ORIGINAL RESEARCH

Microvascular Dysfunction Is Associated With Impaired Myocardial Work in Obstructive and Nonobstructive Hypertrophic Cardiomyopathy: A Multimodality Study

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BACKGROUND: Two-dimensional speckle tracking echocardiography has been shown to correlate with microvascular dysfunction, a hallmark of hypertrophic cardiomyopathy (HCM). We hypothesized that there is an association between myocardial work and left ventricular ischemia, with incremental value to global longitudinal strain, in patients with HCM.

METHODS AND RESULTS: We performed a prospective assessment of patients with HCM, undergoing 2-dimensional speckle tracking echocardiography and stress perfusion cardiac magnetic resonance. Results were stratified according to obstructive or nonobstructive HCM and the presence of significant replacement fibrosis (late gadolinium enhancement ≥15% of left ventricular mass). Seventy-five patients with HCM (63% men, age 55±15 years) were evaluated, 28% with obstructive HCM (mean gradient 89±60 mm Hg). Perfusion defects were found in 90.7%, involving 22.5±16.9% of left ventricular mass, and 38.7% had late gadolinium enhancement ≥15%. In a multivariable analysis, a lower global work index ($r=-0.519$, β-estimate −10.822; $P=0.001$), lower global work efficiency ($r=-0.379$, β-estimate −0.123; $P=0.041$), and impaired global constructive work ($r=-0.532$, β-estimate −13.788; $P<0.001$) significantly correlated with ischemia. A segmental analysis supported these findings, albeit with lower correlation coefficients. A global work index cutoff ≤1755 mm Hg% was associated with hypoperfusion with a sensitivity of 88% and a specificity of 71%, while the best cutoff for global longitudinal strain (>−15.5%) had a sensitivity of 64% and a specificity of 57%. The association between myocardial work and perfusion defects was significant independently of late gadolinium enhancement ≥15% and obstructive HCM.

CONCLUSIONS: Impaired myocardial work was significantly correlated with the extent of ischemia in cardiac magnetic resonance, independently of the degree of left ventricular hypertrophy or fibrosis, with a higher predictive power than global longitudinal strain.

Key Words: coronary microvascular dysfunction ■ hypertrophic cardiomyopathy ■ myocardial deformation ■ myocardial work ■ strain imaging

Hypertrophic cardiomyopathy (HCM)[1] is defined by unexplained left ventricular (LV) wall thickening. In addition to ventricular hypertrophy, other pathophysiological features include diastolic dysfunction, abnormalities in the mitral valve apparatus, and the development of myocardial fibrosis.[2–5] Coronary

CLINICAL PERSPECTIVE

What Is New?

- In hypertrophic cardiomyopathy, impaired myocardial work parameters, including lower global work index, global work efficiency, and global constructive work, were significantly correlated with the presence and extent of myocardial ischemia in a cardiac magnetic resonance perfusion assessment, regardless of the degree of left ventricular hypertrophy or fibrosis.
- A global work index cutoff value of ≤1755 mm Hg% showed a higher predictive power than global longitudinal strain for the presence of myocardial ischemia, regardless of the pattern of hypertrophy.

What Are the Clinical Implications?

- Myocardial work allows for an accurate evaluation of myocardial deformation independently of the afterload, and these findings suggest that myocardial work analysis may have an incremental value over a standard longitudinal strain analysis and can potentially have a role in clinical practice as a marker of ischemia.

Nonstandard abbreviations and acronyms

CMD	coronary microvascular dysfunction
GCW	global constructive work
GLS	global longitudinal strain
GWE	global work efficiency
GWI	global work index
GWW	global wasted work
HCM	hypertrophic cardiomyopathy
LGE	late gadolinium enhancement
MW	myocardial work
NORRE	Normal Reference Ranges for Echocardiography
TTE	transthoracic echocardiogram

microvascular dysfunction (CMD) has also been identified as a prevalent feature playing an important pathophysiological role in HCM, associated with replacement fibrosis, heart failure, and ventricular arrhythmias.[6,7]

Two-dimensional speckle-tracking echocardiography provides a more accurate assessment of the cardiac performance and earlier detection of LV dysfunction when compared with LV ejection fraction[8] and has shown a correlation with the extent of fibrosis by cardiac magnetic resonance (CMR), with a possible role in risk stratification in HCM.[9] However, speckle-tracking echocardiography parameters have several pitfalls, namely, the need for geometrical assumptions; apical foreshortening; measurement variability among operators; and, particularly, load dependency.[10]

Myocardial work (MW) is a novel noninvasive technique that encompasses the evaluation of LV deformation and afterload, incorporating the arterial blood pressure and longitudinal strain acquired by speckle-tracking echocardiography analysis. As MW accounts for dynamic pressures, it allows an enhanced assessment of systolic dysfunction, even in patients with significant changes in afterload, a hallmark of the patients with obstructive HCM.[11] While MW parameters have been associated with the extent of myocardial fibrosis in HCM,[12,13] it is unclear if myocardial ischemia may be linked with MW independently of the scar burden.

A new era of HCM treatment has started with the licensing and introduction of sarcomere modulators for obstructive HCM,[14] and ongoing trials are testing its effect in nonobstructive HCM with promising early results.[15] In this context, the validation of novel and more sensitive imaging biomarkers of systolic function can be relevant, for both trial design and clinical monitoring in the "real-world" context.

In this prospective multimodality imaging study, we hypothesized that there is an association between impaired MW, evaluated by echocardiography, and LV ischemia detected by CMR in patients with HCM. Our analysis was stratified according to the presence of nonobstructive or obstructive HCM and according to the burden of replacement fibrosis, measured by late gadolinium enhancement (LGE) in CMR. A segmental analysis was also performed; due to the intraindividual heterogeneity characteristic of HCM, we hypothesized that by comparing individual LV segments, additional associations could potentially be revealed.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. This prospective study enrolled consecutive adult patients with HCM with follow-up in the dedicated cardiomyopathy units of Santa Marta Hospital (n=63) (Lisbon, Portugal) and Garcia de Orta Hospital (n=12) (Almada, Portugal), from January 2019 to May 2020 and following the principles outlined in the Declaration of Helsinki. The institutional ethics committees approved the study protocol. All patients provided written informed consent. The echocardiographic studies were performed at the Santa Marta Hospital (Lisbon, Portugal), and the CMR studies were performed at the Heart Center, Hospital da Cruz Vermelha Portuguesa (Lisbon, Portugal). Medication was unchanged in the

period between CMR and echo studies, which were performed with a median time interval of 54 (interquartile range, 74) days.

The diagnosis of HCM was established according to current guidelines.[1] The inclusion and exclusion criteria were the same as previously described by Aguiar Rosa et al.[16] Namely, epicardial coronary artery disease was excluded with invasive coronary angiography in symptomatic patients. Asymptomatic patients aged >40 years underwent coronary computerized tomography. In asymptomatic younger patients without cardiovascular risk factors, a low likelihood of obstructive coronary artery disease was assumed.

Transthoracic Echocardiogram

All subjects underwent the same comprehensive transthoracic echocardiogram (TTE) protocol as previously described.[13] Valvular timings obtained from TTE and the instantaneous systolic pressure value were used to estimate a normalized, patient-specific LV pressure curve. In patients with obstructive HCM, the gradient without Valsalva maneuver was added to the systolic blood pressure. MW was then used to evaluate the work during shortening in systole plus negative work during lengthening in isovolumetric relaxation (global constructive work [GCW]), the negative work during lengthening in systole plus the work performed during shortening in isovolumetric relaxation (global wasted work [GWW]), global work efficiency (GWE=GCW/[GCW+GWW]×100%), and the amount of work performed by the LV during systole (area under the pressure-strain curve) (global work index [GWI]).[17]

CMR Protocol and Analysis

All subjects underwent the same stress CMR protocol and analysis, as previously described by Aguiar Rosa et al.[16] Please see Data S1 for the detailed CMR protocol.

For perfusion assessment, the myocardium was divided into 32 subsegments (16 American Heart Association segments subdivided into an endocardial and epicardial layer). Ischemic burden for each patient was calculated as the number of involved subsegments, assigning 3% of myocardium to each subsegment. Each segment was analyzed for the presence or absence of perfusion defects by a single operator, thus avoiding interobserver variability. Artifacts were assessed by using motion correction in the perfusion sequence, and perfusion defects were required to persist for ≥3 beats throughout the stress perfusion sequence. Perfusion defects sparing the subendocardium and coincident with LGE were not considered, as subendocardial involvement is mandatory for microvascular dysfunction defects. The LGE extent was quantitatively assessed on a per-segment basis using

a signal threshold versus reference myocardium of ≥6 standard deviations. Extensive fibrosis was defined by the involvement of ≥15% of total LV mass.[5] CMR data was evaluated by 1 reader, who was blinded to the echocardiographic results.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 23.0 for Windows (IBM, Armonk, NY). Point estimates and 95% CIs are described for all mean estimates.

Descriptive statistics are presented as absolute frequency (number) and relative frequency (percentage) for categorical variables and as the mean or median for continuous variables. Normal distribution of continuous variables was verified by the Kolmogorov–Smirnov test. Correlations between continuous variables were assessed using Spearman's correlation. For the assessment of differences between 2 groups for continuous variables, Student's t test (for normally distributed variables) and the Mann–Whitney U test (for nonnormally distributed variables) were used. For the comparison among 3 groups for continuous variables, the independent-samples Kruskal–Wallis test was used.

MW parameters were explored by a receiver operating characteristic curve to determine the optimal cutoff values for predicting perfusion defects. The best cutoff value was defined as the point combining the highest sum of sensitivity and specificity. The Hanley and McNeil test was used to assess the significance of the difference between the areas under the curves (AUCs) from 2 receiver operating characteristic curves derived from independent samples.

Univariable linear regression analyses were performed to assess the correlation between MW parameters, perfusion defects, and the burden of LGE (percentage of total LV mass). Subsequently, multivariable analyses, adjusted for potential confounders, were performed. Variables with a significant correlation in the univariate analysis (linear regression with a P value <0.05) were included in the multivariable analyses. Results were stratified according to the presence of obstructive or nonobstructive HCM and according to the presence of extensive fibrosis. A segment-by-segment analysis was performed to assess the correlation among MW, ischemia, and fibrosis, calculated with univariable and multivariable linear regressions.

Statistical differences with a P value <0.05 were considered significant.

RESULTS

A total of 75 patients were enrolled. The baseline characteristics of the patients are presented in Table 1. Mean age was 55±15 years, with 47 (63%) male patients

Table 1. Baseline Characteristics of the Study Population

Characteristics	All (n=75)	With perfusion defects (n=68)	Without perfusion defects (n=7)	P value
Age, y, mean±SD	55±15	54±15	56±12	0.718
Male sex, n (%)	47 (63)	41 (60)	6 (86)	0.186
NYHA class ≥II, n (%)	34 (45)	31 (46)	3 (43)	0.890
Body mass index, kg/m², mean±SD	29±5	29±5	28±5	0.805
Body mass index >25 kg/m², n (%)	59 (79)	55 (81)	4 (57)	0.162
Hypertension, n (%)	38 (51)	36 (53)	2 (29)	0.262
Diabetes, n (%)	12 (16)	12 (18)	0 (0)	0.589
Obstructive HCM, n (%)	21 (28)	20 (29)	1 (14)	0.396
HCM risk-SCD score, %, mean±SD	3±2	3±2	2±1	0.123
Beta-blockers, n (%)	54 (72)	50 (74)	4 (57)	0.392
CCB, n (%)	18 (24)	18 (27)	0 (0)	0.186
LVEDD by TTE, mm, mean±SD	50±5	50±5	54±4	0.033
MWT by TTE, mm, mean±SD	20±4	21±4	16±1	<0.001
LVEF by TTE, %, mean±SD	68±7	68±7	68±6	0.950
GLS by TTE, %, mean±SD	−14±4	−14±4	−16±2	0.013
LVEDV by CMR, mL, mean±SD	120±33	119±34	131±20	0.208
LV mass index by CMR, g/m², mean±SD	97±30	98±31	84±14	0.048
LVEF by CMR, %, mean±SD	72±8	72±9	71±5	0.726
Segments with perfusion defects, n, mean±SD	6±4	6±4	…	…
Perfusion defects, % of LV mass, mean±SD	23±17	23±17	…	…
Number of segments with LGE, n, mean±SD	9±5	9±4	4±3	0.002
LGE, % of LV mass, mean±SD	13±9	14±9	5±5	0.002
GWI, mm Hg%, median (IQR)	1282 (992–1621)	1228 (967–1517)	1768 (1396–1985)	0.012
GCW, mm Hg%, median (IQR)	1500 (1213–1763)	1446 (1195–1745)	2036 (1567–2158)	0.012
GWW, mm Hg%, median (IQR)	146 (88–220)	150 (91–223)	101 (28–193)	0.167
GWE, %, median (IQR)	87 (81–93)	86 (81–93)	95 (91–98)	0.005

CCB indicates calcium channel blocker; CMR, cardiac magnetic resonance; GCW, global constructive work; GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index; GWW, global wasted work; HCM, hypertrophic cardiomyopathy; IQR, interquartile range; LGE, late gadolinium enhancement; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MWT, maximal wall thickness; NYHA, New York Heart Association; SCD, sudden cardiac death; and TTE, transthoracic echocardiogram.

and a mean LV ejection fraction by TTE of 68%±7%. A pattern of asymmetrical septal hypertrophy was present in 46 (61%) patients, while 22 (29%) had apical hypertrophy and 7 (9%) had concentric hypertrophy. The maximal LV wall thickness was 20.4±4.2 mm. LV outflow tract obstruction was present in 21 (28%) patients (mean maximal LV outflow tract gradient of 89±60 mm Hg). A significant proportion of patients were symptomatic, as shown by a New York Heart Association class ≥II in 34 (45%) patients.

TTE and CMR were performed on all 75 patients. A total of 1200 segments were analyzed in the segmental analysis. Stress perfusion images were interpretable in all patients. LGE images were not interpretable in 1 patient due to artifact. Perfusion defects were found in 68 (90.7%) patients, in a mean 5.7±3.9 segments. The mean burden of ischemia was 22.5%±16.9% of LV mass. Only 4 (5%) patients had no LGE. The mean LGE was 12.7%±8.6% of the LV mass, with 29 (39%) patients having at least 15% of LGE (of total LV mass) and a mean 8.7±4.6 segments with fibrosis.

According to the reference values from the European Association of Cardiovascular Imaging NORRE (Normal Reference Ranges for Echocardiography) study,[18] values lower than the normal range of GWI, GWE, and GCW were found in 36 (48%), 45 (60%), and 44 (56%) patients, respectively (Table 2). Increased values of GWW were found in 14 (20%) patients. Five (7%) patients had GCW values higher than the mean reference (2232 mm Hg%).

Table 2. Myocardial Work Parameters in HCM—Percentage of Patients Below the Reference Values (According to the EACVI NORRE Study[18]), Stratified According to Sex and Pattern of Hypertrophy

Myocardial work	Reference values*	Patients with impaired myocardial work parameters		
		Male (n=47)	Female (n=28)	All (n=75)
GWI, n (%)	Male >1270 mm Hg% Female >1310 mm Hg%	24 (51)	12 (43)	36 (48)
GCW, n (%)	Male >1650 mm Hg% Female >1544 mm Hg%	32 (68)	12 (43)	44 (56)
GWW, n (%)	Male <238 mm Hg% Female <239 mm Hg%	7 (15)	7 (25)	14 (20)
GWE, n (%)	Male >90% Female >91%	28 (60)	17 (61)	45 (60)
Myocardial work	Reference values*	Septal (n=46)	Apical (n=22)	Concentric (n=7)
GWI, n (%)	Male >1270 mm Hg% Female >1310 mm Hg%	21 (46)	9 (41)	6 (86)
GCW, n (%)	Male >1650 mm Hg% Female >1544 mm Hg%	29 (63)	8 (36)	7 (100)
GWW, n (%)	Male <238 mm Hg% Female <239 mm Hg%	8 (17)	3 (14)	3 (43)
GWE, n (%)	Male >90% Female >91%	28 (61)	11 (50)	6 (86)

EACVI indicates European Association of Cardiovascular Imaging; GCW, global constructive work; GWE, global work efficiency; GWI, global work index; GWW, global wasted work; HCM, hypertrophic cardiomyopathy; and NORRE, Normal Reference Ranges for Echocardiography.

*As published by Manganaro et al.[18]

The pattern of hypertrophy was also related to the MW parameters. The majority of patients with concentric hypertrophy presented with significantly impaired MW, with values lower than the normal range of GWI, GWE, and GCW found in 86%, 86%, and 100%, respectively, and higher values of GWW found in 43% (Table 2). A concentric pattern of hypertrophy was associated with lower GWI (P=0.029) and lower GCW (P=0.006; Table 3). An example of the GWI and GWE values obtained in patients with asymmetric septal, apical, or concentric HCM and respective LV pressure-strain loops are presented in Figure 1.

Patients with apical HCM showed a slightly lower GWI in apical segments (1354±9389 mm Hg% versus 1446±645 mm Hg%, with no statistical significance [P=0.317]) and a significantly lower GWE in apical segments (84%±16% versus 92%±9%, P<0.001) compared with nonapical segments.

There were no significant sex differences in MW parameters. Patients with LGE ≥15% of total LV mass presented with significantly lower GWI (1147 [862–1363] mm Hg% versus 1381 [1139–1744]; P=0.010) and lower GCW (1374 [1108–1450] versus 1656 [1406–1926]; P=0.002) compared with patients with LGE <15%. While patients with obstructive HCM showed slightly lower values of GWI, GCW, and GWE, there was no significant statistical difference in MW parameters compared with patients with nonobstructive HCM (Table 3).

The results of univariable regression analysis for individual MW parameters associated with perfusion defects are presented in Table S1. Subsequently, a multivariable regression analysis, adjusted for potential confounders, was performed (Table 4).

In a multivariable analysis (Table 4), lower values of GWI significantly correlated with a higher burden of ischemia (r=−0.519, β-estimate −10.822; P=0.001). Likewise, impaired values of GCW were linked to a higher percentage of hypoperfusion (r −0.532, β-estimate −13.788; P<0.001). Moreover, lower values of GWE correlated with an increased number of segments with perfusion defects (r −0.477, β-estimate −0.794; P=0.002) and with a higher burden of ischemia (r −0.379, β-estimate −0.123, P=0.041). In this multivariable model adjusted for potential confounders, these associations were independent of the maximal wall thickness, of the LV mass index, of the pattern of hypertrophy, and of the burden of LGE. In a univariable analysis, the presence of a higher GWW was associated with a higher number of segments with perfusion defects (r 0.280, β-estimate 5.463; P=0.014). These associations are presented in Figure 2.

Receiver operating characteristic curve analysis (Figure S1) revealed that a GWI cutoff value of ≤1755 mm Hg% was associated with the presence of perfusion defects with a sensitivity of 88% and a specificity of 71% (AUC, 0.806; P=0.008), while the best cutoff for GLS (>−15.5%) had only a sensitivity of 64% and a specificity of 57% and did not reach statistical significance (AUC, 0.705; P=0.076). The positive predictive value of GWI ≤1755 mm Hg% was 97%, and the negative predictive value was 38%. GWI AUC values did not differ significantly between a pattern of asymmetrical septal or apical hypertrophy (AUC 0.785 versus 0.895; P=0.521).

Table 3. Myocardial Work Parameters in HCM Stratified According to Pattern of LV Hypertrophy, Sex, LVOT Obstruction, and Severe Fibrosis (LGE ≥15%)

Myocardial work parameters				
	Septal (n=46)	Apical (n=22)	Concentric (n=7)	
	Median (IQR)	Median (IQR)	Median (IQR)	P value
GWI, mmHg%	1306 (1036–1583)	1493 (1064–1703)	1025 (624–1228)	0.029
GCW, mmHg%	1498 (1232–1743)	1738 (1260–1945)	1180 (773–1397)	0.006
GWW, mmHg%	143 (88–212)	154 (71–218)	173 (137–343)	0.738
GWE, %	87 (83–93)	88 (81–95)	81 (75–87)	0.116
	Male (n=47)	Female (n=28)		
	Median (IQR)	Median (IQR)		P value
GWI, mmHg%	1228 (1025–1493)	1357 (885–1677)	…	0.734
GCW, mmHg%	1441 (1203–1740)	1638 (1330–1884)	…	0.333
GWW, mmHg%	143 (89–207)	181 (76–250)	…	0.145
GWE, %	87 (83–93)	87 (76–94)	…	0.622
	Obstructive HCM (n=21)	Nonobstructive HCM (n=54)		
	Median (IQR)	Median (IQR)		P value
GWI, mmHg%	1190 (871–1500)	1339 (1076–1659)	…	0.168
GCW, mmHg%	1443 (1170–1716)	1548 (1241–1814)	…	0.375
GWW, mmHg%	156 (120–227)	145 (82–220)	…	0.580
GWE, %	84 (81–90)	88 (84–94)	…	0.104
	LGE≥15% (n=29)	LGE<15% (n=45)		
	Median (IQR)	Median (IQR)		P value
GWI, mmHg%	1147 (862–1363)	1381 (1139–1744)	…	0.010
GCW, mmHg%	1374 (1108–1450)	1656 (1406–1926)	…	0.002
GWW, mmHg%	154 (98–229)	146 (79–219)	…	0.566
GWE, %	86 (79–92)	88 (84–94)	…	0.107

GCW indicates global constructive work; GWE, global work efficiency; GWI, global work index; GWW, global wasted work; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular; and LVOT, left ventricular outflow tract.

Regarding the presence of LV outflow tract obstruction, impaired MW values did not show a significant difference in the correlation with perfusion defects in patients with obstructive HCM compared with patients with nonobstructive HCM (GWI: r −0.518 versus −0.506, P=0.953; GWE: r=−0.591 versus r=−0.317, P=0.201; Table S2 and Figure S2).

Likewise, in patients with significant fibrosis (LGE ≥15% of LV mass), there was no significant difference in the correlation of impaired MW and perfusion defects compared with patients with milder LV fibrosis (LGE <15%; GWI: r=−0.489 versus r=−0.393, P=0.632; GCW: r −0.455 versus r −0.359, P=0.643; Table S3 and Figure S3).

In a segment-by-segment multivariable analysis (Table 5) (univariable analysis presented in Table S4), we found that lower values of GWI (r=−0.294, β-estimate −194.979; P<0.001) and lower values of GWE were linked to a higher burden of ischemia (r −0.242, β-estimate −3.653; P=0.002). As in the global myocardial analysis, these associations were also independent of the wall thickness or the presence of LGE in each segment. Furthermore, the correlation between perfusion defects and segmental GWI (r=−0.294; P<0.001) was superior to that of segmental longitudinal strain (r=−0.076; P=0.014). The distribution and prevalence of perfusion defects and MW parameters in each of 16 American Heart Association segments are displayed in Figure 3.

There was a significant correlation between the presence of LGE and impaired GWI (r=−0.227, β-estimate −193.692; P<0.001) and impaired GWE (r=−0.133, β-estimate −2.477; P=0.019). Lower values of GWI (β-estimate −124.170; P=0.009) and GWE (β-estimate −2.737; P=0.014) were correlated with obstructive HCM (Table 5).

DISCUSSION

In a cohort of patients with HCM, our results revealed an association between CMD and worse LV performance
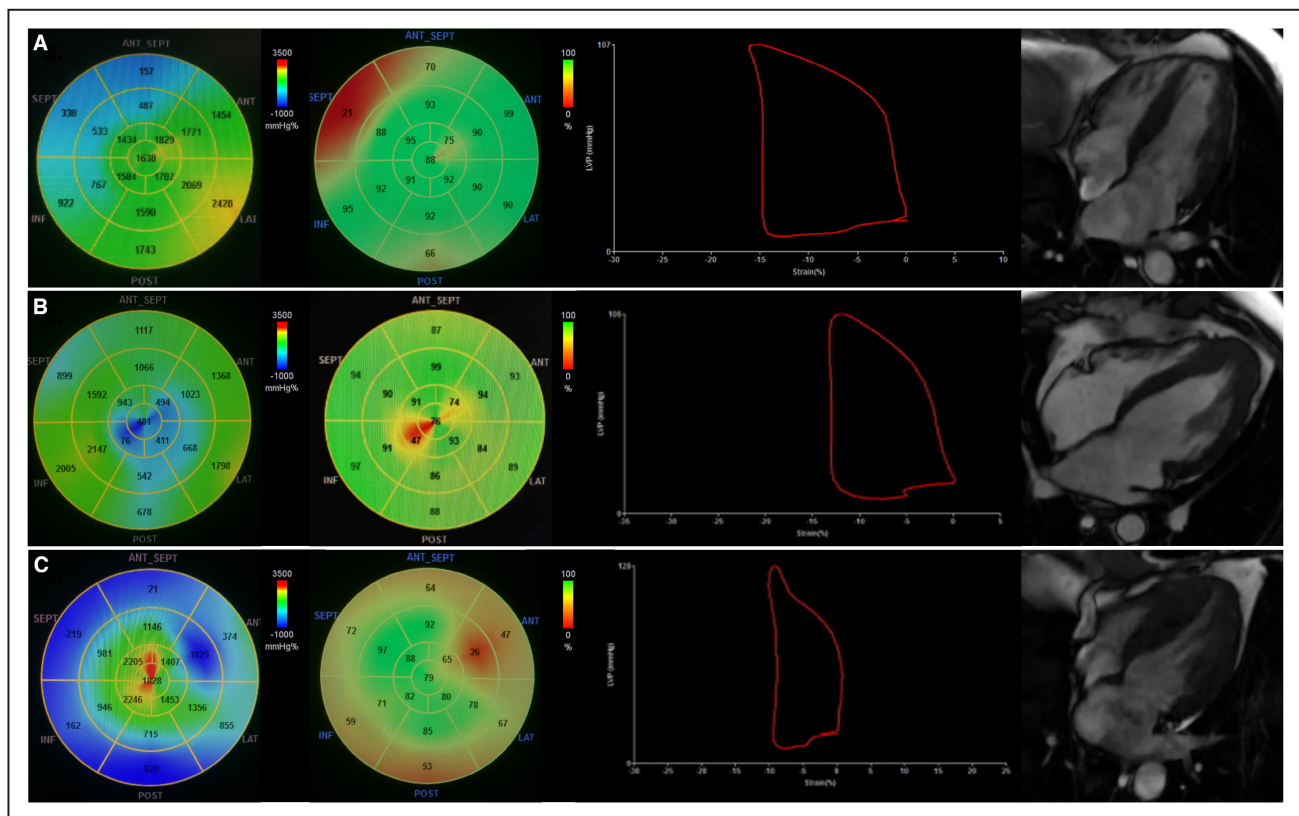
Figure 1. Myocardial work parameters according to different patterns of hypertrophy in hypertrophic cardiomyopathy (HCM).
From left to right: global work index (GWI), global work efficiency (GWE), pressure-strain loop, cardiac magnetic resonance 4-chamber view. **A**, Asymmetric septal HCM. **B**, Apical HCM. **C**, concentric HCM.

assessed by MW parameters, including a lower GWI, GWE, and GCW.

MW parameters have proven prognostic value in several conditions, including cardiac amyloidosis,[19] acute coronary syndromes,[20] reverse remodeling with sacubitril-valsartan,[21] LV dyssynchrony before cardiac resynchronization therapy,[22] and in cardio-oncology patients.[23]

In patients with nonobstructive HCM, impaired MW indices were previously shown to correlate with maximal LV wall thickness, diastolic dysfunction and associated with worse long-term outcomes,[24] with a proposed cutoff of GCW <1730 mm Hg%. In our cohort of patients with HCM, the majority (n=50, 67%) presented with a GCW under this cutoff value.

There are scarce published data regarding patients with obstructive HCM, in which the assessment of MW requires adding the LV outflow tract gradient (without Valsalva maneuver) to the systolic blood pressure.[13] As the estimation of the LV outflow tract gradient may introduce further interoperator variability, this fact poses an added difficulty in the evaluation of MW. In addition, HCM is characterized

by intraindividual phenotypic heterogeneity of different LV segments.[25]

In our study, MW parameters were significantly reduced in patients with HCM, in comparison with the published reference values,[18] with around half the patients presenting impaired GWI and GWE values and 60% impaired GWE values. As expected, patients without perfusion defects had lower LV mass, less burden of fibrosis, and lower GLS (reflecting higher deformation). In this study, we show that these patients are also characterized by higher values of GWI, GCW, and GWE—indicating higher LV deformation. No differences were noted regarding LV ejection fraction (either measured by TTE or CMR) in patients with ischemia compared with patients with no perfusion defects, which might be in keeping with the limitations of LV ejection fraction on the evaluation of LV performance in HCM.[26]

While the role of MW, particularly GCW, as a tool for assessing LV fibrosis has been previously documented,[12,13] this is the first study, to the best of our knowledge, to uncover the association between MW parameters and the extent of myocardial ischemia.

Table 4. Multivariable Linear Regression Analysis of LV Myocardial Work Parameters

	Correlation coefficient (r)	P value	β-estimate	95% CI	P value
Global work index					
No. segments ischemia, n	−0.532	<0.001	−45.781	−70.612 to −20.950	<0.001
Ischemia burden, % of LV mass	−0.519	<0.001	−10.822	−16.772 to −4.872	0.001
MWT	−0.471	<0.001	−26.773	−48.837 to −4.710	0.018
LV mass index	−0.558	<0.001	−5.759	−10.210 to −1.308	0.012
Concentric hypertrophy	−0.257	0.028	−251.743	−597.081 to 93.595	0.150
No. segments LGE, n	−0.331	0.005	−26.334	−47.904 to −4.764	0.017
LGE, % of LV mass	−0.285	0.015	−13.862	−25.073 to −2.651	0.016
Diabetes	−0.246	0.036	−198.763	−438.733 to 41.208	0.103
Global constructive work					
No. segments ischemia, n	−0.519	<0.001	−46.770	−70.956 to −22.584	<0.001
Ischemia burden, % of LV mass	−0.532	<0.001	−10.342	−15.911 to −4.772	<0.001
MWT	−0.504	<0.001	−32.568	−56.703 to −8.433	0.009
LV mass index	−0.616	<0.001	−6.970	−10.222 to −3.718	<0.001
Concentric hypertrophy	−0.321	0.006	−413.459	−740.48 to −86.435	0.014
No. segments LGE, n	−0.404	<0.001	−39.237	−60.077 to −18.397	<0.001
LGE, % of LV mass	−0.372	0.001	−17.466	−28.408 to −6.525	0.002
Global wasted work					
No. segments ischemia, n	0.280	0.017	3.845	−3.347 to 11.037	0.219
Diabetes	0.231	0.051	61.728	−17.309 to 140.765	0.124
Hypertension	0.239	0.043	55.402	−1.315 to 112.119	0.055
Global work efficiency					
No. segments ischemia, n	−0.477	<0.001	−0.794	−1.288 to −0.300	0.002
Ischemia burden, % of LV mass	−0.379	0.001	−0.123	−0.241 to −0.005	0.041
MWT	−0.361	0.002	−0.387	−0.865 to 0.092	0.111
LV mass index	−0.459	<0.001	−0.093	−0.160 to −0.027	0.007
No. segments LGE, n	−0.263	0.026	−0.327	−0.727 to 0.073	0.107
Diabetes	−0.323	0.006	−7.909	−12.845 to −2.972	0.002

LGE indicates late gadolinium enhancement; LV, left ventricular; and MWT, maximal wall thickness.

Importantly, this association was independent of the degree of LV hypertrophy, the pattern of hypertrophy, and the burden of replacement fibrosis.

Microvascular dysfunction is a cardinal feature of HCM, playing a transversal role through its pathophysiology, including tissue characteristics and clinical manifestations, as we have previously described.[16,25,27] Furthermore, coronary microvascular rarefaction and defects in arteriolar control of coronary flow have been described in patients with HCM, contributing to impaired capillary supply and coronary reserve.[28,29] An increased burden of ischemia has been linked to LV hypertrophy, higher values of native T1 mapping and more extensive replacement fibrosis and diffuse tissue abnormalities.[16,25] Increased severity of ischemia was associated with higher incidence of atrial fibrillation, worse functional capacity, and worse outcomes,

including progressive heart failure.[16,27] Diabetes was associated with CMD in our cohort, which is in keeping with published evidence showing that CMD is prevalent in patients with type 2 diabetes and a strong independent predictor of cardiovascular mortality in this population.[30,31]

Among the assessed MW parameters, GWI and GCW showed the highest correlation with CMD, and a GWI cutoff of ≤1755 mm Hg% had a high accuracy to predict ischemia in HCM. This finding is in line with previously published data, as impaired MW has been shown to be correlated with worse outcomes and extent of fibrosis.[13,24] While lower GWE significantly correlated with CMD, the association was weaker. Nevertheless, impaired GWE was the individual MW parameter observed in a higher percentage of patients in our cohort (n=45; 60%), underscoring the impairment
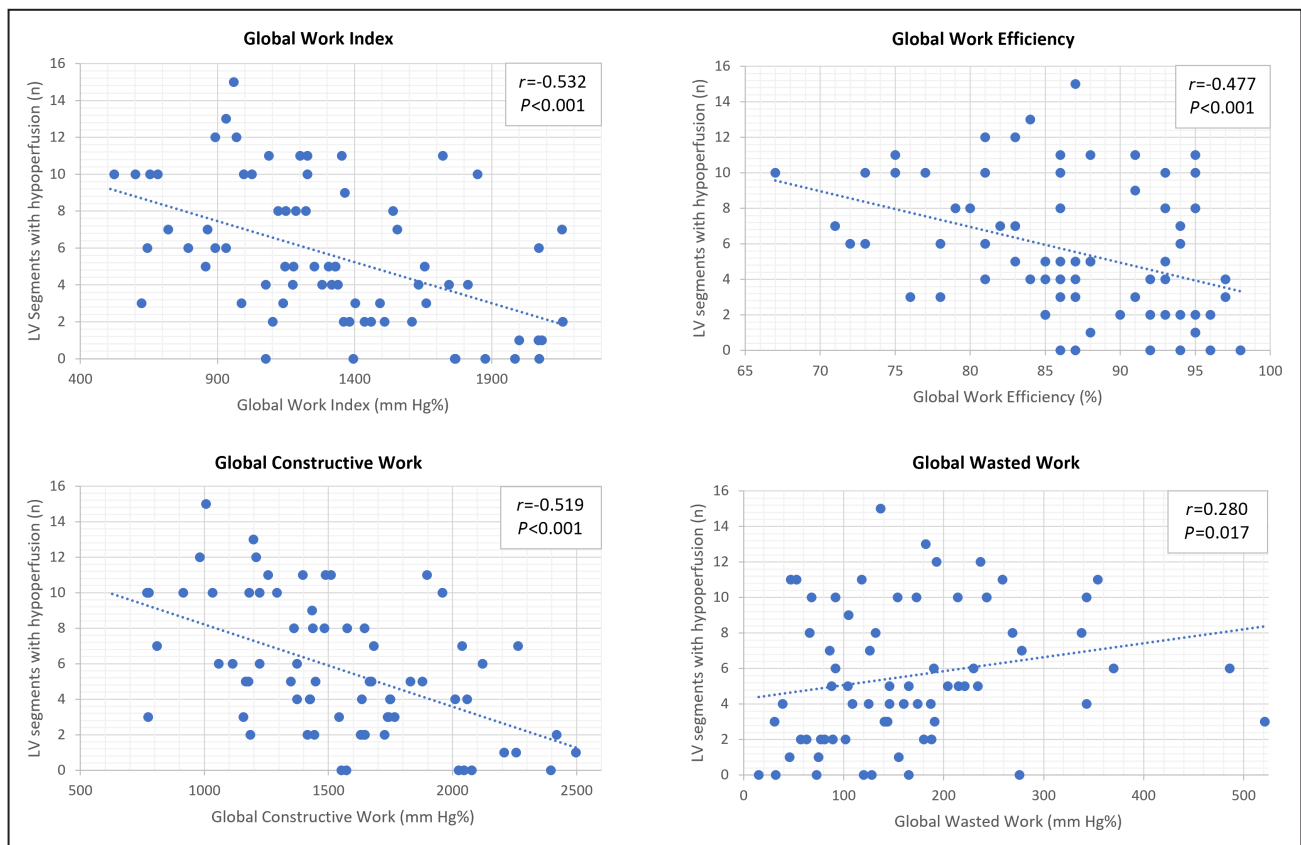
Figure 2. Correlation between myocardial work parameters and perfusion defects.
LV indicates left ventricular.

in LV systolic performance in HCM despite the characteristic hypercontractility. Although an increased GWW (compared with reference values) was present in 20% of enrolled patients with HCM, GWW revealed only a minor relationship with ischemia.

MW allows for an accurate evaluation of myocardial deformation independently of the afterload by assessing contractility, taking into account noninvasive blood pressure measurements, unlike the assessment of GLS.[11] Therefore, a possible advantage of the use of MW indices compared with GLS is the reduction of overdiagnosis of LV subclinical dysfunction of patients with HCM and arterial hypertension or other causes of increased afterload. In our cohort, a GWI cutoff value of ≤1755 mm Hg% showed a higher predictive power than GLS for the presence of perfusion defects, and the latter did not reach statistical significance. This finding suggests that MW analysis may have an incremental value over a standard longitudinal strain analysis and can potentially have a role in clinical practice as a marker of ischemia. Furthermore, the predictive value of MW was similar regardless of the pattern of hypertrophy.

The independent association of MW parameters and ischemia was also shown in a segmental analysis,

although with an inferior correlation compared with the global LV assessment, which may be explained by the inherent intraindividual phenotypic heterogeneity of LV segments in HCM. However, while there was no association of MW parameters and obstructive HCM in a global LV assessment, by performing a segment-by-segment evaluation, we uncovered an independent correlation between impaired GWI and GWE and obstructive HCM.

In the evaluation of scar, we found that MW indices were correlated with the severity of LV fibrosis. Patients with LGE ≥15% of LV mass presented with significantly impaired GWI and GCW comparing to patients with milder fibrosis (LGE <15%). The relationship between MW and the extent of myocardial fibrosis is currently not well established, with 1 retrospective study including 82 patients with nonobstructive HCM showing that GCW was significantly reduced and associated with the extent of qualitative assessment of LGE, albeit without quantification of the percentage of LGE.[12] Further studies have reproduced this correlation, with a GCW cutoff of ≤1550 mm Hg% being proposed as potentially useful in clinical practice to detect significant LV fibrosis.[13] In our current study, there was no significant difference between the correlation of MW

Table 5. Segmental Multivariable Linear Regression Analysis of LV Myocardial Work Parameters

	Correlation coefficient (r)	P value	β-estimate	95% CI	P value
Global work index					
Perfusion defect	−0.294	<0.001	−194.979	−289.115 to −100.843	<0.001
LGE	−0.227	<0.001	−193.692	−2828.445 to −104.938	<0.001
Wall thickness ≥15 mm	−0.422	<0.001	−37.429	−47.019 to −27.838	<0.001
Wall thickness 12–14 mm	−0.289	<0.001	−73.126	−94.332 to −51.930	<0.001
Obstructive HCM	…	…	−124.170	−217.892 to −30.449	0.009
Diabetes	…	…	−162.011	−281.331 to −42.691	0.008
Global work efficiency					
Perfusion defect	−0.242	<0.001	−3.653	−5.913 to −1.393	0.002
LGE	−0.133	<0.001	−2.477	−4.538 to −0.416	0.019
Wall thickness ≥15 mm	−0.233	<0.001	−0.274	−0.505 to −0.043	0.020
Wall thickness 12–14 mm	−0.174	<0.001	−0.754	−1.214 to −0.294	0.001
Obstructive HCM	…	…	−2.737	−4.912 to −0.563	0.014
Diabetes	…	…	−5.055	−7.670 to −2.440	<0.001

HCM indicates hypertrophic cardiomyopathy; LGE: late gadolinium enhancement; and LV, left ventricular.

and CMD in patients with significant fibrosis versus patients with milder fibrosis.

In the subgroup of patients with concentric HCM, a higher proportion showed significantly impaired MW parameters, in comparison with patients with asymmetric septal or apical HCM, maybe reflecting the widespread tissue abnormalities in patients with concentric HCM versus the predominantly focal hypertrophy in other hypertrophy patterns.

As novel pathophysiology-directed medications are introduced and given the observed association with other imaging parameters of clinical relevance and the sensitive measurement of contractility it provides, future studies should test the usefulness of myocardial work as an early imaging biomarker for the assessment of the effect of sarcomere modulators.

Future validation of the MW parameters' prognostic capabilities regarding clinical manifestations, arrhythmic events, risk stratification, and long-term outcomes is crucial to evaluate its clinical utility.

Limitations

Our study has some limitations that should be acknowledged. One is the relatively small population. The MW indices were performed in resting conditions, while ischemia was evaluated during stress CMR. This is in line with most studies on MW, which assess indices in resting conditions, and currently there are no robust data to support its use with vasodilator stress. Additionally, CMR and echocardiography studies were conducted with a median time interval of 54 (interquartile range, 74) days, and although therapy was unchanged in the

period between studies, this might have led to minor differences in blood pressure or heart rate measurements. Perfusion defects, a surrogate for myocardial ischemia, were evaluated through a semiquantitative visual analysis of ischemia in 32 segments, as used in previous studies comparing stress CMR with invasive evaluation of fractional flow reserve.[32] While the adopted method is readily available and easily applicable, it relies on visual assessment and the total of LV assessed is 96% (3% for each segment). Significant replacement fibrosis was defined as LGE ≥15% of LV mass (as proposed by Chan et al[5]), but there is currently no universal consensus on the percentage of LGE that defines significant. Six (8%) enrolled patients were in atrial fibrillation, which may contribute to further heterogeneity in MW indices assessment.

In our cohort, there was a significantly high burden of perfusion defects and replacement fibrosis. While consecutive patients were enrolled, this may be partly due to selection bias. Thus, the findings in our study may not be applicable to a general HCM population. As knowledge on MW continues to expand, the MW indices reference values are still not entirely defined.

CONCLUSIONS

In HCM, impaired MW parameters, including lower GWI, GWE, and GCW, were significantly correlated with the presence and extent of myocardial ischemia in a CMR perfusion assessment, regardless of the degree of LV hypertrophy or fibrosis, and GWI showed a higher predictive power than GLS, regardless of the
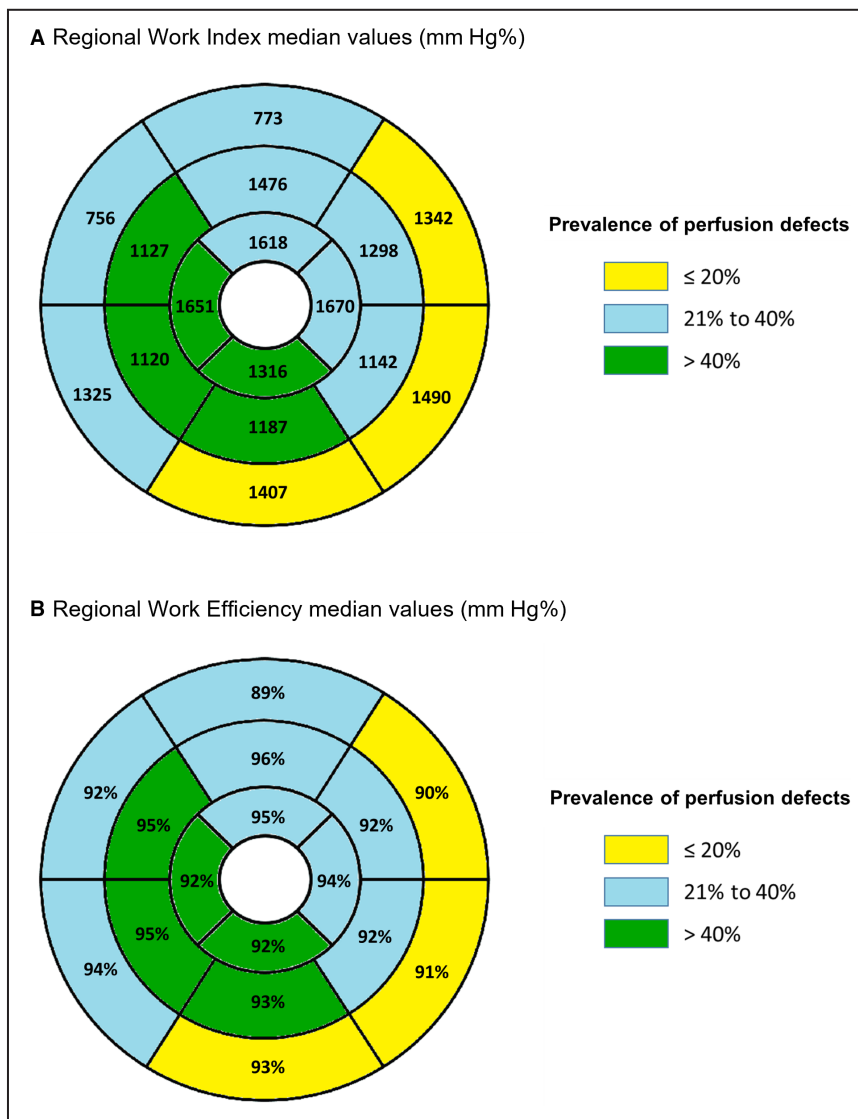
Figure 3. Work index (A) and work efficiency (B) median values compared with prevalence of ischemia (colors) in individual segments.

pattern of hypertrophy. A segmental analysis supported these findings.

ARTICLE INFORMATION

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SUPPLEMENTAL MATERIAL

Supplemental Methods

Data S1. Cardiac Magnetic Resonance acquisition protocol and analysis

All subjects underwent CMR performed on a 1.5T system (Sola, Siemens, Erlangen, Germany) and abstained from caffeine for at least 24 hours. Cardiac localizers were obtained to plan the cardiac axis views. Using Compressed Sensing-based sequence, cine images in 3 long-axis planes and sequential short-axis slices spanning the entire left ventricle from the base to the apex were acquired. Stress perfusion CMR 90 seconds after hyperemia was induced by regadenoson (400 mcg bolus) using 0.05 mmol/kg of gadolinium (Gadovist, Bayer Schering Pharma AG, Berlin, Germany) followed by 20ml saline flush injected at 5ml/s. Images were acquired apex to base during breath-hold at the first pass of contrast (60 measurements). A gradient echo sequence with a flip angle of 12⁰, bandwith 651 Hz per pixel, nonsection-selective saturation preparation, field of view 380 mm, acquisition matrix 127x160, slice thickness 10 mm, and standard motion correction was used. LGE images were acquired 10–15 minutes after intravenous administration of additional 0.15 mmol/kg of gadolinium at end diastole, using a breath-held segmented inversion-recovery steady state free precession sequence with a flip angle of 55⁰, a field of view 400mm, and voxel size of 1.6×1.6×8.0mm after determining the optimal inversion time (TI) using a scout sequence. CMR interpretation was performed by one physician using commercially available software (CMR42, version 5.11, Circle Cardiovascular Imaging, Calgary, Alberta, Canada). LV wall thickness, LV mass, end diastolic volume (EDV), end systolic volume (ESV), and LV ejection fraction (EF) were measured from short axis cine images excluding papillary muscles and trabeculations. Microvascular dysfunction was considered present if a visual perfusion defect was observed. Perfusion defects were considered surrogates for ischemia. For perfusion assessment

and semi-quantification, the myocardium was divided into 32 subsegments (16 American Heart association segments subdivided into an endocardial and epicardial layer). Ischemic burden for each patient was calculated based on the number of involved sub-segments, assigning 3% of myocardium to each sub-segment. Each segment was analyzed for the presence or absence of perfusion defect. Artifacts were assessed by using motion correction in the perfusion sequence and perfusion defects were required to persist for three or more beats throughout the stress perfusion sequence. Perfusion defects sparing the subendocardium and coincident with LGE were not considered, as subendocardial involvement is mandatory for microvascular dysfunction defects. The LGE was analyzed per-segment basis using a signal threshold versus reference myocardium of ≥6 standard deviation. Total LGE was expressed as a proportion of LV mass.

Table S1. Univariable linear regression analysis of left ventricular

myocardial work parameters

	Correlation Coefficient (r)	p-value	β-estimate	95% confidence interval	p-value
Global Work Index					
N. segments ischemia (n)	-0.532	**<0.001**	-56.465	-78.163 to -34.767	**<0.001**
Ischemia burden (% of LV mass)	-0.519	**<0.001**	-12.667	-17.778 to -7.554	**<0.001**
MWT	-0.471	**<0.001**	-45.357	-66.554 to -24.160	**<0.001**
LV mass index	-0.558	**<0.001**	-7.319	-10.163 to -4.476	**<0.001**
Concentric hypertrophy pattern	-0.257	**0.028**	-372.156	-701.390 to -42.922	**0.027**
N. segments LGE (n)	-0.331	**0.005**	-29.263	-50.427 to -8.100	**0.007**
LGE (% of LV mass)	-0.285	**0.015**	-15.058	-26.234 to -3.882	**0.009**
Obstructive HCM	-0.163	0.169	-136.897	-359.551 to -85.757	0.224
Diabetes	-0.246	**0.036**	-290.443	-562.397 to -18.489	**0.037**
Hypertension	-0.059	0.619	-45.352	-245.780 to 155.076	0.653
BMI >25 kg/m^2	-0.031	0.868	-60.464	-576.600 to 455.672	0.813
Male sex	-0.040	0.737	-28.073	-237.522 to 181.376	0.790
Global Constructive Work					
N. segments ischemia (n)	-0.519	**<0.001**	-59.373	-80.971 to -37.774	**<0.001**
Ischemia burden (% of LV mass)	-0.532	**<0.001**	-13.788	-18.798 to -8.778	**<0.001**
MWT	-0.504	**<0.001**	-47.400	-68.319 to -26.482	**<0.001**
LV mass index	-0.616	**<0.001**	-8.193	-10.885 to -5.501	**<0.001**
Concentric hypertrophy pattern	-0.321	**0.006**	-447.802	-771.116 to -124.489	**0.007**
N. segments LGE (n)	-0.404	**<0.001**	-37.389	-57.919 to -16.859	**0.001**
LGE (% of LV mass)	-0.372	**0.001**	-17.782	-28.693 to -6.872	**0.002**
Obstructive HCM	-0.105	0.379	-114.085	-337.643 to 109.474	0.312
Diabetes	-0.201	0.091	-248.689	-522.722 to 25.345	0.075
Hypertension	-0.032	0.789	-2.722	-204.462 to 199.018	0.979
BMI >25 kg/m^2	-0.061	0.738	-20.286	-542.004 to 501.433	0.937
Male sex	-0.115	0.337	-72.659	-281.949 to 136.632	0.491
Global Wasted Work					
N. segments ischemia (n)	0.280	**0.017**	5.463	1.902 to 9.024	**0.014**
Ischemia burden (% of LV mass)	0.199	0.094	0.711	-1.016 to 2.438	0.415
MWT	0.210	0.076	4.245	-2.566 to 11.057	0.218
LV mass index	0.258	**0.029**	0.584	-0.369 to 1.537	0.226
Concentric hypertrophy pattern	0.118	0.322	35.833	-62.410-134.076	0.469
N. segments LGE (n)	0.153	0.203	1.919	-4.705 to 8.543	0.565
LGE (% of LV mass)	0.018	0.881	0.269	-3.202 to 3.740	0.877
Obstructive HCM	0.066	0.584	19.423	-45.639 to 84.485	0.553
Diabetes	0.231	0.051	82.361	3.565 to 161.156	**0.041**
Hypertension	0.239	**0.043**	67.500	11.329 to 123.671	**0.019**
BMI >25 kg/m^2	0.338	0.059	75.357	-38.855 to 189.569	0.188
Male sex	-0.110	0.358	-44.321	-104.221 to 15.579	0.145
Global Work Efficiency					
N. segments ischemia (n)	-0.477	**<0.001**	-0.833	-1.244 to -0.422	**<0.001**

Ischemia burden (% of LV mass)	-0.379	**0.001**	-0.156	-0.255 to -0.057	**0.003**
MWT	-0.361	**0.002**	-0.530	-0.931 to -0.130	**0.010**
LV mass index	-0.459	**<0.001**	-0.101	-0.155 to -0.048	**<0.001**
Concentric hypertrophy pattern	-0.200	0.092	-6.138	-11.975 to -0.302	**0.040**
N. segments LGE (n)	-0.263	**0.026**	-0.376	-0.765 to 0.014	0.058
LGE (% of LV mass)	-0.161	0.180	-0.158	-0.363 to 0.048	0.130
Obstructive HCM	-0.193	0.105	-2.758	-6.683 to 1.167	0.166
Diabetes	-0.323	**0.006**	-7.185	-11.834 to -2.536	**0.003**
Hypertension	-0.181	0.127	-2.861	-6.360 to 0.638	0.107
BMI >25 kg/m^2	-0.313	0.081	-6.286	-15.313 to 2.742	0.165
Male sex	0.059	0.625	2.052	-1.627 to 5.731	0.270

p-values were obtained by mixed effects regression models.

LV: left ventricular, MWT: maximal wall thickness, LGE: late gadolinium enhancement, HCM: hypertrophic cardiomyopathy, BMI: body mass index

Table S2. Correlation between myocardial work parameters and ischemia according to obstructive hypertrophic cardiomyopathy (HCM) versus nonobstructive HCM

Perfusion defects	Obstructive HCM (n=21)		Nonobstructive HCM (n=54)		p-value (interaction)
	Correlation Coefficient (r)	p-value	Correlation Coefficient (r)	p-value	
Global Work Index					
N. segments (n)	-0.518	**0.019**	-0.506	**<0.001**	0.953
Ischemia burden (% of LV mass)	-0.524	**<0.001**	-0.414	0.071	0.606
Global Constructive Work					
N. segments (n)	-0.564	**0.010**	-0.520	**<0.001**	0.816
Ischemia burden (% of LV mass)	-0.524	**<0.001**	-0.420	0.065	0.625
Global Wasted Work					
N. segments (n)	0.158	0.506	0.190	0.178	0.904
Ischemia burden (% of LV mass)	0.155	0.514	0.298	**0.032**	0.582
Global Work Efficiency					
N. segments (n)	-0.591	**0.006**	-0.317	**0.022**	0.201
Ischemia burden (% of LV mass)	-0.484	**0.030**	-0.409	**0.003**	0.732

HCM: hypertrophic cardiomyopathy, LV: left ventricular

Table S3. Correlation between myocardial work parameters and ischemia according to the presence of significant replacement fibrosis (LGE ≥15% versus LGE <15%)

Perfusion defects	LGE ≥ 15% (n=29)		LGE < 15% (n=45)		
	Correlation Coefficient (r)	p-value	Correlation Coefficient (r)	p-value	p-value (interaction)
Global Work Index					
N. segments (n)	-0.489	**0.007**	-0.393	**0.009**	0.632
Ischemia burden (% of LV mass)	-0.472	**0.010**	-0.471	**0.001**	0.995
Global Constructive Work					
N. segments (n)	-0.455	**0.013**	-0.359	**0.019**	0.643
Ischemia burden (% of LV mass)	-0.431	**0.019**	-0.408	**0.007**	0.911
Global Wasted Work					
N. segments (n)	0.218	0.165	0.124	0.520	0.697
Ischemia burden (% of LV mass)	0.317	**0.040**	0.209	0.277	0.640
Global Work Efficiency					
N. segments (n)	-0.351	**0.022**	-0.303	0.110	0.829
Ischemia burden (% of LV mass)	-0.474	**0.002**	-0.362	0.054	0.584

LGE: late gadolinium enhancement, LV: left ventricular

Table S4. Segmental univariable linear ventricular regression analysis of left myocardial work parameters.

	Correlation Coefficient (r)	p-value	β-estimate	95% confidence interval	p-value
Global Work Index					
Perfusion defect	-0.294	**<0.001**	-415.325	-502.732 to -327.918	**<0.001**
LGE	-0.227	**<0.001**	-320.131	-405.665 to -234.597	**<0.001**
Wall thickness ≥15 mm	-0.422	**<0.001**	-52.975	-60.801 to -45.148	**<0.001**
Wall thickness 12-14 mm	-0.289	**<0.001**	-85.948	-105.501 to -66.395	**<0.001**
Obstructive HCM	——	——	-158.461	-250.316 to -66.606	**0.001**
Diabetes	——	——	-146.564	-259.618 to -33.511	**0.011**
Hypertension	——	——	-63.451	-146.639 to 19.737	0.135
BMI >25 kg/m²	——	——	-77.494	-176.738 to 21.751	0.126
Male sex	——	——	-76.704	-162.193 to 8.784	0.079
Global Work Efficiency					
Perfusion defect	-0.242	**<0.001**	-5.635	-7.723 to -3.548	**<0.001**
LGE	-0.133	**<0.001**	-4.408	-6.400 to -2.417	**<0.001**
Wall thickness ≥15 mm	-0.233	**<0.001**	-0.630	-0.821 to -0.438	**<0.001**
Wall thickness 12-14 mm	-0.174	**<0.001**	-0.905	-1.331 to -0.478	**<0.001**
Obstructive HCM	——	——	-3.251	-5.273 to -1.229	**0.002**
Diabetes	——	——	-5.744	-8.318 to -3.171	**<0.001**
Hypertension	——	——	-2.874	-4.745 to -1.003	**0.003**
BMI >25 kg/m²	——	——	-1.469	-3.749 to 0.810	0.206
Male sex	——	——	-0.050	-1.972 to 1.871	0.959

LGE: late gadolinium enhancement, HCM: hypertrophic cardiomyopathy, BMI: body mass index

Figure S1. Receiver operating characteristic (ROC) curve of the

association between Global Work Index and the presence of perfusion defects
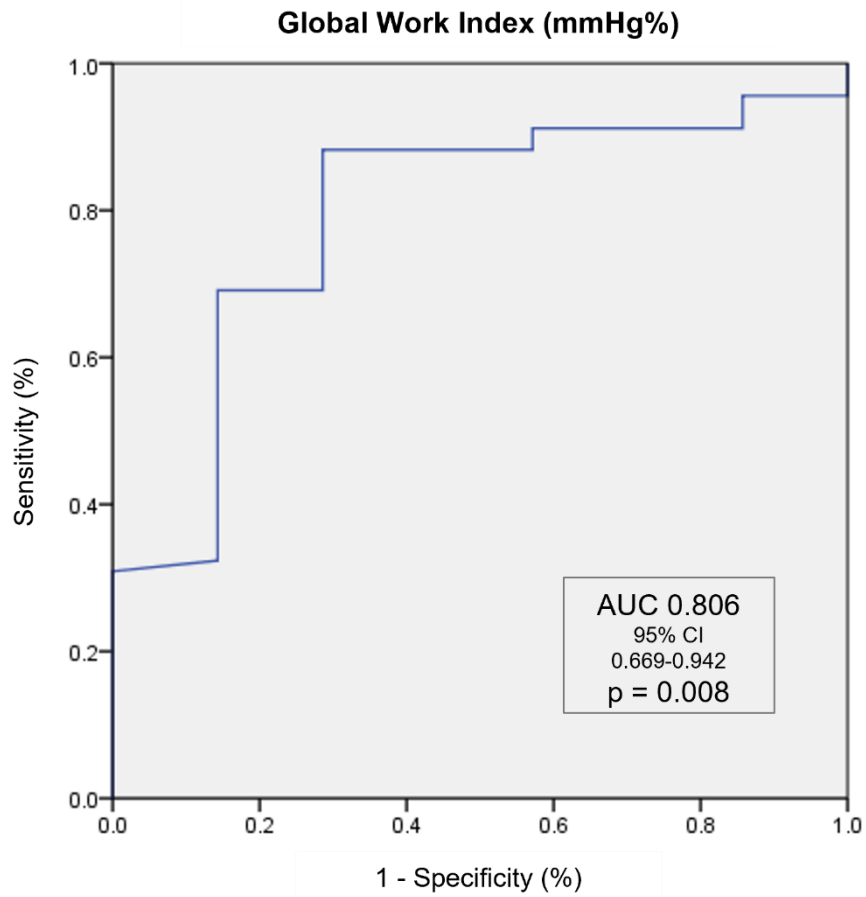
Figure S2. Correlation between myocardial work parameters and ischemia according to obstructive hypertrophic cardiomyopathy (HCM) versus nonobstructive HCM
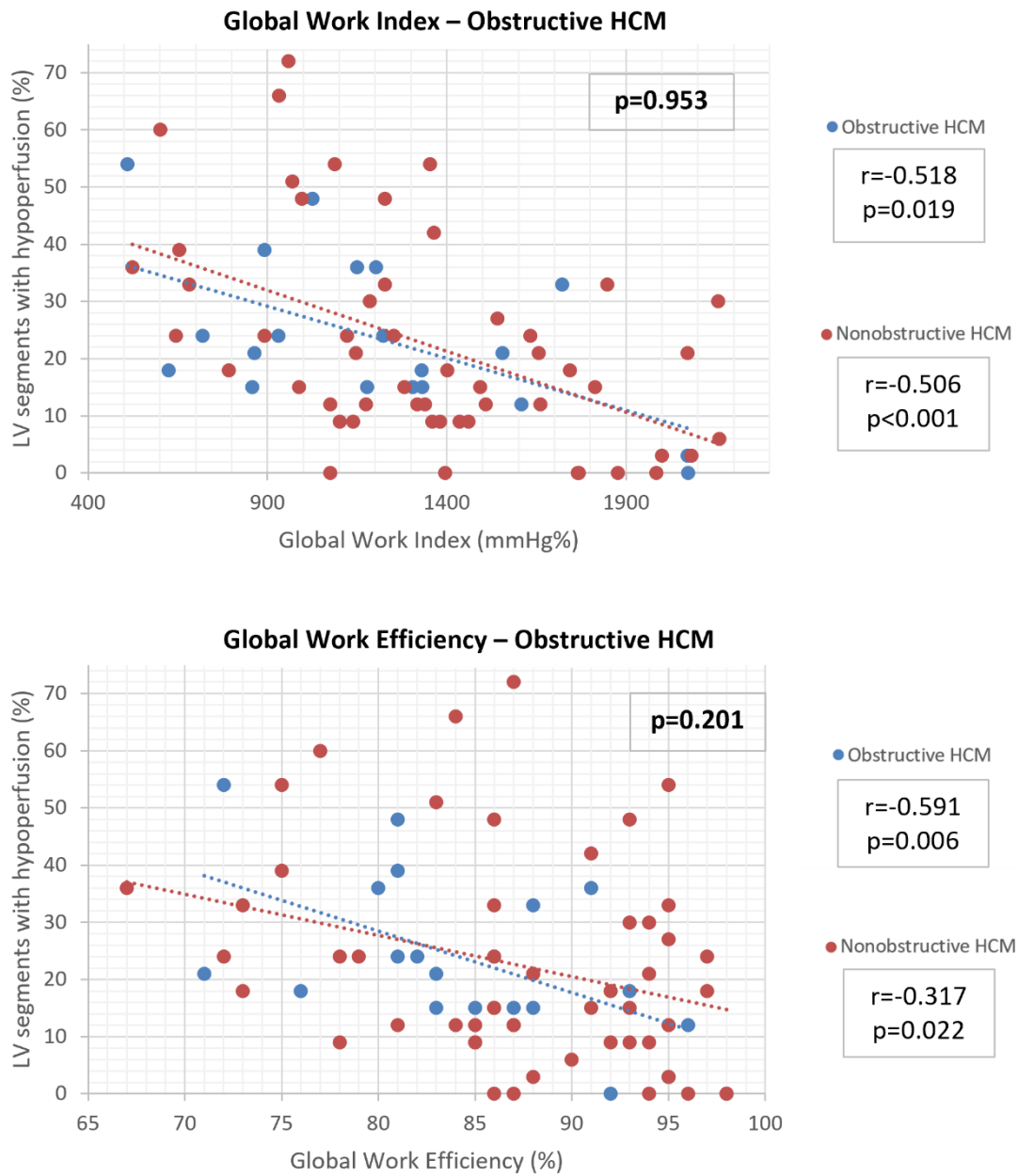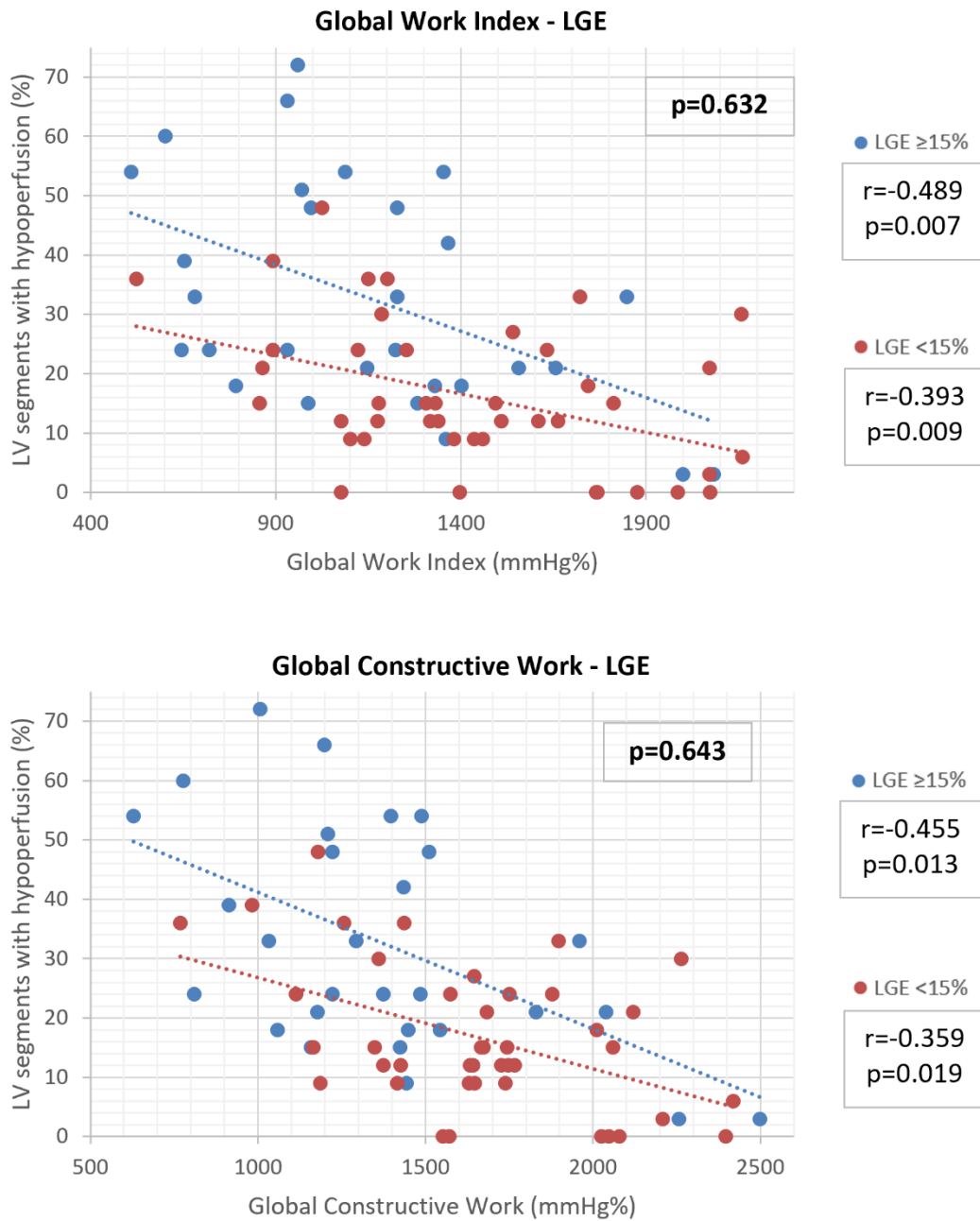
Global Work Index – Obstructive HCM

p=0.953

● Obstructive HCM

r=-0.518
p=0.019

● Nonobstructive HCM

r=-0.506
p<0.001

Global Work Index (mmHg%)

LV segments with hypoperfusion (%)

Global Work Efficiency – Obstructive HCM

p=0.201

● Obstructive HCM

r=-0.591
p=0.006

● Nonobstructive HCM

r=-0.317
p=0.022

Global Work Efficiency (%)

LV segments with hypoperfusion (%)

Figure S3. Correlation between myocardial work parameters and ischemia according to the presence of significant replacement fibrosis (late gadolinium enhancement [LGE] ≥ 15% vs LGE < 15%).

LGE: late gadolinium enhancement