Myocardial work in nonobstructive hypertrophic cardiomyopathy: implications for outcome

Hiemstra, Y.L.; Bijl, P. van der; Mahdiui, M. el; Bax, J.J.; Delgado, V.; Marsan, N.A.

Myocardial Work in Nonobstructive Hypertrophic Cardiomyopathy: Implications for Outcome

Yasmine L. Hiemstra, MD, Pieter van der Bijl, MD, Mohammed el Mahdiui, MD, Jeroen J. Bax, MD, PhD, Victoria Delgado, MD, PhD, and Nina Ajmone Marsan, MD, PhD, *Leiden, the Netherlands*

Background: Noninvasive left ventricular (LV) pressure-strain loop analysis is emerging as a new echocardiographic method to evaluate LV function, integrating longitudinal strain by speckle-tracking analysis and sphygmomanometrically measured blood pressure to estimate myocardial work. The aims of this study were (1) to describe global and segmental myocardial work in patients with hypertrophic cardiomyopathy (HCM), (2) to assess the correlation between myocardial work and other echocardiographic parameters, and (3) to evaluate the association of myocardial work with adverse outcomes.

Methods: One hundred ten patients with nonobstructive HCM (mean age, 55 ± 15 years; 66% men), with different phenotypes (apical, concentric, and septal hypertrophy), and 35 age- and sex-matched healthy control subjects were included. The following myocardial work indices were included: myocardial work index, constructive work (CW), wasted work, and cardiac efficiency. The combined end point included all-cause mortality, heart transplantation, heart failure hospitalization, aborted sudden cardiac death, and appropriate implantable cardioverter-defibrillator therapy.

Results: Mean global CW (1,722 ± 602 vs 2,274 ± 574 mm Hg%, $P < .001$), global cardiac efficiency (93% [89%–95%] vs 96% [96%–97%], $P < .001$), and global MWI (1,534 ± 551 vs 1,929 ± 473 mm Hg%) were significantly reduced, while global wasted work (104 mm Hg% [66–137 mm Hg%] vs 71 mm Hg% [49–92 mm Hg%], $P < .001$) was increased in patients with HCM compared with control subjects. Segmental impairment in CW colocalized with maximal wall thickness (HCM phenotype), and global CW correlated with LV wall thickness ($r = -0.41$, $P < .001$), diastolic function ($r = -0.27$, $P = .001$), and QRS duration ($r = -0.28$, $P = .001$). Patients with global CW > 1,730 mm Hg% (the median value) experienced better event-free survival than those with global CW < 1,730 mm Hg% ($P < .001$).

Conclusions: Myocardial work, assessed noninvasively using echocardiography and blood pressure measurement, is reduced in patients with nonobstructive HCM; it correlates with maximum LV wall thickness and is significantly associated with a worse long-term outcome. (J Am Soc Echocardiogr 2020;33:1201-8.)

Keywords: Hypertrophic cardiomyopathy, Myocardial work, Left ventricular pressure-strain loop, Echocardiography

Hypertrophic cardiomyopathy (HCM) is the most prevalent inherited cardiomyopathy and is characterized by increased myocardial wall thickness, accompanied by myocardial fiber disarray and interstitial fibrosis. These alterations lead to subtle myocardial systolic and diastolic dysfunction that are not always detectable using standard echocardiographic parameters.[1,2] Previous studies have shown that left ventricular (LV) global longitudinal strain (GLS), measured using speckle-tracking echocardiography, is often impaired in patients with HCM, despite normal LV ejection fraction (LVEF), and is significantly correlated with the presence of myocardial fibrosis as assessed using cardiac magnetic resonance imaging.[3] Moreover, impaired LV GLS has been associated with adverse outcomes in patients with HCM, such as all-cause mortality, sudden cardiac death (SCD), heart failure, and ventricular arrhythmias.[4-8] LV GLS, however, remains a load-dependent measure of LV function, which might limit the assessment of LV performance under certain hemodynamic conditions and when performing follow-up evaluations. A noninvasive technique of myocardial work estimation has been introduced as a novel method to evaluate myocardial

From the Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands.

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Reprint requests: Nina Ajmone Marsan, MD, PhD, Department of Cardiology, Leiden University Medical Centre, 2 Albinusdreef, 2333 ZA Leiden, the Netherlands (E-mail: *n.ajmone@lumc.nl*).

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Abbreviations

AUC = Area under the curve

CE = Cardiac efficiency

CW = Constructive work

GLS = Global longitudinal strain

GMWI = Global myocardial work index

HCM = Hypertrophic cardiomyopathy

ICD = Implantable cardioverter-defibrillator

IQR = Interquartile range

LA = Left atrial

LV = Left ventricular

LVEF = Left ventricular ejection fraction

LVH = Left ventricular hypertrophy

PSL = Pressure-strain loop

SCD = Sudden cardiac death

WW = Wasted work

performance. This approach takes into account both LV deformation and afterload by constructing an LV pressure-strain loop (PSL), which integrates noninvasively measured arterial blood pressure and longitudinal strain acquired by echocardiographic speckle-tracking analysis.[9-11] An initial study showed that constructive work (CW) is impaired in patients with HCM and is associated with LV fibrosis as assessed using cardiac magnetic resonance.[12] However, segmental analysis of myocardial work has not been performed in these patients, despite the frequently heterogenous distribution of LV hypertrophy (LVH), and importantly, the potential prognostic value of these novel cardiac work measures is currently unknown. Therefore, the aims of this study were (1) to describe global and segmental indices of myocardial work in patients with HCM compared with healthy individuals, (2) to assess the correlations of myocardial work with other echocardiographic parameters, and (3) to evaluate the association of myocardial work with adverse outcomes.

METHODS

Study Population

Patients with diagnoses of HCM were identified from an ongoing clinical registry. HCM was diagnosed according to current guidelines: maximal LVH ≥ 15 mm (or ≥13 mm in case of affected first-degree relatives), which could not be explained by abnormal loading conditions.[1] Patients with obstructive HCM, defined as an LV outflow tract gradient ≥ 30 mm Hg at rest or during provocation, were excluded. Patients were also excluded when speckle-tracking was not feasible or when noninvasive blood pressure values were not available at the time of the echocardiogram used for the calculation of myocardial work. Clinical data were collected from the departmental cardiology information system (EPD-Vision; Leiden University Medical Center, Leiden, the Netherlands), and the first echocardiogram available was used for analysis. In addition, 35 healthy individuals with structurally normal hearts were selected from the echocardiography database as control subjects and matched for age, sex, and LVEF. The study complied with the Declaration of Helsinki. Because of the retrospective design of this study, the local ethics committee waived the need to obtain individual, written informed consent.

Echocardiography

A commercially available ultrasound machine (Vivid E9; GE Vingmed Ultrasound, Horten, Norway) was used to perform standard two-dimensional transthoracic echocardiography. Images were digitally stored and analyzed offline using proprietary software (EchoPAC 202; GE Vingmed Ultrasound). LV dimensions, LV septal thickness, LV posterior wall thickness, and left atrial (LA) diameter were measured from the parasternal long-axis view. Maximum LV wall thickness was assessed from short-axis views at different levels from base to apex to ascertain the different patterns of LVH. Septal HCM was diagnosed in the presence of asymmetric LVH, isolated to the septal and/or anteroseptal segments of the left ventricle, while apical HCM was defined when LVH was limited to the apical segments of the left ventricle. Concentric HCM was defined as symmetric LVH in all LV segments. LV volumes, LVEF, and LA volume were measured using the Simpson method and indexed to body surface area.[13] LV diastolic function was assessed using Doppler mitral inflow peak E-wave velocity, divided by the peak early diastolic velocity (E′) of the lateral mitral annulus, expressed as the E/E′ ratio.[14] The grade of mitral regurgitation was assessed using a multiparametric approach, according to current recommendations.[15] LV outflow tract peak gradient at rest was quantified using continuous-wave Doppler. Peak systolic pulmonary artery pressure was estimated by adding the peak velocity of the tricuspid regurgitation jet on continuous-wave Doppler to the right atrial pressure (estimated by the diameter and percentage inspiratory collapse of the inferior vena cava).[16]

Myocardial Work

LV myocardial work was calculated by integrating longitudinal strain and sphygmomanometrically measured blood pressure, as previously described by Russell *et al.*[10] LV longitudinal strain was measured using speckle-tracking analysis in the standard two-, three-, and four-chamber apical views. The region of interest was automatically created and manually adjusted when necessary. LV GLS was then calculated by averaging the peak longitudinal strain in 17 segments from the three apical views. The peak systolic LV pressure was assumed to be equal to the peak arterial systolic pressure, on the basis of the brachial cuff blood pressure measurements. A noninvasive LV pressure-strain curve was then constructed using proprietary software (EchoPAC 202) and adjusted according to the duration of the ejection and isovolumetric phases, which were defined by the opening and closure of the mitral and aortic valves.

During the LV ejection period, defined as the period between mitral valve closure and mitral valve opening, the total work within the area of the LV PSL represented the global myocardial work index (GMWI), the myocardial work performed during segmental shortening represented CW, and myocardial work performed during segmental elongation represented wasted work (WW). During isovolumetric relaxation, this definition was reversed, such that myocardial work during shortening was considered WW and myocardial work during lengthening was considered CW. CW and WW were calculated for each LV segment, according to the 17-segment model, and global CW and WW were calculated as the averages of the segmental values. Cardiac efficiency (CE) was then expressed as CW/(CW + WW) × 100% per segment and the global CE as an average of all segmental values (Figure 1). To evaluate segmental differences, the mid and basal segments were combined, as well as the apical segments, resulting in seven segments: septal, anteroseptal, inferior, lateral, posterior, anterior, and apical.

Clinical Outcomes

The end point of this study was a combined end point of all-cause mortality, heart transplantation, heart failure hospitalizations, aborted

HIGHLIGHTS

- Myocardial work parameters are impaired in patients with HCM.
- CW is associated with adverse events in patients with HCM.
- Segmental differences of CW were observed among HCM phenotypes.

SCD, and appropriate implantable cardioverter-defibrillator (ICD) therapy. Aborted SCD was defined as a successful resuscitation from cardiac arrest with documented ventricular arrhythmias, while appropriate ICD therapy was defined as shock or antitachycardia pacing for ventricular arrhythmias. The occurrence of events during follow-up was obtained from survival status in municipal civil registries, review of medical charts, and liaison with general practitioners.

Statistical Analysis

Continuous variables are presented as mean ± SD when normally distributed or as median (interquartile range [IQR]) when not normally distributed. Categorical variables are presented as absolute numbers and percentages. Differences in clinical and echocardiographic characteristics between patients with HCM and control subjects were compared using Student's *t* test, the Mann-Whitney *U* test, or the χ^2 test, as appropriate. Receiver operating characteristic curves were constructed to determine which myocardial work parameter had the highest area under the curve (AUC) to predict outcome. A Kaplan-Meier curve was then constructed to estimate the cumulative survival free of the end point and compared using the log-rank test between patients with CW above the median (>1,730 mm Hg) and those with CW below the median (<1,730 mm Hg). Correlations of CW with other clinical and echocardiographic parameters were assessed using Pearson's method and Spearman's method for continuous normally distributed and ordinal and continuous non-normally distributed parameters, respectively. Segmental differences among the various HCM phenotypes were analyzed using analysis of variance and the Kruskal-Wallis test. Intraclass correlation coefficients were calculated for interobserver and intraobserver agreement in 10 randomly selected patients to evaluate reproducibility. Statistical analysis was performed using SPSS version 23 (IBM, Armonk, NY). *P* values < .05 were considered to indicate statistical significance.

RESULTS

Study Population

The study population consisted of 145 individuals: 110 patients diagnosed with HCM (mean age, 55 ± 15 years; 66% men) and 35 healthy control subjects (mean age, 52 ± 16 years; 51% men). Clinical characteristics of both groups are presented in Table 1. By definition, no differences were observed between the two groups regarding age and sex. Compared with control subjects, patients with HCM showed slightly higher systolic blood pressure values and longer QRS durations. Previous atrial fibrillation was reported in 19 patients with HCM (17%); 22 patients (20%) had heart failure symptoms (New York Heart Association functional class ≥ II), and 21 patients (19%) had received ICDs.

Standard Echocardiographic Characteristics

In Table 2, echocardiographic characteristics are compared between patients with HCM and healthy control subjects. Patients with HCM had thicker interventricular septa and posterior walls, as well as greater maximum LV wall thickness (19 ± 5 vs 9 ± 2 mm, *P* < .001). Regarding different patterns of LVH, the majority expressed a septal phenotype (66%), followed by concentric HCM (24%), and apical HCM was observed in 10% of patients. LV dimensions were smaller in patients with HCM compared with control subjects, whereas LA dimensions and volumes were higher in patients with HCM compared with control subjects. No differences were observed between patients with HCM and control subjects regarding LVEF, although LV volumes were slightly lower in patients with HCM and LV diastolic function was more often impaired. LV GLS was significantly impaired in patients with HCM compared with control subjects (−14 ± 5% vs −19 ± 2%, *P* < .001). Furthermore, mitral regurgitation grade ≥ 2 was observed in 17 of the patients with HCM(16%), and the LV outflow tract gradient was within the normal range (as per inclusion criteria).

Myocardial Work: Global Indices

Global myocardial work indices are summarized in Figure 2. Patients with HCM showed significantly lower values of GMWI (1,534 ± 551 vs 1,929 ± 473 mm Hg%, *P* < .001) and global LV CW compared with control subjects (1,722 ± 602 vs 2,274 ± 574 mm Hg%, *P* < .001) as well as higher values of global LV WW (104 mm Hg% [IQR: 66–137 mm Hg%] vs 71 mm Hg% [IQR: 49–92 mm Hg%], *P* < .001). This resulted in lower global LV CE, with a median of

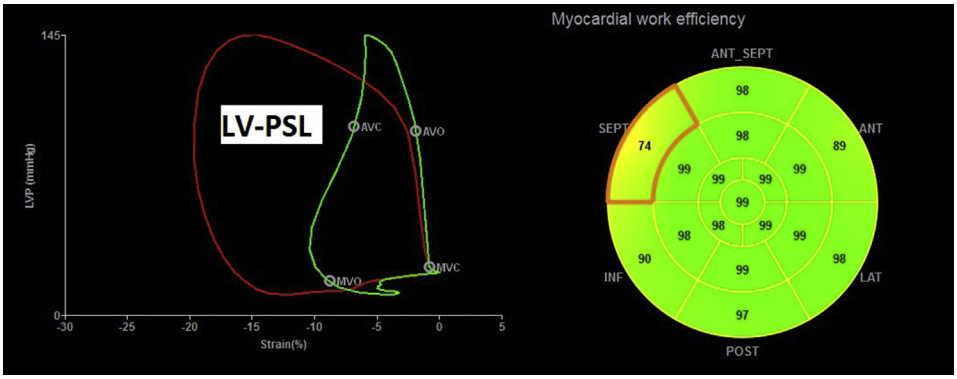

Figure 1 Examples of a LV PSL and CE. The *red curve* represents a normal LV PSL, while the *green curve* reflects the deviating PSL of a septal segment in a patient with HCM. The bull's-eye plot on the *right* shows significantly decreased CE in the septal segment. *ANT*, Anterior; *ANT_SEPT*, antero-septal; *INF*, inferior; *LAT*, lateral; *POST*, posterior; *SEPT*, septal.

Table 1 Clinical and ECG characteristics of patients with HCM and control subjects

	Control subjects (n = 35)	Patients with HCM (n = 110)	P
Clinical characteristics			
Age, year	52 ± 16	55 ± 15	.450
Sex, male	18 (51)	73 (66)	.159
Systolic BP, mm Hg	126 ± 18	135 ± 19	.016
Diastolic BP, mm Hg	77 ± 9	80 ± 12	.124
(Previous) atrial fibrillation	0 (0)	19 (17)	.007
NYHA functional class			.002
I	35 (100)	88 (80)	
II	0 (0)	19 (17)	
III/IV	0 (0)	3 (3)	
ICD	0 (0)	21 (19)	.002
ECG characteristics			
Heart rate, beats/min	66 ± 11	66 ± 11	.964
QRS duration, msec	94 ± 10	109 ± 25	.001
LBBB/RBBB	0 (0)	14 (13)	.022
Ventricular pacing	0 (0)	11 (10)	.066

BP, Blood pressure; *ECG*, electrocardiographic; *LBBB*, left bundle branch block; *NYHA*, New York Heart Association; *RBBB*, right bundle branch block.
Data are expressed as mean ± SD or number (percentage).

Table 2 Echocardiographic characteristics of patients with HCM and control subjects

Echocardiographic parameters	Control subjects (n = 35)	Patients with HCM (n = 110)	P
IVS, mm	8 ± 2	18 ± 4	<.001
PW, mm	9 ± 1	12 ± 2	<.001
Maximal LVH, mm	9 ± 2	19 ± 5	<.001
HCM phenotype			NA
Septal	—	73 (66)	
Concentric	—	26 (24)	
Apical	—	11 (10)	
LVESV, mL	45 ± 14	39 ± 15	.032
LVEDV, mL	116 ± 31	103 ± 29	.039
LVEF, %	61 ± 6	63 ± 10	.331
LV GLS, %	−19 ± 2	−14 ± 5	<.001
LA diameter, mm	34 ± 4	40 ± 6	<.001
LAVI, mL/m^2	22 ± 6	36 ± 13	<.001
E/E′ ratio	8 (6 to 9)	10 (7 to 14)	<.001
Resting LVOT gradient, mm Hg	5 (3 to 5)	7 (5 to 11)	<.001
MR grade ≥ 2	0 (0)	17 (16)	.013
sPAP, mm Hg	22 (18 to 26)	25 (21 to 31)	.003

IVS, Interventricular septum; *LAVI*, LA volume index; *LVEDV*, LV end-diastolic volume; *LVESV*, LV end-systolic volume; *LVOT*, LV outflow tract; *MR*, mitral regurgitation; *NA*, not applicable; *PW*, posterior wall; *sPAP*, systolic pulmonary artery pressure.
Data are expressed as mean ± SD, number (percentage), or median (interquartile range).

93% (IQR: 89%–95%) for patients with HCM compared with 96% (IQR: 96%–97%) for control subjects ($P < .001$).

Correlations of Global CW with Other Parameters. Global CW showed significant correlations with LA volume index ($r = -0.37$, $P < .001$), maximum LV wall thickness ($r = -0.41$, $P < .001$), LV diastolic function ($r = -0.27$, $P = .001$), and QRS duration ($r = -0.28$, $P = .001$). Global CW showed also a high correlation with LV GLS ($r = 0.85$, $P < .001$). However, global CW was not significantly related to LV volumes (LV end-diastolic volume, $r = 0.034$, $P = .681$; LV end-systolic volume, $r = -0.11$, $P = .187$).

Association of Global CW with Outcomes. During median follow-up period of 5.4 years (IQR: 3.0–7.8 years), 24 patients (22%) reached the combined end point: one patient underwent heart transplantation, one patient experienced aborted SCD, 10 patients had appropriate ICD therapy, one patient was admitted for heart failure, and 11 patients died. The cause of death was cardiac in four patients, noncardiac in three patients, and unknown in the remaining four patients. To assess which of the global myocardial work parameters had the strongest association with the end point, receiver operating characteristic curves were constructed. LV GLS showed an AUC of 0.74 (95% CI: 0.63–0.85; $P < .001$), and GMWI also showed a good association with the end point, with an AUC of 0.77 (95% CI: 0.66–0.87; $P < .001$). However, global LV CW had the largest AUC of 0.78 (95% CI: 0.68–0.88; $P < .001$), while global LV WW showed no significant association with the end point, with an AUC of 0.53 (95% CI: 0.39–0.68; $P = .61$), and global CE showed a borderline association with the end point, with an AUC of 0.63 (95% CI: 0.48–0.77; $P = .06$). Subsequently, survival analysis was performed using global LV CW. When using the median value of the study population, patients with more impaired global LV CW (<1,730 mm Hg%) had a significantly worse survival free of the end point compared with patients with more preserved global LV CW (>1,730 mm Hg%; log-rank 13.2, $P < .001$), as shown in Figure 3.

Intra- and Interobserver Variability of Myocardial Work Parameters. The intraclass correlation coefficients for repeated measurements by the same observer (intraobserver agreement) were excellent for GLS (0.98; 95% CI: 0.92–0.99; $P < .001$), GMWI (0.97; 95% CI: 0.92–0.97; $P < .001$), and global CW (0.99; 95% CI: 0.96–0.99; $P < .001$) and good for global WW (0.82; 95% CI: 0.27–0.96; $P = .009$) and global CE (0.86; 95% CI: 0.43–0.97; $P = .004$). The intraclass correlation coefficients for measurements between two different observers (interobserver agreement) were also excellent for GLS (0.97; 95% CI: 0.88–0.99; $P < .001$), GMWI (0.96; 95% CI: 0.89–0.97; $P < .001$), and global CW (0.97; 95% CI: 0.89–0.99; $P < .001$) and good for global WW (0.76; 95% CI: 0.05–0.94; $P = .022$) and global CE (0.91; 95% CI: 0.65–0.98; $P = .001$).

Myocardial Work: Segmental Analysis

Segmental values of myocardial work parameters are presented in Table 3 and compared between patients with HCM and healthy control subjects. In LV all segments, CW was lower in patients with HCM compared with control subjects. Interestingly, differences in WW

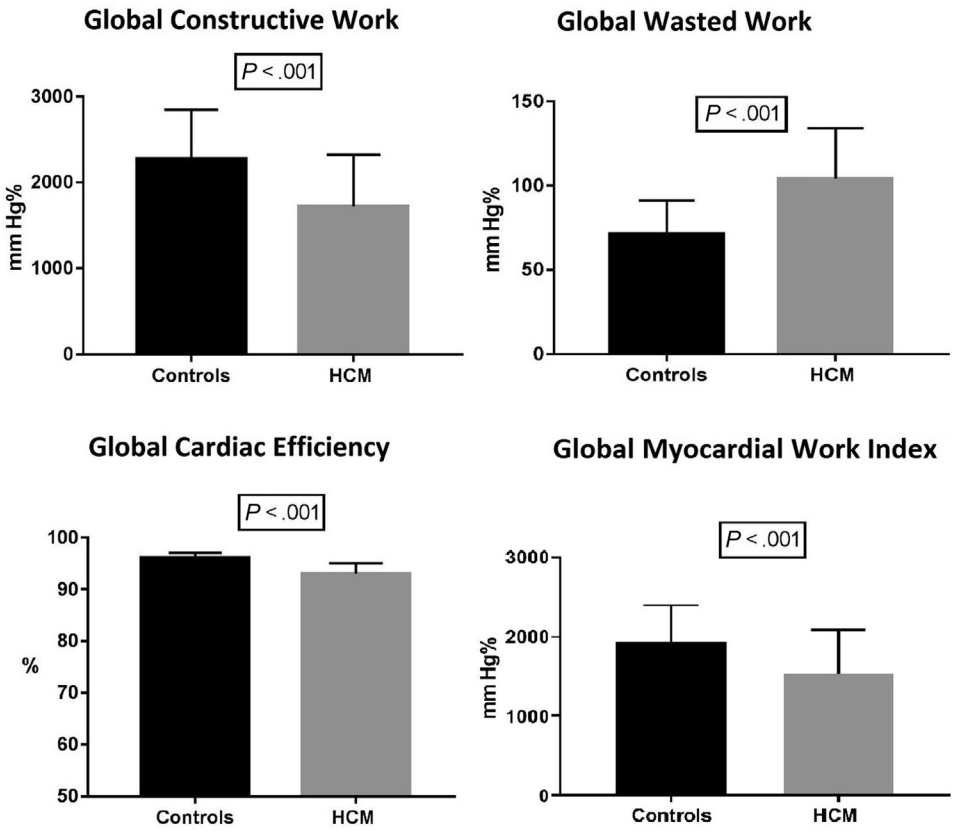

Figure 2 Myocardial work parameters in control subjects and patients with HCM.

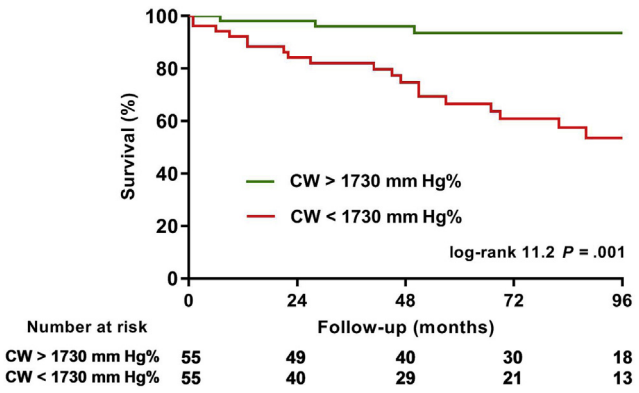

Figure 3 Kaplan-Meier survival curves depicting time to cumulative, event-free survival (all-cause mortality, heart failure hospitalization, aborted SCD, and appropriate ICD therapy) in patients with HCM. Data are shown according to LV CW > 1,730 mm Hg % and CW < 1,730 mm Hg% (the median value).

were less evident. Only in the apical and anterior segments was WW higher in patients with HCM compared with control subjects, while in the other segments, no differences in WW were observed between the two groups. Segmental CE was significantly lower for patients with HCM in the apical, anteroseptal, posterior, lateral, and anterior segments compared with control subjects. Regarding the septal segments, CE was not significantly different between patients with HCM (94%; IQR: 90%–98%) and control subjects (95%; IQR: 93%–97%; $P = .388$).

Figure 4 shows segmental CW for the different HCM phenotypes. In patients with apical HCM, CW of the apical segments (1,123 ± 747 mm Hg%) was significantly lower compared with patients with septal HCM (2,255 ± 860 mm Hg%) and concentric HCM (1,946 ± 920 mm Hg%; $P < .001$). Similarly, septal CW was lower in patients with septal HCM (1,385 ± 579 mm Hg%) and concentric HCM (1,126 ± 479 mm Hg%) compared with patients with apical HCM (1,693 ± 860 mm Hg%; $P = .025$). In patients with concentric HCM, all segments (except for the apical segments) tended to have lower values of CW, although this difference was statistically significant only for the inferior segments (1,408 ± 584 mm Hg% for concentric HCM vs 1,691 ± 636 mm Hg% for septal HCM and 1,980 ± 905 mm Hg% for apical HCM; $P = .040$).

DISCUSSION

The main findings of the present study can be summarized as follows: (1) patients with HCM showed impaired values of global LV myocardial work parameters—GMWI, CW, WW, and CE—compared with healthy individuals; (2) global LV CW showed correlations with maximum LV wall thickness, diastolic function, and QRS duration and was significantly associated with adverse outcomes; and (3) segmental differences of CW were observed among different HCM phenotypes.

Myocardial Work in HCM

HCM is characterized by LVH, myocardial fiber disarray, and interstitial fibrosis, which can all significantly affect LV diastolic and systolic

Table 3 Segmental analysis of myocardial work parameters in patients with HCM compared with control subjects

	CW (mm Hg%)		WW (mm Hg%)		CE (%)	
LV segment	Control subjects	Patients with HCM	Control subjects	Patients with HCM	Control subjects	Patients with HCM
Apical	2,670 ± 792	2,068 ± 922*	43 (24–77)	102 (54–188)*	98 (96–99)	94 (90–97)*
Septal	1,813 ± 472	1,354 ± 606*	77 (50–103)	60 (22–119)	95 (93–97)	94 (90–98)
Anteroseptal	2,107 ± 575	1,521 ± 613*	56 (30–103)	73 (32–148)	97(94–98)	94 (86–98)*
Inferior	2,050 ± 500	1,652 ± 669*	70 (35–133)	61 (21–139)	96 (93–98)	96 (90–98)
Posterior	2,246 ± 729	1,676 ± 758*	88 (40–207)	111 (49–223)	94 (92–98)	93 (85–96)*
Lateral	2,160 ± 559	1,625 ± 666*	55 (27–102)	80 (31–151)	97 (95–98)	95 (89–98)*
Anterior	2,077 ± 684	1,466 ± 733*	35 (21–72)	76 (29–134)*	98 (96–98)	94 (85–98)*

Data are expressed as mean ± SD or median (interquartile range).
*$P < .05$.

function, without an overt impairment of LVEF.[17] Consequently, several echocardiographic measurements have been proposed to better assess LV function in patients with HCM. Over the past few years, LV GLS, as derived from speckle-tracking analysis, has emerged as a promising measure of LV function in patients with HCM and has shown a good correlation with histologically proven myocardial fibrosis.[18] Moreover, several studies have demonstrated the prognostic value of LV GLS for predicting adverse outcomes in patients with HCM.[3-8] However, LV GLS remains load dependent, which might represent a limitation in case of changes in the hemodynamic conditions.[19] Myocardial work has been introduced as a new parameter of LV function that takes into account LV deformation as well as LV afterload by constructing an LV PSL on the basis of noninvasive LV pressure (sphygmomanometric blood pressure) measurements. Russell *et al.*[10] validated this method against invasive LV pressure measurements, and LV PSL area demonstrated a robust correlation with myocardial metabolism when assessed on positron emission tomography.

Several studies have already applied myocardial work measurements to various cardiac conditions.[12,20-25] A study by Chan *et al.*[24] evaluated GMWI in patients with different loading conditions (i.e., with hypertension or ischemic and nonischemic cardiomyopathies). In this study, patients with hypertension showed higher GMWI compared with control subjects, whereas global CE was preserved because of a proportional increase in global CW and global WW. In a study by van der Bijl *et al.*,[23] the prognostic value of global CE in patients referred for cardiac resynchronization therapy was evaluated. Lower values of global CE were associated with better outcome after cardiac resynchronization therapy, likely reflecting the potential correction of LV dyssynchrony and recruitment of contractile reserve obtained with cardiac resynchronization therapy in these patients. Only a single study evaluated myocardial work in patients with HCM: Galli *et al.*[12] showed that global CW was reduced in 82 patients with HCM compared with control subjects (1,599 ± 423 vs 2,248 ± 249 mm Hg%, $P < .001$), while global WW was similar between patients with HCM and control subjects (141 ± 125 vs 101 ± 88 mm Hg%, $P = .18$). The present study revealed similar values of global CW, which were significantly reduced in patients with HCM compared with control subjects. The values of global WW in patients with HCM observed in the present study were also similar to those reported by Galli *et al.*, but we measured lower values of global WW in control subjects, accentuating the difference of global WW between patients with HCM and control subjects. Galli *et al.* demonstrated that global CW < 1,623 mm Hg% was predictive of myocardial fibrosis on cardiac magnetic resonance, which might also explain the correlation of CW with diastolic dysfunction and LV thickness observed in the present study. In addition, a correlation between global CW and QRS duration was found, probably reflecting the influence of (mild) LV dyssynchrony on myocardial work parameters. However, the association of myocardial work with clinical outcomes has never been evaluated in patients with HCM, and the present results demonstrate a significant association of global CW with clinical outcomes.

Moreover, in the present study we evaluated segmental differences of myocardial work in patients with HCM. CW was impaired in all myocardial segments compared with healthy individuals. Interestingly, WW was significantly impaired only in the apical and anterior segments, whereas it was comparable with WW in control subjects in the remaining segments. Because WW is affected mostly by dyssynchrony,[9] and the prevalence of left or right bundle branch block was low in the present population (13%), relatively preserved values of WW were observed, in line with the findings of Galli *et al.*[12] Similarly, CE (defined as CW/[CW + WW]) showed only mildly impaired values in most myocardial segments. Thus, CW was the most impaired myocardial work parameter in patients with HCM, on both global and segmental levels. Moreover, differences in CW were also observed in different HCM phenotypes: patients with apical HCM had the most impaired CW in the apical segments, whereas in patients with septal and concentric HCM, CW was preserved in the apical segments but impaired in the other segments. Segmental CW might therefore also be helpful to identify the specific HCM phenotype.

Clinical Implications

The introduction of myocardial work parameters in the routine assessment of patients with HCM might improve our understanding of cardiac performance in these patients, at both global and segmental levels, overcoming the load dependency of other echocardiographic parameters by incorporating afterload. This is particularly relevant in patients with HCM, as afterload might change with medication use or geometric changes and increase of wall thickness over time. This would provide clinicians a more sophisticated tool to refine follow-up of LV function in these patients, when blood pressure might vary between visits, and to assess the potential effect of different therapies. Furthermore, it might also represent a new risk stratification tool to assess prognosis in patients with HCM. Global CW might help especially in identifying "low-risk" patients, as a cumulative event-

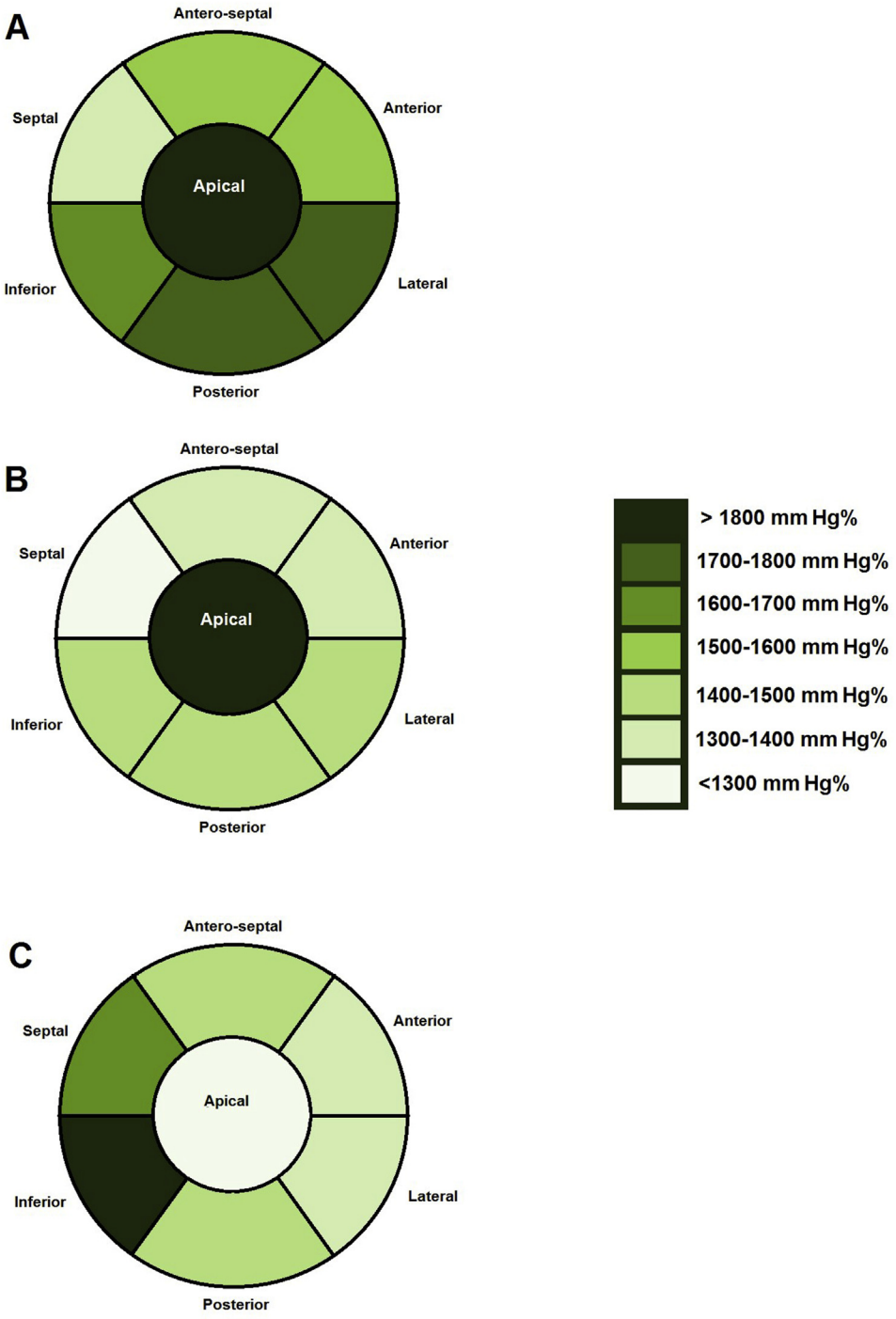

Figure 4 Segmental analysis of LV CW for different HCM phenotypes: **(A)** septal HCM, **(B)** concentric HCM, and **(C)** apical HCM.

free survival rate of 97% after 5 years was observed for patients with global CW > 1,730 mm Hg%, whereas event-free survival was only 64% after 5 years in patients with global CW < 1730 mm Hg%.

Limitations

Several limitations of the present study should be mentioned. Some patients were excluded because blood pressure measurements were not available at the same time as echocardiography; a few patients were excluded when speckle-tracking analysis failed. Therefore we cannot exclude that this issue introduced bias in the assessment. Furthermore, patients with obstructive HCM were excluded, because the estimated LV PSL on the basis of noninvasively measured blood pressure does not reflect accurately LV pressure in these patients.[10] Further prospective research is required to confirm our results and to establish the clinical utility of myocardial work parameters in patients with HCM.

CONCLUSION

Myocardial work, assessed noninvasively using echocardiography and blood pressure measurement, is impaired in patients with HCM. Global LV CW is correlated with maximum LV wall thickness, diastolic function, and QRS duration and is significantly associated with adverse outcomes. Characteristic segmental patterns of CW can be depicted for different HCM phenotypes.

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