1.127 (1.001–1.268)	.048
E/e′ > 14	2.420 (0.901–6.499)	.079
RV FW strain	1.081 (1.011–1.156)	.022
PASP	1.026 (0.981–1.074)	.262
LV GWI, per 100 mm Hg% increase	0.902 (0.843–0.964)	.002
LV GCW, per 100 mm Hg% increase	0.931 (0.881–0.983)	.011
LV GWW	1.002 (0.998–1.05)	.343
LV GWE	0.923 (0.853–0.999)	.047

AF, Atrial fibrillation; *COPD*, chronic obstructive pulmonary disease; *FW*, free wall; *Hb*, hemoglobin; *LVEDV*, LV end-diastolic volume; *MI*, myocardial infarction; *OR*, odds ratio; *PASP*, pulmonary artery systolic pressure.

using echocardiography-derived LV systolic pressure and LV GLS is feasible. In the present cohort, in contrast to more commonly used indices of LV myocardial function (such as LVEF and LV GLS), lower values of LV GWI and GCW (indicating incomplete adaptation of the left ventricle to increased afterload) showed an independent association with the presence of NYHA functional class III or IV HF symptoms. Therefore, LV myocardial work indices may provide further insights into LV remodeling and maladaptation in patients with severe AS that could improve risk stratification with echocardiography.

Evaluation of LV Myocardial Function and Remodeling in Patients with Severe AS

According to current guidelines,[4,5] AVR is recommended in patients with severe AS and symptoms or LV systolic dysfunction. The identification of LV maladaptation is pivotal to define the optimal timing of intervention in patients with severe AS. LV decompensation is currently identified on the basis of patient symptoms and/or impairment of LVEF (<50%). These are late markers of LV remodeling in AS and are associated with a dismal prognosis without surgical or transcatheter interventions. Reduction in LVEF is usually secondary to increase in afterload, but in approximately a quarter of patients, this reduction is irreversible even after AVR and is associated with worse long-term outcomes.[6,7,20,21] Recently, several studies have proposed different imaging parameters to assess LV function and identify LV decompensation.[22-24] LV GLS was associated with long-term outcomes independently of AS severity and LVEF.[22] Localized and diffuse LV fibrosis assessed using cardiac magnetic resonance late-gadolinium enhancement, T1 mapping, and extracellular volume assessment has shown a strong relation with prognosis in patients with severe AS.[23-25] Nevertheless, echocardiography remains the main imaging modality to diagnose and grade AS and also to assess LV adaptation to increased afterload.[26] Recently, Russell *et al.*[8,9] developed a method to noninvasively calculate LV myocardial work indices, demonstrating that these parameters correlated well with invasive measures of myocardial work and metabolism evaluated using positron emission tomography. For patients with severe AS, LV myocardial work indices may be particularly useful, as they offer an estimation of LV systolic function that accounts for afterload, providing further insight into LV function and remodeling. The calculation of LV myocardial work indices is based on the construction of LV pressure-strain loops. To derive them, the software relies on LV strain measurements, cardiac event timing derived from aortic and mitral valve opening and closure, and the estimation of LV pressures. However, in severe AS, noninvasively measured systolic blood pressure does not reflect LV pressure, as the stenotic aortic valve poses an obstruction to LV outflow; consequently, LV myocardial work has never been characterized in this disease. In this study, this apparent limitation of the technique was effectively overcome by adding the mean aortic valve pressure gradient estimated with echocardiography to the aortic systolic pressure to derive LV systolic pressure. Although the use of the echocardiography-derived mean aortic valve pressure gradient to estimate LV systolic pressure can be affected by the pressure recovery phenomenon,[17] there was excellent

Table 5 Odds ratios adjusted for RV free wall strain to predict the presence of NYHA functional class III or IV HF symptoms

Variable	Adjusted* OR (95% CI)	*P*	C statistic
LV GLS	1.092 (0.964–1.237)	.168	0.67 (0.57–0.78)
LV GWI, per 100 mm Hg% increase	0.912 (0.849–0.980)	.012	0.69 (0.59–0.79)
LV GCW, per 100 mm Hg% increase	0.941 (0.887–0.998)	.042	0.68 (0.58–0.79)
LV GWE	0.941 (0.870–1.017)	.126	0.68 (0.57–0.79)

OR, Odds ratio.
*For RV free wall strain.

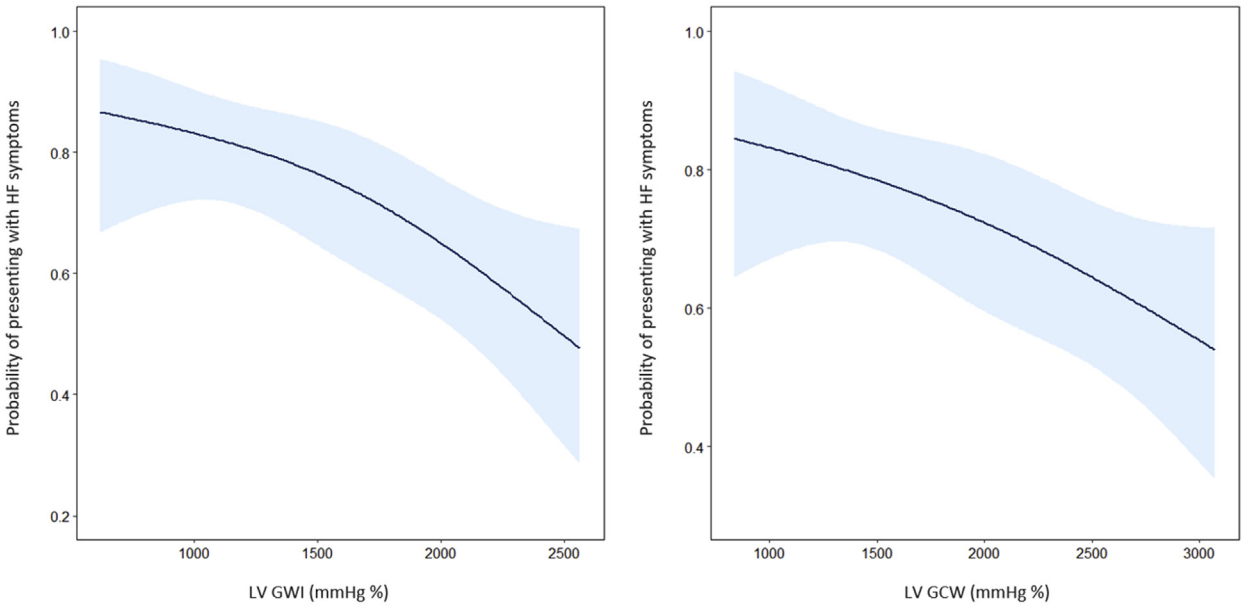

Figure 2 Probability of presenting with NYHA functional class III or IV HF symptoms according to LV GWI and LV GCW. The *blue curves* with overlaid 95% CIs represent the probability of presenting with NYHA functional class III or IV HF symptoms (y axis) according to values of LV GWI and LV GCW (x axes). The curves demonstrate that lower values of LV GWI and GCW (indicating a less efficient adaptation of the left ventricle to the increased afterload) were associated with higher probability of presenting with HF symptoms.

agreement between LV myocardial work indices derived with invasive and echocardiography-based LV systolic pressure, suggesting no clinically important effect.

In our study, we demonstrated for the first time the feasibility of echocardiography-based calculation of LV myocardial work indices in patients with severe AS. LV GCW and GWI, which provide an estimation of LV adaptation to severely increased afterload, demonstrated significantly lower values in patients presenting with NYHA functional class III or IV HF symptoms and low-flow, low-gradient AS. Moreover, after adjusting for potential confounders identified in the univariate logistic regression analysis (i.e., RV free wall strain), in contrast to commonly used echocardiographic parameters of LV systolic function (such as LVEF and LV GLS), LV GCW and GWI were the only two echocardiographic indices of LV function independently associated with NYHA functional class III or IV HF symptoms. This association underscores the importance of LV myocardial work indices that may be of aid in identifying patients who may benefit from AVR with echocardiography.

LV Myocardial Work in Severe AS: Clinical Implications

Conventional indices of LV systolic function (such as LVEF and LV GLS) are based on the evaluation of myocardial shortening and do not take into account LV afterload. The novel indices of LV myocardial work incorporate LV afterload into their calculation and correct the estimation of LV systolic function for afterload, which is of high relevance in patients with severe AS. Figure 3 shows two patients with identical LV GLS values but very different values of LV myocardial work indices due to differences in afterload conditions. Notably, the patient displayed in Figure 3A and B, despite having the same LV GLS, showed higher values of LV GCW and GWI and was less symptomatic at presentation (NYHA functional class II) compared with the second patient, illustrated in Figure 3C and D (NYHA functional class III). This explanatory case and our findings may reflect the importance of correcting for LV afterload when analyzing myocardial function with echocardiography in patients with severe AS. Echocardiographic LV shortening indices (such as LVEF and LV GLS) can be strongly influenced by afterload and appear falsely reduced in the setting of high LV systolic pressure. By incorporating afterload, LV myocardial work indices, specifically LV GCW and GWI, may improve the assessment and follow-up of LV systolic function and the identification of the optimal timing for interventions in patients with severe AS.

Limitations

The limitations of this single-center retrospective study are inherent to the study design. Although most of the echocardiographic examinations were performed close to the procedure, the difference in loading conditions between this assessment and the time when the blood pressure data were recorded may have affected our results. Although we demonstrated that LV myocardial work indices (i.e., LV GWI and GCW) were the only two echocardiographic parameters of LV function independently related to NYHA functional class III or IV HF symptoms, the utility of these novel indices in optimizing the timing for interventions in severe AS would require further investigation as well as their potential role in further risk-stratifying specific hemodynamic categories of severe AS (such as low-flow, low-gradient AS). Finally, the commercial software required for the measurement of LV myocardial work is provided by only a single vendor, thereby limiting its widespread application.

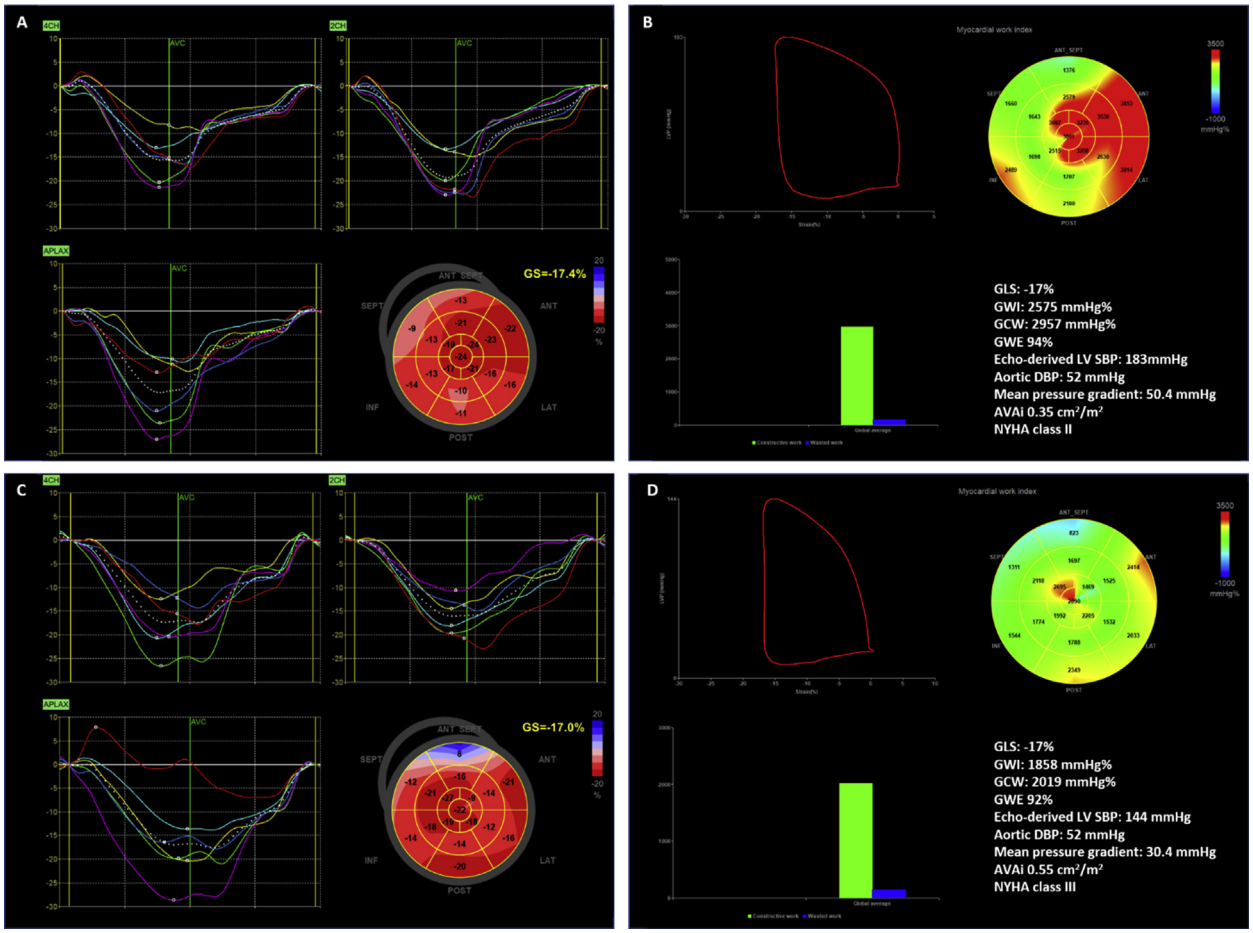

Figure 3 Comparison between two patients with the same LV GLS and different myocardial work indices. **(A,B)** and **(C,D)** display the LV GLS and myocardial work indices (derived from the pressure-strain loops; *red loops*) of two patients with severe AS. Despite presenting with identical LV GLS (**A** vs **C**), the first patient was less symptomatic and presented with higher values of LV GWI and GCW compared with the second patient (**B** vs **D**), indicating a better adaptation of the left ventricle to the increased afterload. *AVAi*, Aortic valve area index; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure.

CONCLUSION

Echocardiography-based calculation of LV myocardial work indices is feasible in severe AS by integrating LV GLS and echocardiography-derived LV afterload. LV GCW and GWI (which give an estimation of LV adaptation to increased afterload) showed an independent association with NYHA functional class III or IV HF symptoms and may provide additional information on myocardial function compared with afterload-dependent echocardiographic parameters of LV systolic function.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2020.10.014.

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