

# Myocardial Work Appraisal in Transthyretin Cardiac Amyloidosis and Nonobstructive Hypertrophic Cardiomyopathy



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**Global left ventricular (LV) myocardial work (MW) indexes can be recognized at ultrasound imaging from the LV pressure/global longitudinal strain (GLS) loop analysis. A total of 4 indexes, global work index (GWI), global constructive work (GCW), global wasted work (GWW), and global work efficiency (GWE), have been demonstrated to overcome the methodological limitations of GLS and provide useful information on myocardial dysfunction in some clinical settings. Although impaired MW indexes have been demonstrated in patients with transthyretin cardiac amyloidosis (ATTR) or with nonobstructive hypertrophic cardiomyopathy (HCM), there are no comparative studies at present. This study aimed to describe the characteristics of MW in both these clinical settings compared with patients with well-controlled hypertension (HTN). A total of 83 patients, 32 with ATTR (aged  $70 \pm 11$  years, 32% mutated, 68% wild-type, 72% men), 29 with HCM (aged  $57 \pm 17$  years), and 22 HTN controls (aged  $56 \pm 5.6$  years, 59% men) were prospectively enrolled at 2 clinical centers. All participants had New York Heart Association class I or II. Overall, the LV mass index was greater in both study groups than in HTN, whereas the LV ejection fraction (EF) was significantly lower in ATTR compared with other groups. Based on this finding, patients with ATTR were further divided into 2 subgroups: ATTR1 (LVEF  $\leq 0.50$ ),  $n = 14$  (44%) and ATTR2 (LVEF  $> 0.50$ ),  $n = 18$  (56%). Overall, the GWI and GCW were lower in all ATTR patients (mostly in ATTR1) than in the other groups ( $p < 0.001$ ), whereas only small differences in GWE and none in GWW were found among the groups. Of interest, the pairwise comparison and receiver operating characteristic analysis in preserved LVEF patients showed that GWI was a better discriminator of ATTR2 from HCM patients than GLS, with the cut-off value  $\leq 1,419$  mm Hg% (89% sensitivity; 55% specificity;  $p = 0.013$ ). In conclusion, MW analysis was confirmed to be a modern way to investigate myocardial function in patients with hypertrophic phenocopies. GWI and GCW were more impaired in patients with ATTR compared with HCM and HTN controls. Furthermore, this study likely revealed an additional discriminative value of GWI over GLS alone in preserved LVEF settings. © 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) (Am J Cardiol 2023;208:173–179)**

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The pathophysiology and management of cardiac amyloidosis (CA) and hypertrophic cardiomyopathy (HCM) are unceasingly under investigation. Despite similarities in left ventricular (LV) chamber size and wall thickness

on standard echocardiography investigation, discrepancies on LV function are detected by advanced imaging.<sup>1,2</sup> HCM is a genetic sarcomere disorder of the myocytes, often resulting in a variable tissue fibrosis, whereas CA is an interstitial disease caused by misfolded amyloid fibril deposit, with ensuing ceaseless electromechanical dysfunction. Amyloid disease is the consequence of a disorder involving the carrier protein called transthyretin, either genetically determined (transthyretin CA [ATTR] mutated [ATTRv]) or acquired (ATTR wild-type [ATTRwt]), as well as due to hematologic dyscrasia (amyloid light chain [AL] form). Typically, cardiac involvement is more frequent in the ATTRwt variant, largely affecting older male patients.<sup>3,4</sup>

Patients with either ATTR-CA (hereinafter ATTR) or HCM often present to outpatient clinics for several reasons, which includes typical and atypical symptoms, exercise

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intolerance, or just for clinical examination. As in the steady-state disease, their echocardiographic picture cannot be easily differentiated because such patients show analogous LV mass and LV ejection fraction (LVEF), albeit a greater impairment in LV systolic and diastolic function may be found in CA.<sup>2-4</sup>

Modern ultrasound techniques provide attractive functional markers, such as tissue Doppler imaging, automated endocardial border detection, 3-dimensional imaging, and speckle-tracking derived global longitudinal strain (GLS), that can help physicians in making a diagnosis, understanding pathophysiology, and addressing proper treatment in the various cardiac settings.<sup>5,6</sup>

Although GLS well identifies subclinical LV dysfunction in patients with hypertrophic phenotypes, it suffers from being load-dependent. More recently, the analysis of pressure-strain loop derived myocardial work (MW) has been proposed as an advanced method for assessing myocardial function overcoming the GLS limitation.<sup>6</sup>

MW provides a wide-ranging investigation of myocardial function, covering the systolic phase and diastolic active relaxation and reflecting the whole heart's mechanics, such as in invasive hemodynamic testing.<sup>7-9</sup> Although studies on MW are available from hypertrophic patients, comparative studies in patients with ATTR versus HCM are missing.

This study aimed to describe the characteristics of the MW indexes in both clinical settings and compared with patients with well-controlled systemic hypertension.

## Methods

From September 2022 to March 2023, all patients consecutively admitted to the outpatient heart failure (HF) clinics at Messina and Catania University Hospitals (Italy) for scheduled clinical follow-up previously or newly diagnosed with ATTR or HCM were enrolled in this observational prospective study.

According to the 2021 European Society of Cardiology guidelines, the preliminary assessment was based on electrocardiogram (ECG) findings. The diagnosis of either ATTRv or ATTRwt required imaging criteria at ultrasound or cardiac magnetic resonance and was confirmed by total body technetium-99m pyrophosphate bone scintigraphy (Perugini score 2 or 3) and/or molecular genetic testing.<sup>4</sup> Patients with AL forms were excluded.

Sarcomere HCM was diagnosed based on the current American Heart Association/American College Cardiology (ACC) guidelines<sup>10</sup> as follows: (1) LV wall thickness  $\geq 15$  mm in any segment in a nondilated chamber in the absence of relevant causes leading to LV hypertrophy; (2) typical ECG pattern; (3) family history of HCM, except in case of probands; and (4) nonobstructive physiology (as for LV outflow gradient:  $>30$  mm Hg at rest, exercise, and/or Valsalva maneuver).

The control group was composed of well-treated patients in stage 1 hypertension (HTN) according to the 2017 US guideline,<sup>11</sup> although a peak office systolic value of 140 mm Hg was accepted in someone at enrollment. The occurrence of a high BP was also recognized in both study groups. All participants had no history of acute coronary

syndrome, stable or unstable angina, end-stage heart disease, atrial fibrillation, and/or moderate-to-severe heart valve disease.

A commercially available ultrasound machine (Vivid E9; GE Vingmed Ultrasound, Horten, Norway) was used to perform transthoracic echocardiography at both clinical centers. Suitable acoustic windows for cardiac chamber size and functional measurements, color Doppler sampling, strain, and MW analysis were mandatory at patient enrollment. The standard measurements were achieved by 2 expert examiners from parasternal long-/short-axis views and 2-, 3-, and 4-chamber apical views.<sup>12</sup> The maximum LV wall thickness from the base to the apex served to ascertain the hypertrophic phenotype. Left cardiac chamber (atrial and ventricular) volumes were measured using the biplane Simpson rule method, indexed to body surface area, and the LVEF calculated automatically by the ultrasound machine software. Diastolic function was investigated using the Doppler mitral inflow peak E-wave velocity, divided by the peak early diastolic tissue velocity as the mean value from the septum and mitral annulus, expressed as the E/e' ratio. As previously mentioned, dynamic obstructive physiology was ruled out by measuring the LV outflow tract peak systolic gradient at continuous-wave Doppler sampling under color-Doppler guidance at rest or/and stress.

For the GLS and MW assessment, digitally stored video-clips were analyzed offline using a dedicate software (EchoPAC; GE Vingmed Ultrasound, Horten, Norway). An automated speckle-tracking quantification of GLS was performed at an ultrasound frame rate of  $\geq 50$  frame per second and manually amended by an expert software-skilled examiner (physician). The LV pressure/strain loop analysis was performed to achieve the MW indexes (Figure 1). Systolic blood pressure was measured just before the ultrasound examination, after the patient had been at rest for 15 minutes and using an appropriate brachial cuff. The MW indexes were calculated at the working station as the average values of the respective segmental values (17-segment model).<sup>12</sup> According to opinion leaders from the ACC and European Society of Cardiology, the MW indexes were termed as follows: (1) global work index (GWI; mm Hg%), which is the total work performed from the mitral valve closure until its opening plus isovolumetric contraction and relaxation; (2) global constructive work (GCW; mm Hg%), which is the MW performed during LV shortening; (3) global wasted work (GWW; mm Hg%), which is the work during LV stretching and lengthening but with no contribution to cardiac output (lost energy); and (4) global work efficiency (GWE; mm Hg%), which is the ratio between GCW and the sum of GCW + GWW.<sup>7,8,13</sup>

Continuous variables are presented as mean  $\pm$  SD, median (interquartile range), or median  $\pm$  standard error, when appropriate. Categorical variables are expressed as absolute numbers and respective percentages (%). The comparison between 2 or more groups for continuous variables were performed using the 1-way analysis of variance on log-transformation data. Scheffé testing was applied for multiple group comparison. Categorical variables were compared using the chi-square test for overall test and the Fisher's exact test for pairwise group analysis. Receiver

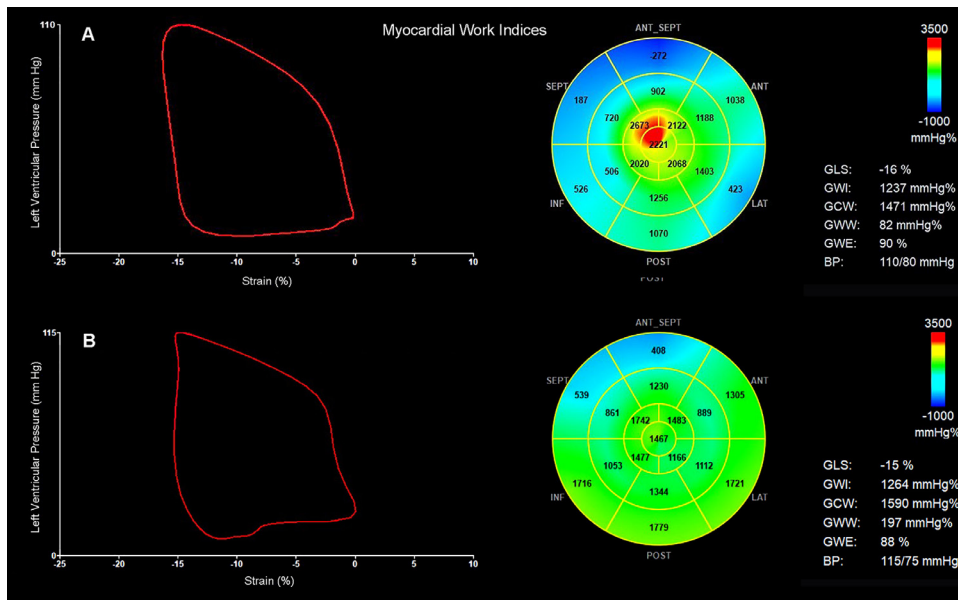


Figure 1. Illustration of myocardial work bull's-eye analysis (color scale) in 2 patients from our study population, affected by ATTR2 (A) or HCM (B). Red lines in graphics indicate respective pressure/strain loop analyses for myocardial work.

operating characteristic (ROC) curves were also performed for discriminating patients with ATTR from those with HCM by GWI and GLS measurements. The area under the curve, sensitivity, and specificity were calculated from the true/false and positive/negative classifications using standard definitions.

The intraobserver variability for MW parameters and GLS was calculated on a subset of 20 patients by repeating the measurements 3 times on different days. The null hypothesis was rejected at 2 tails for  $p < 0.05$ .

Every patient gave written informed consent to the echocardiographic study. The local cardiology research board approved the observational design of the study, warranting all personal information to be concealed.

## Results

A total of 83 patients, 32 with ATTR (mean aged  $70 \pm 11$  years), 29 with HCM (mean aged  $57 \pm 17$  years) and 22 HTN controls (mean aged  $56 \pm 5.6$  years) were enrolled. Demographic and clinical characteristics are listed in Table 1. Apart from in HTN controls, stage 1 HTN was also recognized in some patients from both study groups, mainly in the HCM group. Most patients (73% ATTR, 50% HCM, and 40% HTN) had New York Heart Association class II and nobody had NYHA III or IV. A total of 22 patients with ATTR were classified as ATTRwt (69%) and 10 were ATTRv (31%). Consequently, these patients were older than those with HCM and controls ( $p < 0.01$ ). No differences were observed regarding body surface area, heart

Table 1  
Baseline demographic and clinical characteristics of the study population

Variable	ATTR (n=32)	HCM (n = 29)	HTN (n = 22)	p-value
Age (years)	$70 \pm 11$	$54 \pm 17$	$56 \pm 6$	<0.01
Males (%)	23 (72 %)	21 (72 %)	13 (59 %)	-
BSA (m <sup>2</sup> )	$1.8 \pm 0.2$	$1.9 \pm 0.2$	$1.9 \pm 0.2$	0.134
Systolic blood pressure (mmHg)	123 (IQR 110-132)	130 (IQR 120-140)	136 (IQR 120-140)	0.005
Diastolic blood pressure (mmHg)	81 (IQR 75-85)	80 (IQR 69-85)	82 (IQR 79-86)	0.095
Hypertension stage 1	2 (6.5 %)	10 (34 %)	22 (100 %)	0.001
Heart rate (bpm)	$71 \pm 9$	$67 \pm 11$	$69 \pm 12$	0.375
NYHA Class I	10 (31 %)	15 (52 %)	13 (59 %)	0.046
NYHA Class II	22 (69 %)	14 (48 %)	9 (41 %)	0.035
Cigarette Smoke	3 (9.4 %)	6 (21 %)	8 (36 %)	<0.01
Beta-blockers	9 (28 %)	23 (79 %)	10 (45 %)	0.001
ACE-inhibitors/ARB	4 (12 %)	7 (24 %)	18 (82 %)	0.001
Dihydropyridine CCB*	-	3 (10 %)	10 (45 %)	<0.01
Verapamil/Diltiazem	-	5 (17 %)	-	-
Diuretics	16 (50 %)	3 (10 %)	7 (32 %)	<0.01

Data are presented as mean  $\pm$  SD, median (IQR) or number (%).

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blockers; CCB = calcium channel blockers.

\* Alone or in a combination with ACE-in or ARB.

Table 2  
Main echocardiographic findings

Variable	ATTR (n=32)	HCM (n=29)	HTN (n=22)	ATTR vs HCM	HCM vs HTN	ATTR vs HTN
Left atrial volume index (ml/m <sup>2</sup> )	47 ± 13	46 ± 21	29 ± 7	0.845	<0.001	<0.001
LV end-diastolic volume index (ml/m <sup>2</sup> )	50 ± 17	50 ± 17	48 ± 11	0.951	0.623	0.536
LV end-systolic volume index (ml/m <sup>2</sup> )	26 ± 10	18 ± 7	19 ± 4	<0.001	0.475	0.001
LV ejection fraction (%)	49 ± 10	64 ± 7	60 ± 5	<0.001	0.022	<0.001
Stroke volume (ml)	43 ± 15	60 ± 26	54 ± 15	0.002	0.300	0.033
LV mass index (g/m <sup>2</sup> )	161 ± 40	146 ± 42	80 ± 15	0.165	<0.001	<0.001
E/E' ratio	17 ± 6	10 ± 4	6.5 ± 2	<0.001	<0.001	<0.001
Global longitudinal strain, GLS (%)	-12 ± 4	-14 ± 4	-19 ± 2	0.008	<0.001	<0.001
Global work index, GWI (mm Hg%)	1039 ± 354	1442 ± 404	1947 ± 305	<0.001	<0.001	<0.001
Global constructive work, GCW (mm Hg%)	1267 ± 391	1633 ± 440	2326 ± 329	0.001	<0.001	<0.001
Global wasted work, GWW (mm Hg%)	145 ± 114	143 ± 141	131 ± 53	0.955	0.677	0.599
Global work efficiency, GWE (%)	86 ± 7	90 ± 7	94 ± 2	0.053	0.016	<0.001

Numbers are mean value ± SD. Pairwise group analyses were performed at Fisher's exact test.

ATTR = transthyretin cardiac amyloidosis; HCM = hypertrophic cardiomyopathy; HTN = hypertensive patients; E/E' = early diastolic mitral inflow velocity / tissue early Doppler velocity (average value); LV = left ventricular/ventricle.

rate, blood pressure at rest, and LV mass index between the study groups.

The main echocardiographic measurements and MW indexes are listed in Table 2. Atrial chamber size and LV mass index were greater in patients with ATTR and HCM than in controls. LV ejection fraction and stroke volume were lower in the ATTR group because of some patients who had LVEF ≤0.50. This implied that the end-systolic LV volume was greater in size than in patients with HCM and HTN who all had LVEF >0.50. GLS was impaired in both study groups than in HTN, but in ATTR the most (p = 0.008), as well as GWI and GCW (p <0.001). GWE was similarly lower in patients with ATTR and HCM than in controls; however, there was no difference regarding the GWW.

In addition, according to the recent remonstrations of a potential prognostic impact for GWI <1,043 mm Hg% in patients with CA,<sup>14</sup> lower values were found in 71% of ATTR1, 28% of ATTR2, and 21% of HCM but in none in patients with HTN (p <0.001).

Considering the proportion of patients with ATTR with mildly impaired LVEF according to the 2022 ACC/American Heart Association HF guidelines,<sup>15</sup> we divided those patients into 2 subgroups: (1) ATTR1, with LVEF ≤0.50 (n = 14, 44%) and (2) ATTR2 (n = 18, 56%), with LVEF >0.50. As expected, MW indices were impaired primarily in the formed subgroup, with a mean GWI value of 864 ± 323 mm Hg% in patients with ATTR1 versus 1,175 ± 322 mm Hg% in ATTR2 (p = 0.01); GCW was 1,071 ± 355 versus 1,420 ± 355 mm Hg% (p = 0.01), respectively. Only small differences in GWE and none in GWW were found among groups (Figure 2), as well as LV mass index was comparable at Fisher's exact test (160.3 ± 40.1 vs 146.2 ± 41.7 g/m<sup>2</sup>, respectively, p = 0.26).

Interestingly, the pairwise evaluation of the heart failure with preserved ejection fraction settings, such as ATTR2 versus HCM groups, once more confirmed GWI as the best discriminator of infiltrative from sarcomere disease, with a mean value of 1,175 ± 322 mm Hg% in ATTR2 versus 1,442 ± 404 mm Hg% in patients with

HCM (p <0.02). The superiority of GWI was further validated at the ROC analysis, with an associated value of 1,419 mm Hg% and area under the curve = 0.693 compared with GLS (Figure 3).

Overall, the intraobserver variability for the MW parameters and GLS was excellent. The index variability was ±1.0% for GWI (bias 20.7 mm Hg%), ±4.6% for GCW (bias 62.2 mm Hg%), ±7.0% for GWW (bias 2.2 mm Hg%), ±0.3% for GWE (bias 0.3 mm Hg%), and 4.8% (bias -0.4%) for GLS.

## Discussion

MW analysis represents an innovation in the ultrasound assessment of LV function in cardiac patients.<sup>7,8,13</sup> Original pathophysiologic insights are emerging from present studies to better understand the complex mechanics and energetic expenditure of the myocardial wall in various clinical settings, including hypertrophic phenocopies.<sup>14,16-18</sup>

Using the proposed indexes, this study demonstrates that myocardial performance is significantly impaired in terms of active contraction and relaxation in patients with ATTR (mainly) and HCM compared with healthy HTN controls who are expected to have some degree of myocardial impairment.<sup>19</sup> In effect, according to reference values provided by the Normal Reference Ranges for Echocardiography (NORRE) study,<sup>20</sup> The GWI, GCW, and GWE were also mildly impaired in HTN controls.

The most important discriminators in our study population were GWI and GCW, and the main findings likely confirmed their supportive value for a better recognition of the underlying mechanism of LV dysfunction, especially in preserved LVEF settings such as in ATTR2 and HCM, at risk for advanced disease progression.<sup>3,4</sup> In these patients, the ROC analysis suggests that GWI value ≤1,419 mm Hg% can discriminate infiltration from sarcomere cardiomyopathy with quite good sensitivity but with modest specificity, likely because of the multifaceted characteristics of such diseases.<sup>2-4,17</sup>

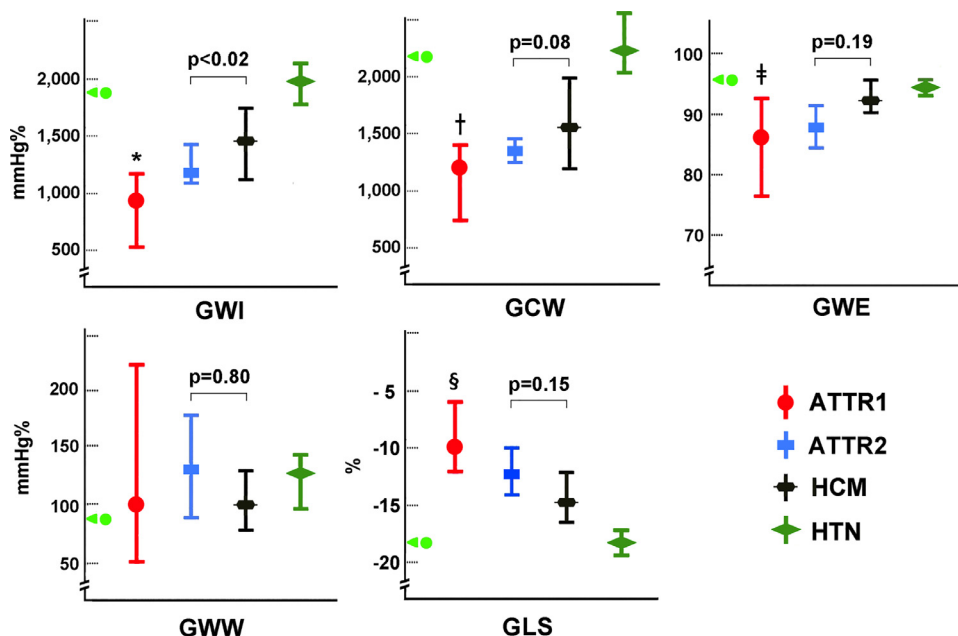


Figure 2. Graphics illustrating the median values  $\pm$  SE of MW indexes in patients with ATTR1 (LVEF  $\leq$ 50%), ATTR2 (LVEF >50%), HCM, and HTN. Green arrows on the y-axis indicate the reference values for each index, as reported by Manganaro et al<sup>20</sup> in the NORRE study. ANOVA on log-transformed data comparison among the groups:  $p < 0.001$  for GWI and GCW,  $p = 0.001$  for MWE, and  $p = \text{NS}$  for MWW. Scheffé comparison for ATTR1: \* $p < 0.05$  (vs all groups); † $p < 0.05$  (vs all groups); ‡ $p < 0.01$  (vs HTN); and § $p < 0.05$  (vs HCM/HTN). ANOVA = analysis of variance.

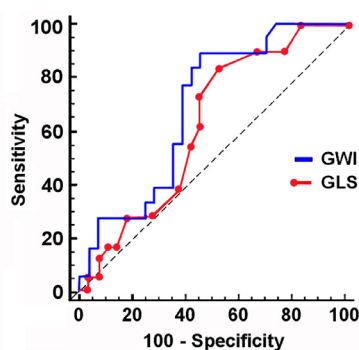
Despite the difference in GWI, GCW, and GWE among the groups, it was surprising not to find any discrepancy in GWW, which is probably caused by a wide range of measurements. In this regard, our findings are in accordance with the results by Palmiero et al,<sup>18</sup> who also found no differences in GWW between patients with ATTRwt and controls ( $79.7 \pm 34.6$  vs  $92.2 \pm 26.9$ ,  $p = \text{NS}$ ).

In our opinion, GLS remains a valid marker of LV dysfunction in most clinical settings, despite the above mentioned load dependency.<sup>21,22</sup> It should be remarked that MW indexes strictly derive from GLS, and the increasing body of evidence underscores the extra value of MW in replicating (noninvasively) the time-honored pressure/volume functional loop of the heart in several cardiac settings.<sup>7-9,13</sup> Of interest, the combination of GWI  $< 1.419$  mm Hg% and

GLS  $\geq -15\%$  from our ROC analysis may be advantageous for discriminating between ATTR and HCM and worthy to be tested in larger study populations.

Clemmensen et al<sup>14</sup> found that patients with amyloid disease and GWI  $< 1,043$  mm Hg% were at a higher risk of MACEs and/or mortality (GWI  $< 1,039$  mm Hg%), albeit their study included 34% of AL forms. According to these results, we disclosed a GWI value  $< 1,050$  mm Hg% in  $> 70\%$  of our patients with ATTR1, 28% of ATTR2, and 20% of HCM, then suggestive of a different prognostic impact.

This unlocks another issue that is the complex systolic and diastolic interplay linked to interstitial deposits of misfolded fibrils in patients with ATTR and AL forms, which likely conveys a different cardiovascular risk.<sup>4,14,23,24</sup> Despite the same level of myocardial hypertrophy, AL forms were found with significantly higher tissue inhibitor metalloproteinase-1 levels and metalloproteinase-9<sup>23</sup> and mechanical dispersion,<sup>24</sup> leading to much quicker LV dysfunction and worse outcomes than ATTR senile forms. Unfortunately, even these latter patients experience a manifold disease, as confirmed by the mislaid discriminating role for GWW in our study. Amyloid deposits not only involve the ventricles but also the atrial chambers,<sup>25</sup> cardiac valves, and extraventricular structures.<sup>26</sup> Hemodynamic conditions rapidly worsen with the systemic disease once neurologic manifestations, dysautonomia, unstable blood pressure, postural blood shift changes, and vascular disease become clinically relevant to a greater extent compared with patients with nonobstructive HCM.<sup>27,28</sup> Accordingly, most patients with ATTR are intolerant to antihypertensive and/or  $\beta$ -blocker drugs, which are advantageous therapies for patients with HCM and HTN who are free of autonomic disorders.<sup>3,10</sup> However, clinical improvements are expected



Variable	AUC	95% C.I.	Associated Value	Sensitivity	Specificity	P-value
GWI	0.693	0.541-0.819	$\leq 1,419$ mm Hg%	89%	55%	0.013
GLS	0.622	0.468-0.759	$\geq -15\%$	83%	48%	0.141

Figure 3. ROC curves for GWI and GLS discriminating patients with ATTR2 from patients with HCM. AUC = area under the curve; CI = confidence interval.

from modern treatment opportunities of ATTR misfolded proteins.<sup>4,29,30</sup>

Although the cardiovascular risk is higher in patients with nonobstructive HCM than in the general population, they usually get the clinical diagnosis in the fifth decade of life (and approximately 40% are women) or remain undiagnosed throughout life. Indeed, patients with HCM can be asymptomatic or have trivial symptoms for years, with preserved LV function for a long time. Diagnosis is often made on occasion ECG or intercurrent disease, and most patients are unaware that they are carriers of an inherited disease.<sup>3,10,31</sup> In these settings, other than cardiac resonance imaging,<sup>2</sup> transthoracic echocardiography is a mainstay of the diagnostic workup, and advanced techniques such as GLS and MW offer further chances to recognize subclinical LV dysfunction.<sup>12,13,22</sup>

The present findings also confirm the results by Galli et al<sup>32</sup> who found significantly impaired GCW but analogous GWW in patients with HCM (GCW = 1,599 ± 423 mm Hg%) compared with control subjects (2,248 ± 249 mm Hg%,  $p < 0.001$ ), which is somehow consistent with the presence of interstitial fibrosis. Hiemstra et al<sup>17</sup> observed the segmental GCW to decrease according to increased wall thickness in size, whereas the GWW in the anterior and apical segments was related to the presence of LV dyssynchrony.

A reason supporting the differences we found in GWI between patients with HCM and ATTR2 is the contractile compensation in the early stages of sarcomere hypertrophic disease. An increased number of myosin-actin crossbridge has been reported in response to the abnormal disarray-related generation of forces that increases calcium ion sensitivity of troponin complex and ATPase activity.<sup>33,34</sup> This mechanism likely subtends the better GWI as expression of the total ventricular work performed, at least in patients with preserved LVEF.

This study should be considered in light of potential technical and numerical limitations. Speckle-tracking-derived functional markers, including MW, need optimized acoustic windows for ultrasound examination and precise assessment of multiple parameters (including fluctuating blood pressure measurements). Although the software for calculating MW is mostly provided by a unique vendor, small errors in the assessment of GLS and postprocessing can result in a substantial in-group and/or between-group variability. Top quality imaging from each echocardiographic section is mandatory when processing functional markers,<sup>6–9</sup> and the proficient use of the working station for MW measurements require appropriate training (in our laboratory, there were 50 to 100 verified case analyses). These items may hinder a large consistency of the study population, and we preferred a single best skilled operator in each clinical Center for the purpose of our study. Thus, we cannot provide interobserver variability; however, our intraobserver reproducibility was excellent.

The case number was also limited by the rarity of patients with ATTR referred to our HF centers during the enrollment period, and this group was heterogeneous because 31% of the patients had ATTRv that may carry a different myocardial impairment than senile forms.<sup>4,14</sup>

Because of the consistency of our study, we could not investigate further (clinical or functional) discrepancies. Neither the effect of therapy nor the LV chamber in size and related changes in MW indexes were investigated. Lastly, it is important to consider the strong impact of aging on cardiovascular outcomes as a time-honored issue. Our ATTR group was much older than the others, and this unquestionably concurs to the greater MW impairment in such patients. Further studies on the role for MW indexes in detecting the evolutive progression toward obstructive physiology in HCM and overt HF in patients with ATTR are likewise encouraged.

In conclusion, this study underscored the usefulness of MW indexes in the recognition of LV dysfunction in hypertrophic phenocopies. Specifically, GWI and GCW were more impaired in patients with ATTR than in those with HCM and similar LV mass, and in both groups than in HTN controls. Although GLS remains an important functional marker in such settings, our findings also indicate an incremental value of GWI in discriminating patients with ATTR2 from patients with HCM, both with preserved LVEF. Further larger studies are needed to confirm the present results and shed light on the still unanswered pathophysiological issues.

#### Declaration of Competing Interest

The authors have no competing interests to declare.

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