

# Noninvasive Myocardial Work for the Functional Characterization and Differentiation of Nonobstructive Hypertrophic Cardiomyopathy and Hypertensive Heart Disease: A Cross-Sectional Study

**Daniel Rabischoffsky**

**daniel\_rab@hotmail.com**

Universidade do Estado do Rio de Janeiro (UERJ) – Hospital Universitário Pedro Ernesto

**Bruno Reznik Wajsbrodt**

Universidade do Estado do Rio de Janeiro (UERJ) – Hospital Universitário Pedro Ernesto

**Rafael Rabischoffsky**

Hospital Pró-Cardíaco

**Ana Luiza Ferreira Sales**

Universidade do Estado do Rio de Janeiro (UERJ) – Hospital Universitário Pedro Ernesto

**Angelo Antunes Salgado**

Universidade do Estado do Rio de Janeiro (UERJ) – Hospital Universitário Pedro Ernesto

**Pedro Pimenta Mello Spinetti**

Universidade do Estado do Rio de Janeiro (UERJ) – Hospital Universitário Pedro Ernesto

**Marcelo Imbroinise Bittencourt**

Universidade do Estado do Rio de Janeiro (UERJ) – Hospital Universitário Pedro Ernesto

**Ricardo Mourilhe-Rocha**

Universidade do Estado do Rio de Janeiro (UERJ) – Hospital Universitário Pedro Ernesto

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## Research Article

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# Abstract

## Purpose

Left ventricular hypertrophy of sarcomeric and hypertensive etiology shares morphological features but differs in the underlying mechanics. We compared noninvasive myocardial work (MW) indices among nonobstructive hypertrophic cardiomyopathy (HCM), hypertensive heart disease (HHD), and controls, and assessed their diagnostic performance.

## Methods

In this cross-sectional study, 92 individuals were stratified into HCM (n = 31), HHD (n = 31), and controls without structural heart disease (n = 30). All underwent echocardiography with analysis of global work index (GWI), global constructive work (GCW), global wasted work (GWW), and global work efficiency (GWE). ROC analysis assessed functional parameters for HCM versus non-HCM and, restricted to the overlap zone, for HCM versus HHD.

## Results

GWl and GCW were significantly lower in HCM than in HHD and controls despite preserved ejection fraction, and did not differ between HHD and controls. GWW and GWE were impaired in both pathological groups without a significant difference between them. MW correlated with markers of hypertrophy and diastolic dysfunction but not with ejection fraction. In multivariable regression, an HCM diagnosis independently predicted lower GWl and GCW, exceeding systolic pressure in magnitude. Among functional parameters, GCW showed the highest accuracy (HCM vs non-HCM: AUC 0.852; HCM vs HHD: AUC 0.799) and best reproducibility, with accuracy numerically higher than that of global longitudinal strain and significantly higher within the HCM–HHD overlap zone.

## Conclusion

MW indices identify subclinical mechanical dysfunction with pathophysiologically distinct patterns between nonobstructive HCM and HHD. GCW was the most robust functional discriminator and may complement morphological assessment in borderline cases.

## Clinical trial registration

Not applicable (observational study).

## INTRODUCTION

Left ventricular hypertrophy (LVH) is one of the most prevalent echocardiographic findings in cardiology and an independent marker of cardiovascular risk.[1] Among the pathological causes of LVH, hypertrophic cardiomyopathy (HCM) and hypertensive heart disease (HHD) are the two most prevalent and clinically relevant conditions, and also those that most frequently overlap morphologically, confronting the clinician with the challenge of identifying distinct pathophysiological mechanisms from a similar echocardiographic phenotype.

HCM is the most common genetic cardiomyopathy, with an estimated prevalence of 1:200 to 1:500, caused predominantly by sarcomeric mutations, and characterized by myofibrillar disarray and interstitial fibrosis that compromise ventricular mechanics well before any reduction in ejection fraction. [2, 3] HHD is the cardiac manifestation of systemic arterial hypertension, in which chronic pressure overload induces progressive remodeling mediated by neurohumoral activation and interstitial fibrosis. [4, 5] Both conditions typically present with increased wall thickness and preserved ejection fraction, configuring a diagnostic grey zone. It is estimated that 13–31% of patients with HCM display symmetric septal hypertrophy and 4–47% of hypertensive patients display asymmetric hypertrophy;[6, 7] cardiac magnetic resonance has been shown to modify the initial echocardiographic diagnosis in a substantial proportion of hypertrophied hearts, underscoring the insufficiency of conventional morphological parameters for precise etiological differentiation.[8]

Ejection fraction remains normal or supranormal in most patients with either condition, and is insensitive to early mechanical impairment. Global longitudinal strain (GLS) by speckle-tracking echocardiography detects subclinical dysfunction earlier,[9, 10] but remains load-dependent, precluding the distinction between intrinsic contractile impairment and reduced deformation secondary to increased afterload — a limitation of particular relevance when comparing conditions with opposing pressure profiles such as HCM and HHD. Noninvasive myocardial work (MW), obtained by integrating the arterial pressure curve with GLS to construct the pressure-strain loop, explicitly incorporates afterload into the estimation of myocardial deformation, overcoming this fundamental limitation.[11, 12] Its derived indices — global work index (GWI), global constructive work (GCW), global wasted work (GWW), and global work efficiency (GWE) — reflect distinct dimensions of ventricular mechanics.[13]

The comparative behavior of MW indices among individuals with nonobstructive HCM, with HHD, and without structural heart disease, and their utility in differential diagnosis in the morphological overlap zone, remain insufficiently characterized, particularly in a Brazilian population at a quaternary referral center.[14] The present study was designed to compare MW indices across the three groups, to investigate their correlations with structural and functional variables, to assess the influence of clinical variables, and to evaluate the diagnostic performance of the functional parameters, with emphasis on the potential complementary value of GCW in morphologically borderline cases.[15]

## METHODS

### Study design and population

This was a cross-sectional observational study conducted at Hospital Universitário Pedro Ernesto, Universidade do Estado do Rio de Janeiro (HUPE/UERJ), between January 2024 and January 2026. The study was approved by the institutional research ethics committee (CAAE 73088023.0.0000.5259; opinion no. 6.275.829), and all participants provided written informed consent in accordance with National Health Council Resolution 466/12.

Ninety-two patients aged  $\geq 18$  years, of both sexes, drawn from the HUPE/UERJ outpatient clinic and from the investigator's private practice, were stratified into three groups: HCM (n = 31), nonobstructive hypertrophic cardiomyopathy; HHD (n = 31), hypertensive heart disease with concentric remodeling or concentric/eccentric hypertrophy; and control (n = 30), without structural heart disease. Group classification followed clinical and echocardiographic criteria established in current international guidelines for HCM[6, 7] and for hypertensive LVH.

## Diagnostic criteria and group classification

HCM was diagnosed by a maximal LV wall thickness  $\geq 15$  mm, or  $\geq 13$  mm in the presence of a positive family history, in one or more LV segments measured by transthoracic echocardiography or cardiac magnetic resonance, not explained solely by loading conditions, or by a positive genetic test.[6, 7] Exclusion criteria included a resting or provoked LV outflow tract gradient  $> 30$  mmHg, moderate-to-severe valvular disease, prior septal reduction therapy, significant mechanical dyssynchrony, pacemaker or defibrillator, prior myocardial infarction or revascularization, systolic dysfunction, and suboptimal image quality for deformation analysis.

HHD required a self-reported prior physician diagnosis of arterial hypertension and use of antihypertensive medication, associated with documented hypertensive heart disease on echocardiography, represented by one of the following geometric patterns classified by LV mass index and relative wall thickness (RWT): concentric hypertrophy (increased LV mass index [ $> 95$  g/m<sup>2</sup> in women,  $> 115$  g/m<sup>2</sup> in men] with RWT  $> 0.42$ ), concentric remodeling (normal LV mass index with RWT  $> 0.42$ ), or eccentric hypertrophy (increased LV mass with RWT  $\leq 0.42$ ). Controls had no significant cardiovascular symptoms, normal physical examination, no structural heart disease on echocardiography (wall thickness  $\leq 11$  mm, preserved ejection fraction), blood pressure within range (systolic  $< 140$  and diastolic  $< 90$  mmHg), sinus rhythm, and no chronic use of antihypertensive or cardioactive drugs.

## Echocardiographic assessment

A comprehensive echocardiographic examination was performed using a GE Vivid E9 system following American Society of Echocardiography recommendations. Conventional measurements included interventricular septum and posterior wall thickness in diastole, LV diameters, LV volumes and ejection fraction by the Simpson method indexed to body surface area, left atrial volume, diastolic function by

transmitral and tissue Doppler (E/e'), and pulmonary artery systolic pressure. LV mass was calculated using the Devereux formula and RWT as  $2 \times \text{posterior wall} / \text{LV end-diastolic diameter}$ . [16]

GLS was obtained by two-dimensional speckle-tracking echocardiography from the apical four-, two-, and three-chamber views at a frame rate of 40–80 frames per second, as the average of segmental longitudinal strain values, with semiautomatic tracking and manual adjustment when required. [10] Immediately after GLS calculation, systolic and diastolic blood pressures were entered, measured by a calibrated oscillometric device on the left arm with the patient supine, ensuring temporal correspondence with image acquisition. Mitral and aortic valve event timings were determined from pulsed-wave Doppler tracings. Integration of arterial pressure with GLS enabled construction of the pressure-strain loop and automatic generation of GWI, GCW, GWW, and GWE (EchoPAC, GE Healthcare). [12, 13] Studies performed on the HUPE echocardiography service used the EchoPAC software integrated into the GE Vivid E9; studies performed in the private setting were analyzed offline in EchoPAC on a dedicated workstation, using the identical software and analysis algorithm.

## Interobserver variability

A subsample of 21 studies was independently re-analyzed by a second experienced echocardiographer blinded to the original values, who performed independent GLS tracking and MW calculation from the previously stored DICOM images. Agreement was quantified by the intraclass correlation coefficient (ICC; two-way random-effects model, absolute agreement, single measures), Bland-Altman analysis, and coefficient of variation, interpreted according to Koo and Li. [17]

## Statistical analysis

The sample size was estimated by one-way ANOVA for three independent groups using published GWI means and standard deviations; [18] the minimum required was fewer than 15 participants per group, and 30 were included per group to account for population heterogeneity and technical losses. Continuous variables are expressed as mean  $\pm$  standard deviation or median [interquartile range] according to distribution, and categorical variables as absolute and relative frequencies. Normality was assessed by Shapiro-Wilk and Kolmogorov-Smirnov tests. Between-group comparisons used one-way ANOVA with Bonferroni post-hoc for normally distributed variables and Kruskal-Wallis with Dunn post-hoc and Bonferroni correction otherwise. Correlations used the Spearman coefficient.

The influence of clinical variables on MW was assessed by multiple linear regression, with diagnostic group coded as dummy variables (HCM, HHD; control as reference) [19] and adjustment for systolic pressure, age, and sex; absence of multicollinearity was confirmed by tolerance, variance inflation factor, and condition indices. Discriminatory performance was assessed by ROC curves with area under the curve (AUC); the primary functional analysis evaluated the myocardial work parameters and GLS, which do not enter group classification, against the binary outcome of HCM versus non-HCM. A pre-specified secondary analysis restricted to the HCM and HHD groups (excluding controls) evaluated performance

within the morphological overlap zone. Optimal cut-offs were determined by the Youden index. As an exploratory analysis of complementary value, a combined logistic-regression model (maximal-thickness/posterior-wall ratio plus GCW) was compared with morphology alone using the DeLong test (pROC package, R 4.3.1). Morphological variables, which constitute part of the classification criteria, are reported as a diagnostic reference rather than as competing tests. A two-sided  $p < 0.05$  was considered significant. Analyses used IBM SPSS Statistics v31.0. An AI-assisted tool was used to support manuscript drafting and language; all analyses and results were performed and verified by the authors, who take full responsibility for their accuracy.

## RESULTS

### Baseline characteristics

Ninety-two individuals were included (31 HCM, 31 HHD, 30 controls; Table 1). The HHD group was older than controls (median 58.0 vs 46.0 years;  $p = 0.001$ ) and predominantly female (19.4% male vs 54.8% in HCM and 53.3% in controls;  $p = 0.006$ ). Systolic blood pressure was significantly higher in HHD ( $142.1 \pm 15.0$  mmHg) than in HCM ( $125.1 \pm 16.0$  mmHg;  $p < 0.001$ ) and controls ( $125.6 \pm 9.5$  mmHg;  $p < 0.001$ ), without a significant difference between HCM and controls. Arterial hypertension was present in 100% of HHD, 25.8% of HCM, and no control subject. Of the 8 HCM patients with concomitant hypertension, all met echocardiographic HCM criteria (maximal thickness 15–28 mm; asymmetric pattern with maximal-thickness/posterior-wall ratio 1.38–2.55; preserved posterior wall), with less intensive antihypertensive use than the HHD group.

Table 1  
Baseline characteristics of the study groups.

| Variable                                                                                                                                                                                                                                                                                                                                                                                                                                                            | HCM (n = 31)     | HHD (n = 31)     | Control (n = 30)  | p       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------------|-------------------|---------|
| Age, years*                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 55.0 [42.0–67.0] | 58.0 [50.5–67.0] | 46.0 [42.0–55.5]  | 0.002   |
| Male sex, n (%)                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 17 (54.8)        | 6 (19.4)         | 16 (53.3)         | 0.006   |
| BMI, kg/m <sup>2</sup> **                                                                                                                                                                                                                                                                                                                                                                                                                                           | 27.2 ± 4.0       | 28.3 ± 3.6       | 24.7 ± 2.9        | 0.001   |
| SBP, mmHg**                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 125.1 ± 16.0     | 142.1 ± 15.0     | 125.6 ± 9.5       | < 0.001 |
| DBP, mmHg**                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 78.6 ± 9.4       | 85.9 ± 9.4       | 78.5 ± 7.6        | 0.002   |
| eGFR, mL/min/1.73m <sup>2</sup> ‡                                                                                                                                                                                                                                                                                                                                                                                                                                   | 77.5 [63.0–92.8] | 73.5 [66.2–85.8] | 88.0 [78.0–106.0] | 0.009   |
| Hypertension, n (%)                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 8 (25.8)         | 31 (100.0)       | 0 (0.0)           | < 0.001 |
| Diabetes, n (%)                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 3 (9.7)          | 8 (25.8)         | 0 (0.0)           | 0.007   |
| Dyslipidemia, n (%)                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 15 (48.4)        | 24 (77.4)        | 7 (23.3)          | < 0.001 |
| Smoking, n (%)                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 2 (6.5)          | 3 (9.7)          | 0 (0.0)           | 0.238   |
| HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; BMI, body mass index; SBP/DBP, systolic/diastolic blood pressure; eGFR, estimated glomerular filtration rate. *Median [IQR], Kruskal-Wallis with Dunn post-hoc and Bonferroni correction. **Mean ± SD, one-way ANOVA with Bonferroni post-hoc. Categorical: chi-square with Bonferroni correction. ‡Valid n: HCM 28, HHD 22, control 25. Pairwise post-hoc comparisons are reported in the text. |                  |                  |                   |         |

Within the HCM group, 17 (54.8%) had undergone cardiac magnetic resonance, with mesocardial late gadolinium enhancement present in 16/17 (94.1%), and 4 (12.9%) had confirmed sarcomeric mutations (MYBPC3, MYH7, ACTC1, FHOD3), supporting diagnostic accuracy in this subgroup.

## Conventional echocardiographic parameters

The HCM group had the greatest wall thicknesses and the highest maximal-thickness/posterior-wall ratio ( $2.1 \pm 0.5$ ), higher than the other groups ( $p < 0.001$ ; Table 2). Six HHD patients (19.4%) had maximal thickness  $\geq 15$  mm (15–17 mm) but were retained in the HHD group on the basis of a symmetric pattern, a septum/posterior-wall ratio of 1.00–1.25, elevated RWT, absence of a family history of HCM, treated hypertension, and no red flags for amyloidosis.[20] LV mass was greater in both HCM and HHD than in controls ( $p < 0.001$ ) without a significant difference between HCM and HHD. Ejection fraction was preserved in all three groups. GLS decreased progressively from controls (19.0%) to HHD (16.0%) to HCM (14.0%), differing significantly between each pathological group and controls but not between HCM and HHD ( $p = 0.074$ ). E/e' and indexed left atrial volume were higher in HCM than in the other groups ( $p < 0.001$ ).

Table 2  
Conventional echocardiographic parameters.

| Variable                                                                                                                                                                                                                                                                                                                                                                                                                                    | HCM (n = 31)        | HHD (n = 31)       | Control (n = 30) | p       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|--------------------|------------------|---------|
| Septum, mm*                                                                                                                                                                                                                                                                                                                                                                                                                                 | 20.0 [17.5–23.5]    | 14.0 [13.0–14.0]   | 8.0 [8.0–9.0]    | < 0.001 |
| Posterior wall, mm*                                                                                                                                                                                                                                                                                                                                                                                                                         | 10.0 [9.0–11.0]     | 12.0 [11.0–13.0]   | 8.0 [8.0–9.0]    | < 0.001 |
| Maximal thickness, mm*                                                                                                                                                                                                                                                                                                                                                                                                                      | 20.0 [17.5–23.5]    | 14.0 [13.0–14.0]   | 8.0 [8.0–9.0]    | < 0.001 |
| Max-thickness/PW ratio**                                                                                                                                                                                                                                                                                                                                                                                                                    | 2.1 ± 0.5           | 1.1 ± 0.1          | 1.0 ± 0.1        | < 0.001 |
| LVEDD, mm*                                                                                                                                                                                                                                                                                                                                                                                                                                  | 43.0 [40.0–46.0]    | 44.0 [40.0–49.0]   | 44.5 [41.2–46.8] | 0.232   |
| LVESD, mm**                                                                                                                                                                                                                                                                                                                                                                                                                                 | 26.1 ± 4.3          | 27.1 ± 4.1         | 27.0 ± 3.1       | 0.627   |
| LV mass, g/m <sup>2</sup> *                                                                                                                                                                                                                                                                                                                                                                                                                 | 127.0 [112.5–180.5] | 110.0 [97.5–130.5] | 64.5 [57.5–79.0] | < 0.001 |
| Ejection fraction, %*                                                                                                                                                                                                                                                                                                                                                                                                                       | 73.0 [70.0–78.0]    | 70.0 [67.5–74.0]   | 70.5 [68.2–72.0] | 0.044   |
| GLS, absolute %*                                                                                                                                                                                                                                                                                                                                                                                                                            | 14.0 [12.0–16.5]    | 16.0 [15.0–17.5]   | 19.0 [18.0–20.0] | < 0.001 |
| E/e'                                                                                                                                                                                                                                                                                                                                                                                                                                        | 11.0 [10.0–16.5]    | 9.0 [7.0–11.0]     | 7.0 [6.0–8.0]    | < 0.001 |
| LA volume index, mL/m <sup>2</sup> ⊠                                                                                                                                                                                                                                                                                                                                                                                                        | 38.5 [32.0–44.0]    | 25.0 [23.0–31.0]   | 26.0 [22.2–30.0] | < 0.001 |
| PASP, mmHg**⊠                                                                                                                                                                                                                                                                                                                                                                                                                               | 24.3 ± 7.2          | 23.7 ± 7.3         | 22.6 ± 4.1       | 0.685   |
| PW, posterior wall; LVEDD/LVESD, LV end-diastolic/end-systolic diameter; LV, left ventricular; GLS, global longitudinal strain; LA, left atrial; PASP, pulmonary artery systolic pressure. *Median [IQR], Kruskal-Wallis with Dunn post-hoc and Bonferroni correction. **Mean ± SD, one-way ANOVA with Bonferroni post-hoc. ⊠Valid n: HCM 30. ⊠Valid n: HCM 22, HHD 15, control 20. Pairwise post-hoc comparisons are reported in the text. |                     |                    |                  |         |

## Myocardial work parameters

All four indices differed significantly on the global test ( $p < 0.001$ ; Table 3, Fig. 1; Supplementary Figure S1). GWI and GCW were significantly lower in HCM than in HHD and controls, whereas GWW and GWE distinguished only the pathological groups from controls, without a significant difference between HCM and HHD. GWI was lower in HCM ( $1458.8 \pm 431.5$  mmHg%) than in HHD ( $1863.3 \pm 400.1$  mmHg%;  $p = 0.003$ ) and controls ( $2040.9 \pm 227.5$  mmHg%;  $p < 0.001$ ), with no significant difference between HHD and controls ( $p = 0.142$ ). GCW was lower in HCM ( $1598.9 \pm 435.0$  mmHg%) than in HHD ( $2100.5 \pm 414.1$  mmHg%;  $p < 0.001$ ) and controls ( $2233.3 \pm 194.5$  mmHg%;  $p < 0.001$ ), again without a significant difference between HHD and controls ( $p = 0.763$ ). GWW was higher in both pathological groups than in controls (HCM vs control  $p = 0.045$ ; HHD vs control  $p < 0.001$ ; HCM vs HHD  $p = 0.754$ ). GWE was lower in both pathological groups than in controls (both  $p < 0.001$ ; HCM vs HHD  $p = 0.621$ ).

Table 3  
Myocardial work parameters by group.

| Variable     | HCM (n = 31)      | HHD (n = 31)       | Control (n = 30) | p       |
|--------------|-------------------|--------------------|------------------|---------|
| GWl, mmHg%*  | 1458.8 ± 431.5    | 1863.3 ± 400.1     | 2040.9 ± 227.5   | < 0.001 |
| GCW, mmHg%*  | 1598.9 ± 435.0    | 2100.5 ± 414.1     | 2233.3 ± 194.5   | < 0.001 |
| GWW, mmHg%** | 89.0 [64.0–135.0] | 103.0 [73.5–150.5] | 61.5 [48.0–89.2] | < 0.001 |
| GWE, %**     | 94.0 [90.5–95.5]  | 95.0 [92.0–96.0]   | 97.0 [96.0–97.0] | < 0.001 |

GWl, global work index; GCW, global constructive work; GWW, global wasted work; GWE, global work efficiency. \*Mean ± SD, one-way ANOVA with Bonferroni post-hoc. \*\*Median [IQR], Kruskal-Wallis with Dunn post-hoc and Bonferroni correction. Pairwise comparisons: GWl – HCM vs HHD p = 0.003, HCM vs control p < 0.001, HHD vs control p = 0.142. GCW – HCM vs HHD p < 0.001, HCM vs control p < 0.001, HHD vs control p = 0.763. GWW – HCM vs control p = 0.045, HHD vs control p < 0.001, HCM vs HHD p = 0.754. GWE – HCM vs control p < 0.001, HHD vs control p < 0.001, HCM vs HHD p = 0.621.

## Correlations with structural and functional variables

GWl and GCW showed moderate-to-strong negative correlations with maximal thickness ( $\rho = -0.528$  and  $-0.524$ ; both  $p < 0.001$ ), LV mass ( $\rho = -0.505$  and  $-0.469$ ; both  $p < 0.001$ ), and the maximal-thickness/posterior-wall ratio ( $\rho = -0.438$  and  $-0.474$ ; both  $p < 0.001$ ), and strong positive correlations with GLS ( $\rho = 0.708$  and  $0.671$ ; both  $p < 0.001$ ), with no significant correlation with ejection fraction (Table 4). GWE showed its strongest negative correlation with LV mass ( $\rho = -0.650$ ;  $p < 0.001$ ) and correlated negatively with E/e' ( $\rho = -0.363$ ;  $p < 0.001$ ). GWW correlated positively with LV mass ( $\rho = 0.464$ ;  $p < 0.001$ ) and negatively with GLS ( $\rho = -0.476$ ;  $p < 0.001$ ).

Table 4  
Spearman correlations between myocardial work parameters and echocardiographic variables.

| Variable                           | GWl      | GCW      | GWW      | GWE      |
|------------------------------------|----------|----------|----------|----------|
| Maximal thickness, mm              | -0.528** | -0.524** | 0.325**  | -0.546** |
| LV mass, g/m <sup>2</sup>          | -0.505** | -0.469** | 0.464**  | -0.650** |
| Max-thickness/PW ratio             | -0.438** | -0.474** | 0.122    | -0.350** |
| GLS, absolute %                    | 0.708**  | 0.671**  | -0.476** | 0.656**  |
| LA volume index, mL/m <sup>2</sup> | -0.340** | -0.383** | 0.281**  | -0.430** |
| E/e'                               | -0.258*  | -0.275** | 0.215*   | -0.363** |

Abbreviations as in Tables 2 and 3. \*p < 0.05; \*\*p < 0.01. Spearman coefficient ( $\rho$ ).

## Influence of clinical variables

In multivariable regression adjusted for systolic pressure, group, age, and sex, an HCM diagnosis remained an independent negative predictor of GWI ( $B = -564.9$ ;  $\beta = -0.615$ ;  $p < 0.001$ ) and GCW ( $B = -631.3$ ;  $\beta = -0.660$ ;  $p < 0.001$ ), with a standardized coefficient exceeding that of systolic pressure in both models. An HHD diagnosis was also independently associated with lower GWI ( $B = -331.6$ ;  $p = 0.001$ ) and GCW ( $B = -334.3$ ;  $p = 0.001$ ), but of smaller magnitude. Systolic pressure remained a positive independent predictor in both models (both  $p < 0.001$ ). Age and sex were not significant predictors. The models explained 42.7% of the variance in GWI and 47.5% in GCW (Table 5).

Table 5  
Independent predictors of GWI and GCW: multiple linear regression.

| Variable                                                                                                                                                                                                                       | B       | $\beta$ | 95% CI for B       | p       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|---------|--------------------|---------|
| <i>Dependent variable: GWI (adjusted <math>R^2 = 0.427</math>; <math>F = 14.55</math>; <math>p &lt; 0.001</math>)</i>                                                                                                          |         |         |                    |         |
| SBP, mmHg                                                                                                                                                                                                                      | 12.48   | 0.453   | 7.27 to 17.69      | < 0.001 |
| HCM group                                                                                                                                                                                                                      | -564.93 | -0.615  | -737.32 to -392.54 | < 0.001 |
| HHD group                                                                                                                                                                                                                      | -331.59 | -0.361  | -530.39 to -132.79 | 0.001   |
| Age, years                                                                                                                                                                                                                     | -1.85   | -0.057  | -7.47 to 3.76      | 0.514   |
| Sex                                                                                                                                                                                                                            | 88.65   | 0.101   | -61.39 to 238.69   | 0.243   |
| <i>Dependent variable: GCW (adjusted <math>R^2 = 0.475</math>; <math>F = 17.47</math>; <math>p &lt; 0.001</math>)</i>                                                                                                          |         |         |                    |         |
| SBP, mmHg                                                                                                                                                                                                                      | 12.35   | 0.431   | 7.16 to 17.54      | < 0.001 |
| HCM group                                                                                                                                                                                                                      | -631.33 | -0.660  | -803.11 to -459.58 | < 0.001 |
| HHD group                                                                                                                                                                                                                      | -334.30 | -0.350  | -532.38 to -136.9  | 0.001   |
| Age, years                                                                                                                                                                                                                     | 0.43    | 0.013   | -5.17 to 6.02      | 0.880   |
| Sex                                                                                                                                                                                                                            | 22.96   | 0.025   | -126.54 to 172.45  | 0.761   |
| B, unstandardized coefficient; $\beta$ , standardized coefficient; CI, confidence interval; SBP, systolic blood pressure. Control group used as reference. All predictors had VIF < 2.0 and a maximum condition index of 28.2. |         |         |                    |         |

## Diagnostic performance: HCM versus non-HCM

Among the functional parameters, which do not enter group classification, GCW had the highest AUC (0.852; 95% CI 0.755–0.929; cut-off  $\leq 1983$  mmHg%; sensitivity 83.9%, specificity 82.0%), superior to GWI (AUC 0.816;  $p = 0.039$ ) and to GLS (AUC 0.779;  $p = 0.095$ ). GWE showed moderate performance (AUC 0.712) and GWW showed no relevant discrimination (AUC 0.546) (Table 6, Fig. 2). As expected, the morphological reference variables (maximal-thickness/posterior-wall ratio and maximal thickness), which form part of the HCM classification criteria, showed near-perfect AUCs (0.989 and 0.986) and are reported for reference rather than as competing diagnostic tests.

Table 6  
Diagnostic accuracy for HCM versus non-HCM (ROC analysis).

| Variable                                 | AUC   | 95% CI      | Cut-off | Sens % | Spec % | Youden |
|------------------------------------------|-------|-------------|---------|--------|--------|--------|
| Max-thickness/PW ratio <sup>‡</sup>      | 0.989 | 0.964–1.000 | ≥ 1.3   | 96.8   | 98.4   | 0.951  |
| Maximal thickness <sup>‡</sup>           | 0.986 | 0.965–0.999 | ≥ 15 mm | 96.8   | 90.2   | 0.869  |
| GCW, mmHg%                               | 0.852 | 0.755–0.929 | ≤ 1983  | 83.9   | 82.0   | 0.658  |
| GWI, mmHg%                               | 0.816 | 0.707–0.907 | ≤ 1729  | 80.6   | 78.7   | 0.593  |
| GLS, %                                   | 0.779 | 0.667–0.873 | ≤ 16    | 74.2   | 70.5   | 0.447  |
| GWE, %                                   | 0.712 | 0.591–0.819 | ≤ 95    | 74.2   | 59.0   | 0.332  |
| GWW, mmHg%                               | 0.546 | 0.413–0.667 | ≥ 70    | 71.0   | 42.6   | 0.136  |
| Combined (morphology + GCW) <sup>‡</sup> | 0.986 | 0.950–1.000 | ≥ 0.77  | 96.8   | 100.0  | 0.968  |

AUC, area under the ROC curve; other abbreviations as above. <sup>‡</sup>Morphological variables form part of the HCM classification criteria and are reported as a diagnostic reference, not as competing tests (incorporation bias). <sup>‡</sup>Predicted probability from a logistic-regression model combining the max-thickness/PW ratio and GCW; Nagelkerke R<sup>2</sup>=0.935, overall accuracy 98.9%; the near-complete separation limits stable estimation. AUC comparisons (DeLong): morphology vs GCW p < 0.001; GCW vs GWI p = 0.039; GCW vs GLS p = 0.095; morphology vs combined p = 0.532.

In an exploratory combined model (morphology plus GCW), the increment in AUC over morphology alone was not statistically significant (DeLong p = 0.532); at the case level, the three borderline false positives generated by morphology alone were reclassified correctly by normal GCW values (Table 6). Given the small number of discordant cases and near-complete model separation, this observation is hypothesis-generating only.

## Diagnostic performance: HCM versus HHD (morphological overlap zone)

In the pre-specified analysis restricted to HCM and HHD, GCW again had the highest AUC among functional parameters (0.799; 95% CI 0.690–0.908; cut-off ≤ 1988 mmHg%; sensitivity 83.9%, specificity 67.7%; p < 0.001), superior to GWI (AUC 0.747; p < 0.001) and GLS (AUC 0.665; p = 0.018). GWE (AUC 0.593; p = 0.200) and GWW (AUC 0.585; p = 0.242) did not discriminate significantly between the two groups (Table 7, Fig. 3). The stability of the GCW cut-off across the two analyses (≤ 1983 and ≤ 1988 mmHg%) suggests that this threshold reflects a physiological boundary between the two hypertrophies rather than an artifact of the comparison group.

Table 7

Diagnostic accuracy of functional parameters for HCM versus HHD (morphological overlap zone).

| Variable                                                                                                                                                                                                                                                      | AUC   | 95% CI      | Cut-off | Sens % | Spec % |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-------------|---------|--------|--------|
| GCW, mmHg%                                                                                                                                                                                                                                                    | 0.799 | 0.690–0.908 | ≤ 1988  | 83.9   | 67.7   |
| GWI, mmHg%                                                                                                                                                                                                                                                    | 0.747 | 0.624–0.869 | ≤ 1812  | 83.9   | 58.1   |
| GLS, %                                                                                                                                                                                                                                                        | 0.665 | 0.529–0.802 | ≤ 14.5  | 51.6   | 77.4   |
| GWE, %                                                                                                                                                                                                                                                        | 0.593 | 0.451–0.735 | —       | —      | —      |
| GWW, mmHg%                                                                                                                                                                                                                                                    | 0.585 | 0.442–0.728 | —       | —      | —      |
| Analysis restricted to HCM (n = 31) and HHD (n = 31), controls excluded. Positive outcome: HCM. Cut-offs by the Youden index. p-values: GCW < 0.001; GWI < 0.001; GLS 0.018; GWE 0.200; GWW 0.242. For GWE and GWW (non-significant), no cut-off is reported. |       |             |         |        |        |

## Interobserver variability

Agreement was excellent for GWI (ICC 0.967) and GCW (ICC 0.931; coefficients of variation 4.9% and 6.8%), good for GWE (ICC 0.830; CV 1.8%) and GWW (ICC 0.766; CV 34.7%). The higher coefficient of variation for GWW reflects the greater inherent variability of this lower-magnitude parameter (Table 8).

Table 8

Interobserver variability of myocardial work parameters (21 paired measurements).

| Parameter                                                                                                                                                                                                                                                                       | ICC   | 95% CI      | Bias   | 95% LoA           | CV % |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-------------|--------|-------------------|------|
| GWI, mmHg%                                                                                                                                                                                                                                                                      | 0.967 | 0.921–0.987 | + 15.5 | −170.9 to + 201.1 | 4.9  |
| GCW, mmHg%                                                                                                                                                                                                                                                                      | 0.931 | 0.838–0.971 | + 49.3 | −239.1 to + 337.3 | 6.8  |
| GWW, mmHg%                                                                                                                                                                                                                                                                      | 0.766 | 0.517–0.897 | + 15.3 | −52.6 to + 84.2   | 34.7 |
| GWE, %                                                                                                                                                                                                                                                                          | 0.830 | 0.631–0.927 | −0.30  | −4.1 to + 2.3     | 1.8  |
| ICC, intraclass correlation coefficient (two-way random-effects, absolute agreement, single measures); LoA, limits of agreement ( $\pm 1.96$ SD); CV, coefficient of variation. Interpretation per Koo and Li: <0.50 poor; 0.50–0.75 moderate; 0.75–0.90 good; >0.90 excellent. |       |             |        |                   |      |

## DISCUSSION

This study demonstrates that myocardial work parameters identify subclinical mechanical dysfunction and differ characteristically among patients with nonobstructive HCM, with HHD, and without structural heart disease, with patterns that reflect distinct pathophysiological mechanisms. The main findings were: (1) GWI and GCW were significantly lower in HCM than in HHD and controls, despite preserved ejection fraction in all groups; (2) HHD did not differ from controls in GWI or GCW, suggesting that in treated hypertension myocardial work may be preserved; (3) GCW was the functional parameter with the highest diagnostic accuracy, superior to GLS; and (4) in an exploratory combined model, GCW

reclassified the borderline false positives generated by morphology, although without a statistically significant increment in AUC.

## Reduced myocardial work in HCM

The reduction in MW indices in HCM despite preserved ejection fraction is consistent with prior work relating GCW to the extent of fibrosis on late gadolinium enhancement and to prognosis.[21, 22] In this series, 48.4% of HCM patients had GCW < 1550 mmHg%, a previously proposed fibrosis threshold,[23] and 29.0% had GWI below the lower NORRE limit of 1270 mmHg%.[24] Among the 17 HCM patients with available cardiac magnetic resonance, 16 (94.1%) had positive late gadolinium enhancement, and 9 (52.9%) had GCW < 1550 mmHg%, all of them late-gadolinium-positive – an exploratory observation consistent with the hypothesis that GCW reflects the fibrotic substrate, although resonance in the full cohort and larger samples are required to validate this association. This mechanistic link has been extended to the obstructive phenotype using a corrected pressure-strain method, further supporting the association between reduced constructive work and histological fibrosis.[25] Reduced GWE and elevated GWW in HCM reflect the mechanical disorganization arising from myofibrillar disarray and interstitial fibrosis, present even with preserved global ejection fraction. Comparable subclinical impairment has been described in the apical phenotype, reinforcing that MW captures dysfunction across the HCM spectrum.[26]

## Myocardial work behavior in HHD

The absence of a significant difference between HHD and controls in GWI ( $p = 0.142$ ) and GCW ( $p = 0.763$ ) contrasts partly with prior reports of elevated GWI in HHD, interpreted as a compensatory response to chronic pressure overload.[18] Two methodological differences are relevant. First, in this series the HHD group had treated hypertension with multiple antihypertensive classes (angiotensin-receptor blockers in 71.0%, calcium-channel blockers in 61.3%) and a lower mean systolic pressure than earlier studies in which medication was withheld before assessment, which may have attenuated the hemodynamic effect on MW and brought values closer to controls.[18, 27] Second, the HHD group was phenotypically heterogeneous: 9 of 31 patients (29%) had concentric remodeling with elevated RWT but normal LV mass – an earlier adaptive stage – with GWI and GCW close to control values, whereas the 20 patients with established concentric hypertrophy had lower values. This heterogeneity may also explain the absence of a significant GWE difference between HCM and HHD. Notably, GWW and GWE findings were concordant with prior work: both pathological groups showed elevated GWW and reduced GWE relative to controls, without a significant HCM-versus-HHD difference, suggesting that impaired mechanical efficiency is a common feature of ventricular hypertrophy regardless of etiology.[18] Importantly, the study was not powered to exclude a modest elevation of myocardial work in HHD, and the null finding should be interpreted with this limitation in mind.

## Diagnostic performance and differential diagnosis

Because maximal thickness and the maximal-thickness/posterior-wall ratio form part of the HCM classification criteria, their near-perfect AUCs reflect incorporation bias and are reported as a reference, not as competing tests. The clinically meaningful diagnostic question concerns the functional parameters that do not enter classification. Among these, GCW showed the highest accuracy (AUC 0.852 for HCM vs non-HCM; 0.799 for HCM vs HHD), superior to GLS, consistent with its conceptual advantage: by incorporating afterload into the estimation of deformation, GCW distinguishes the intrinsic contractile impairment of HCM from the reduced deformation attributable to pressure overload in HHD. [12, 13] This is coherent with evidence that speckle-tracking strain and work indices outperform isolated morphological parameters in the differential diagnosis of hypertrophic phenotypes,[14, 20] and that MW discriminates infiltrative from sarcomeric disease.[20] The stability of the GCW cut-off across the broad and restricted analyses ( $\leq 1983$  and  $\leq 1988$  mmHg%) supports a physiological rather than sample-dependent threshold.

The combined morphological-functional model is best regarded as hypothesis-generating: the increment in AUC over morphology alone was not significant (DeLong  $p = 0.532$ ), and the reclassification of borderline cases rests on few discordant patients and near-complete model separation. GCW does not replace morphological assessment but may offer a complementary functional dimension in cases with a borderline maximal-thickness/posterior-wall ratio, a hypothesis that could complement existing multiparametric scores[15] and warrants prospective testing in adequately powered cohorts with cardiac magnetic resonance adjudication.

## **Influence of clinical variables and correlations**

Multivariable regression confirmed that an HCM diagnosis is an independent negative predictor of GWI and GCW even after adjustment for systolic pressure, age, and sex, with a standardized coefficient exceeding that of systolic pressure — indicating that the diagnosis exerts a proportionally greater impact on myocardial work than the pressure level. This is pathophysiologically coherent: whereas in HHD the reduction in MW is partly compensated by pressure overload, in HCM the impairment of constructive work is intrinsic to the sarcomeric disease and independent of afterload.[3, 12] Systolic pressure remained a positive independent predictor, consistent with the compensatory role of MW in chronic pressure overload.[27] Age and sex were not significant predictors, indicating that the between-group differences reflect the disease substrate rather than demographic differences — relevant given that the HHD group was significantly older and predominantly female.

The negative correlations of GWI and GCW with maximal thickness, LV mass, and the maximal-thickness/posterior-wall ratio confirm that the degree of hypertrophy, regardless of etiology, conditions the reduction in constructive work. The strong positive correlation between MW and GLS indicates that both methods partly capture the same substrate, while the absence of correlation with ejection fraction reinforces that MW provides information independent of conventional systolic parameters.[9] GWE showed the strongest correlation of the analysis with LV mass, suggesting it predominantly reflects global energetic efficiency common to different forms of hypertrophy rather than an etiology-specific marker, consistent with its lack of discriminatory capacity between HCM and HHD.

# Reproducibility

Interobserver agreement was excellent for GWI and GCW and good for GWE and GWW, comparable to or better than that typically reported for GLS.[28, 29] The excellent reproducibility of GCW is particularly relevant given its role as the most accurate functional discriminator in this series, reinforcing its clinical and research applicability. The higher coefficient of variation for GWW reflects the greater inherent variability of this lower-magnitude parameter, a limitation to be considered in its clinical interpretation.

## Limitations

Several limitations should be acknowledged. The sample size was powered for the large between-group effect observed in HCM and does not protect the null HHD-versus-control finding against a type II error. Optimal cut-offs were derived by the Youden index in the same sample without internal (bootstrap) or external validation and are therefore optimistic; the combined model exhibited near-complete separation, precluding stable coefficient estimates. Group definition for HHD relied on self-reported diagnosis and medication use rather than a formal blood-pressure threshold, introducing partial circularity into the interpretation of preserved MW in treated hypertension. Groups were not matched for age, sex, or systolic pressure, although the multivariable analysis showed that the diagnosis remained an independent predictor after adjustment. The noninvasive estimation of intraventricular pressure assumes equivalence between brachial systolic pressure and peak LV systolic pressure, which may be imprecise in patients with marked arterial stiffness, more prevalent in HHD. The HCM diagnosis was not confirmed by cardiac magnetic resonance or genetic testing in all patients, although resonance was available in 54.8% (late-gadolinium-positive in 94.1%) and sarcomeric mutations were confirmed in 12.9%. Rates of missing data for glomerular filtration rate (18.5%)[30] and pulmonary artery systolic pressure (38.0%) limited interpretation of these variables, none of which was a primary outcome. Finally, the single quaternary-center setting with two care environments may limit generalizability.

## CONCLUSIONS

Myocardial work indices identify subclinical mechanical dysfunction in nonobstructive HCM and HHD with preserved ejection fraction, with pathophysiologically distinct patterns. GWI and GCW were significantly lower in HCM, whereas GWW and GWE were impaired in both pathological groups without a significant difference between them. An HCM diagnosis was an independent predictor of reduced GWI and GCW of greater magnitude than systolic pressure. Among functional parameters, GCW showed the highest diagnostic accuracy and the best reproducibility, and may offer complementary, hypothesis-generating information in morphologically borderline cases. Prospective, adequately powered studies with systematic cardiac magnetic resonance adjudication and validated cut-offs are warranted to confirm the incremental diagnostic value of GCW.

## Non-standard Abbreviations and Acronyms

**GCW** = global constructive work; **GLS** = global longitudinal strain; **GWE** = global work efficiency; **GW** = global work index; **GW** = global wasted work; **HCM** = hypertrophic cardiomyopathy; **HHD** = hypertensive heart disease; **MW** = myocardial work; **RWT** = relative wall thickness.

## Declarations

### Funding statement

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### Conflict of interest disclosure

The authors declare no conflicts of interest.

### Ethics approval statement

The study was approved by the Research Ethics Committee of Hospital Universitário Pedro Ernesto, Universidade do Estado do Rio de Janeiro (CAAE 73088023.0.0000.5259; opinion no. 6.275.829), and was conducted in accordance with the Declaration of Helsinki and Brazilian National Health Council Resolution 466/12.

### Patient consent statement

All participants provided written informed consent prior to inclusion.

### Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request, subject to ethics-committee approval, given restrictions related to patient privacy.

### Artificial intelligence disclosure

The authors used an AI-assisted tool to support the drafting and language editing of the manuscript. All content, including data, analyses, and interpretations, was reviewed, verified, and validated by the authors, who take full responsibility for the accuracy and integrity of the work. AI tools were not used to generate or alter research data, and are not listed as authors.

### Permission to reproduce material from other sources

Not applicable.

### Clinical trial registration

Not applicable (observational study).

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Figures

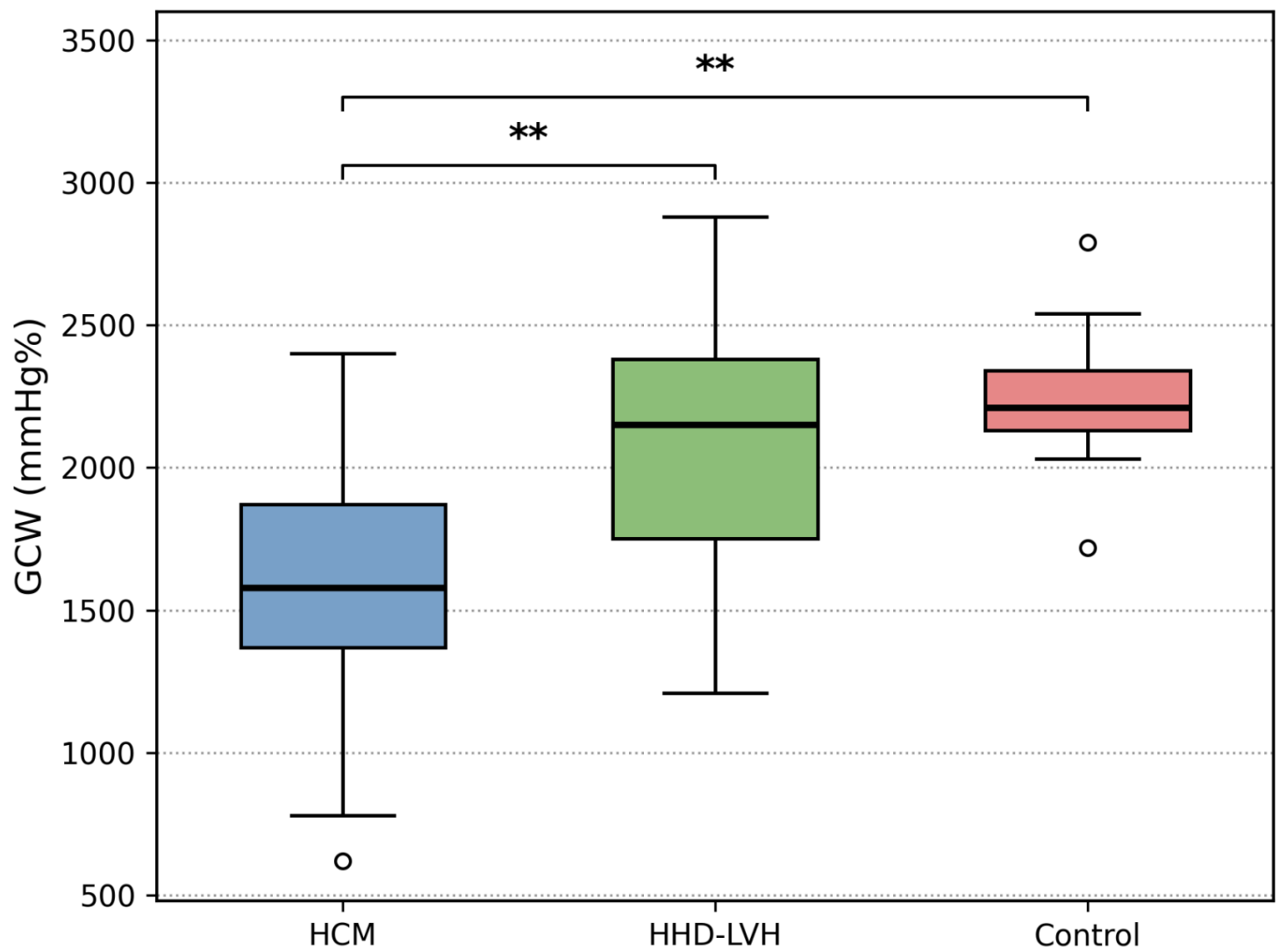


Figure 1

Global constructive work (GCW) across the study groups. GCW was significantly lower in nonobstructive hypertrophic cardiomyopathy (HCM) than in hypertensive heart disease (HHD) and controls, with no significant difference between HHD and controls. Boxes represent the interquartile range, the horizontal line the median, and whiskers the range excluding outliers (circles). \*\*p<0.01 (Bonferroni post-hoc). Between-group comparisons are detailed in Table 3

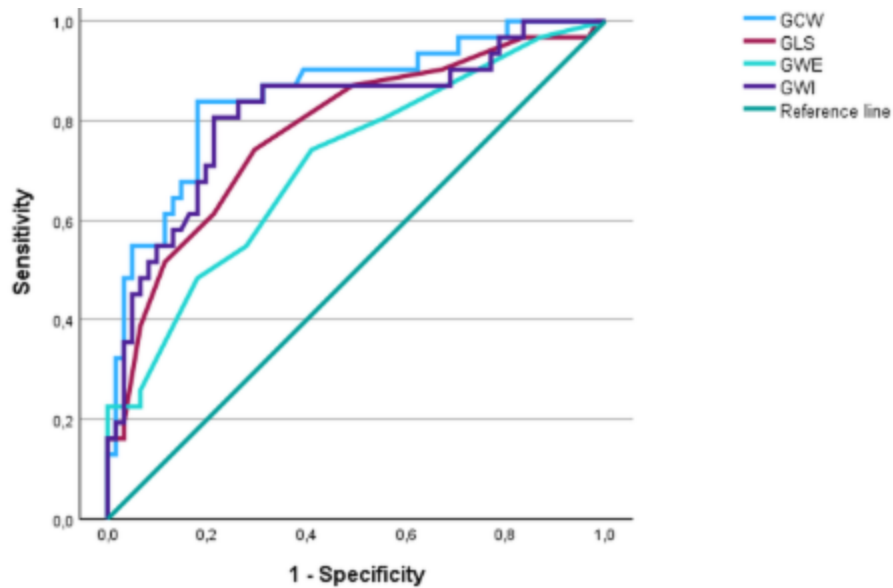


**Figure 2**

ROC curves of myocardial work parameters and global longitudinal strain for the discrimination of HCM versus non-HCM. GCW, global constructive work (AUC 0.852); GWI, global work index (AUC 0.816); GLS (AUC 0.779); GWE (AUC 0.712)

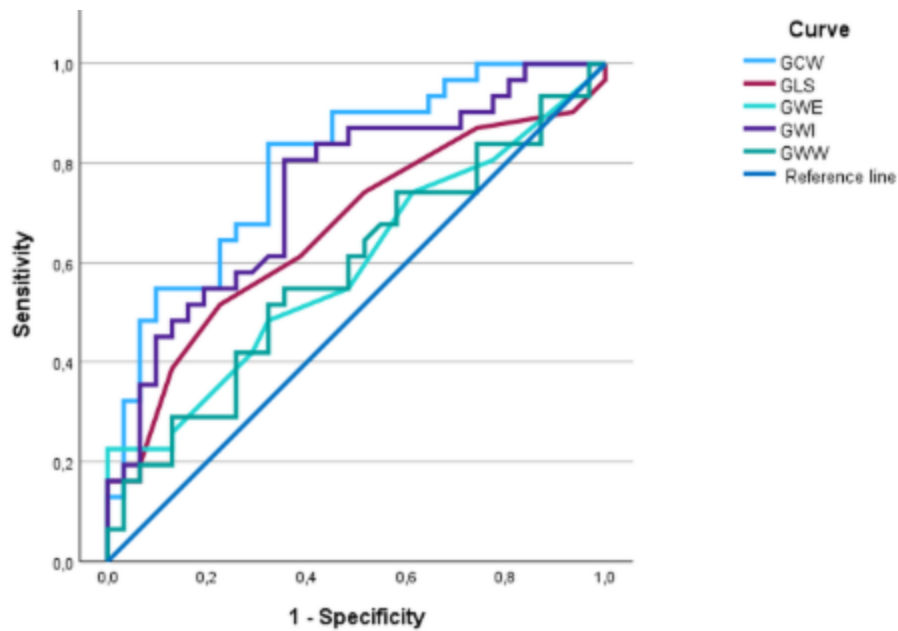


**Figure 3**

ROC curves of functional parameters for the discrimination of HCM versus HHD (controls excluded). GCW, global constructive work (AUC 0.799); GWI (AUC 0.747); GLS (AUC 0.665); GWE (AUC 0.593); GWW (AUC 0.585)