Performance of non-invasive myocardial work to predict the first hospitalization for *de novo* heart failure with preserved ejection fraction

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Abstract

Aims Non-invasive myocardial work (MW) is a validated index of left ventricular (LV) systolic performance, incorporating afterload and myocardial metabolism. The role of MW in predicting the first hospitalization for *de novo* heart failure with preserved ejection fraction (HFpEF) is still unknown. We aim to investigate the diagnostic performance of MW to predict the first *de novo* HFpEF hospitalization in ambulatory individuals with preserved LV ejection fraction.

Methods and results Twenty-nine patients with transthoracic echocardiography performed at least 6 months before the first HFpEF hospitalization were compared with 29 matched controls. MW was derived as the area of pressure–strain loop using speckle-tracking and brachial artery blood pressure. Global work index, global constructive work, global wasted work (GWW), and global work efficiency (GWE) were collected. First HFpEF hospitalization and its combination with cardiovascular death [major adverse cardiovascular events (MACE)] and all-cause of death [major adverse events (MAE)] were assessed. At baseline, future HFpEF patients showed lower global work index, global constructive work, GWE, and higher GWW than controls (all $P < 0.05$). At admission vs. baseline, GWE significantly decreased, and GWW increased in the HFpEF group ($P < 0.05$), whereas no significant difference was observed in the controls over time. GWW, with a cut-off of 170 mmHg%, showed the largest area under the curve (AUC) to predict first HFpEF hospitalization [AUC = 0.80, 95% confidence interval (CI) 0.69–0.91, $P < 0.001$], MACE (AUC = 0.80, 95% CI 0.66–0.90, $P < 0.001$), and MAE (AUC = 0.79, 95% CI 0.62–0.88, $P = 0.001$). GWW > 170 mmHg% was associated with a 4-fold increase of MACE (HR = 4.5, 95% CI 1.59–13.12, $P = 0.005$) and a 3-fold higher risk of MAE (HR = 2.9, 95% CI 1.24–6.6, $P = 0.014$).

Conclusions In ambulatory patients with preserved LV ejection fraction and risk factors, GWW showed high accuracy to predict the first HFpEF hospitalization and its combination with mortality. The GWW routine assessment may be clinically helpful in patients with dyspnoea.

Introduction

Heart failure with preserved ejection fraction (HFpEF) shows a high prevalence and poor clinical outcomes.[1] Precise identifi-cation of HFpEF is challenging as the perception of dyspnea is subjective, and non-cardiac causes of dyspnoea are common. Accordingly to ASE/EACVI guidelines, echocardiographic assessment is the first pivotal step for the characterization of

the diastolic dysfunction and estimation of LV filling pressure.[2] Nevertheless, the performance of conventional parameters and algorithms is suboptimal, leaving a percentage of about 15% of patients with indeterminate diagnosis.[2–5] The persistence of a diagnostic "grey zone", together with an increased epidemiological burden of conditions predisposing to HFpEF, sparked the search for novel echocardiographic parameters. In this regard, LARS, measuring passive LA stretch, turned out to be a sensitive marker of LV diastolic dysfunction.[6,7] In addition, HFpEF is often associated with subtle abnormalities of left ventricular (LV) systolic function and metabolic alterations, which may contribute to exercise intolerance, pulmonary congestion and symptoms.[8–13] Hence, identifying these abnormalities among subjects with risk factors for the development of HFpEF might be clinically helpful to establish the diagnosis and assess the outcomes.

Non-invasive myocardial work (MW) has been recently proposed as a robust and reproducible index of LV systolic performance, which incorporates LV afterload and correlates with myocardial metabolism.[14–16] In HFrEF, MW has been able to predict reverse LV remodelling and outcomes in response to cardiac resynchronization or sacubitril/valsartan.[17–20] However, the clinical utility of MW in HFpEF is unknown. In HFpEF, as a clinical condition characterized by elevated and variable afterload and frequent metabolic alterations, MW might provide more accurate information on myocardial status than load-dependent indices, that is, LV ejection fraction (LVEF) or global longitudinal strain (GLS).[21] Therefore, the present study aimed to assess the performance of MW parameters to identify patients with future HFpEF and to predict the first hospitalization for *de novo* HFpEF in ambulatory individuals with preserved LVEF.

Figure 1 Identification of the study groups and flow chart. Abbreviations: ACS, acute coronary syndrome; BP, blood pressure; HFpEF, heart failure with preserved ejection fraction; LVEF, LV ejection fraction; MW, myocardial work; TTE, 2D-Transthoracic echocardiogram; VHD, valvular heart disease.
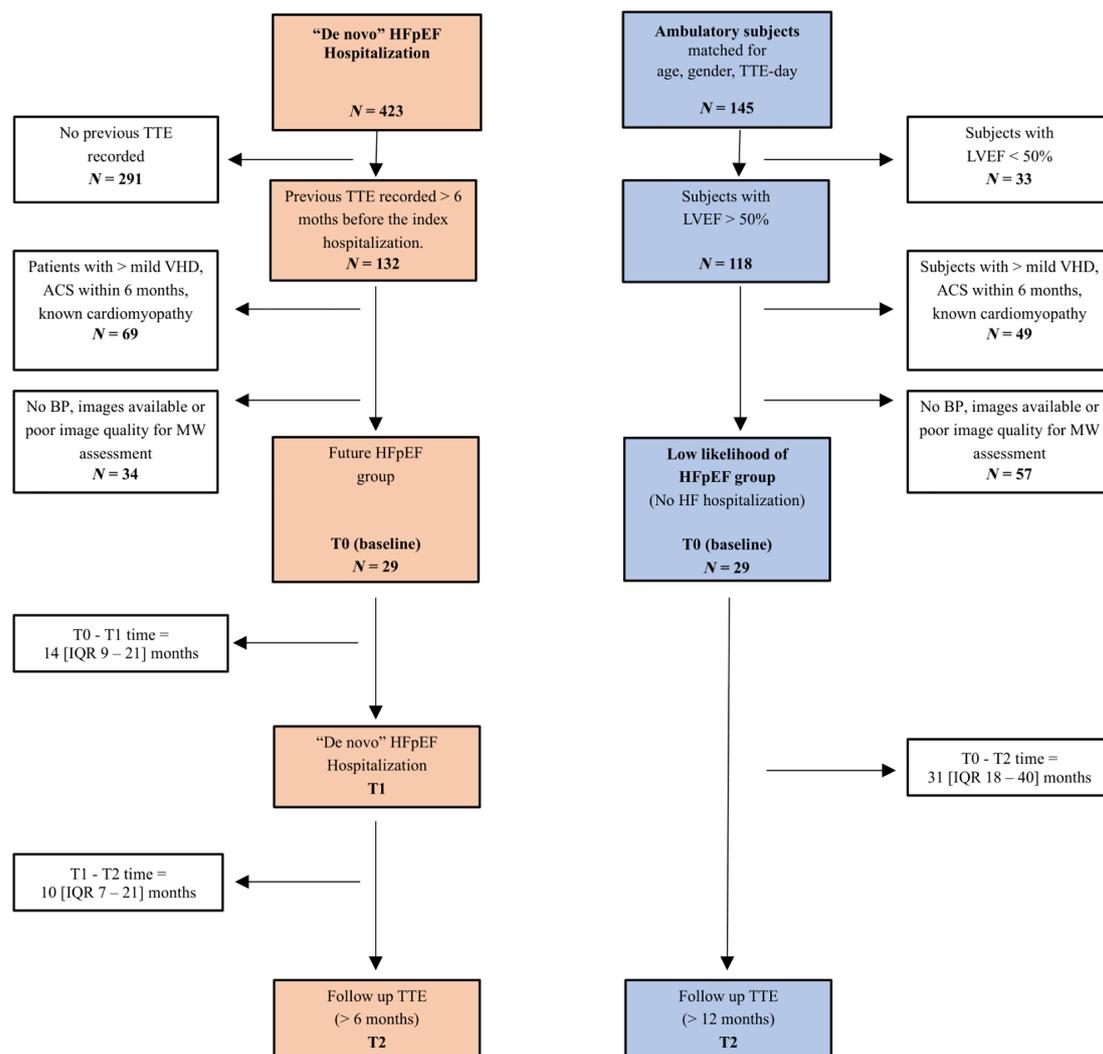
Materials and methods

Study design

This is a retrospective, longitudinal, case–control study designed to identify echocardiographic predictors of HFpEF hospitalization. From January 2017 to December 2019, all consecutive patients admitted with *de novo* primitive HFpEF, diagnosed according to the current ESC Guidelines, were screened for eligibility. The study population was identified according to the following inclusion criteria: (i) no history of documented heart failure; (ii) previous transthoracic echocardiogram (TTE) performed >6 months before the first HFpEF admission for routine indications such as palpitations, angina, or dyspnoea; and (iii) good quality apical views, EKG tracing and recorded blood pressure allowing MW analysis (*Figure 1*). Patients with more than mild valvular heart disease, AV block or pacemaker, acute coronary syndrome or myocardial revascularization in the previous 6 months, cardiomyopathy or amyloidosis, sub-optimal TTE image quality, absence of EKG tracing or blood pressure recording, or severe comorbidities limiting survival were excluded. A control group, named 'low likelihood of HFpEF', consisted of ambulatory subjects without future HFpEF hospitalization matched in a 1:1 ratio for age, gender, LV ejection fraction, indication, and date of TTE. All patients were managed in accordance with the Declaration of Helsinki. The study protocol was performed in accordance with the Ethics Committee of our institution. The need for consent to participate in this research study was waived in view of its observational and anonymous nature. All authors have read and approved the final version of the manuscript and have no conflict of interest to declare about the present work.

Study flowchart and follow-up

The electronic file of all patients admitted for *de novo* HFpEF between January 2017 and December 2019 was individually checked to validate the diagnosis of HFpEF and retrieve patients' demographics, history, medications, lab results, and clinical information. HFpEF was diagnosed according to the consensus recommendation of the European Society of Cardiology (ESC).[22] In the HFpEF group, three TTE examinations were evaluated, that is, >6 months prior to admission (baseline = T0), within 72 h after the admission (T1), and at last available follow-up at least >6 months after discharge (T2). In the low likelihood of HFpEF group, baseline TTE (T0) was compared with a follow-up TTE performed >12 months after the baseline (T2) (*Figure 1*). Follow-up and outcomes data were collected from electronic patients' records. It included all-cause and cardiovascular mortality, hospitalization for HFpEF, major adverse cardiovascular events (MACE), and major adverse events (MAE).[23] MACE was defined as a composite of cardiovascular death and non-fatal HF, while MAE as a composite of all-cause mortality and non-fatal heart failure. The survival was validated in the Belgian Population Register. Complete follow-up information was available for all study subjects.

Echocardiography protocol and data analysis

Subjects received a TTE as part of their routine clinical care. Blood pressure was acquired at the time of the exam in the imaging position using non-invasive brachial artery cuff pressure. All TTEs were performed using a high-quality ultrasound machine (GE E95 or GE S70, GE Healthcare Horten, Norway) with a 3.5 MHz-phased array transducer (M5S). All images were stored for offline analysis by two expert echocardiography cardiologists, blinded to clinical information. Data were analysed offline using dedicated software (EchoPAC PC SW-Only, version 202, GE Healthcare, Milwaukee, WI, USA). A mean of three beats in case of sinus rhythm or at least five beats in atrial fibrillation was taken for each measurement. All patients had a comprehensive two-dimensional (2D) echocardiographic assessment according to the European Association of Cardiovascular Imaging recommendations with the subjects in the left lateral decubitus position using standard parasternal and apical views.[24] LVEF was calculated using Simpson's biplane method. LV diastolic function was assessed by E, e′ velocities, E/e′, left atrial volume index (LAVi), and tricuspid regurgitation velocity. Determination of LV diastolic function was made using the algorithm proposed by the guidelines.[2] The left atrial reservoir strain (LARS) was defined as the first peak positive deflection and represented the LA reservoir function. The LARS was calculated as the mean longitudinal strain in two apical views (four and two chambers) using R–R gating as the zero-reference point.

Myocardial work assessment

Myocardial work was calculated as recommended.[25] In brief, LV GLS was assessed using the automated 2D speckle tracking technique (Echopac PC, General Electric Medical Systems) in the three apical views with temporal resolution between 60–90 frames/s. The regional speckle area of interest was manually adjusted to obtain optimal tracking results. GLS was calculated using a 17-segment model at the time in systole when the value peaked. In patients with atrial fibrillation, we selected loops from the apical four-chamber, two-chamber, and tree-chamber views with comparable R–R intervals for strain calculation. MW was assessed by the combination of LV strain data and a non-invasively estimated LV pressure curve, calculated by entering the subject's brachial cuff blood pressure into the measurement tool as well as setting valvular event timing.[14] Strain and pressure data were synchro-

nized using the onset of R-wave at EKG, and the area of the pressure strain loop is used to derive segmental and global MW. The segmental distribution of MW is displayed in a bull's eye plot. Global work index (GWI) was calculated as the average of segmental values. Constructive work (GCW) was defined as work during segmental shortening in systole and during lengthening in isovolumic relaxation. Conversely, MW performed during lengthening in systole and shortening in isovolumic relaxation, associated with energy loss, was termed wasted work (GWW). The global work efficacy (GWE) is automatically calculated as the ratio of constructive (constructive plus wasted work).[25]

Reproducibility

Fifteen patients were randomly selected and re-measured by two observers blinded to patient data and each other's results. Intra-observer variability was performed by evaluating sonographer on offline data at two different points of time more than 1 month apart. Inter-observer variability was performed by two cardiologist repeating measurements in the same images. Intra-observer and inter-observer reproducibility and variability were calculated by intraclass correlation coefficient (ICC) and limits of agreement.

Statistical analyses

Normality distribution of continuous variables was assessed visually with histograms and with the Shapiro–Wilk test. Continuous variables were summarized using the median and interquartile range (IQR). Categorical variables are presented as frequency counts and percentages. Fisher's exact test was used for comparing categorical variables, while Mann–Whitney tests for continuous ones. One-way ANOVA or Kruskal–Wallis tests were performed to test the difference of continuous variables between more than two groups, when appropriate. Correlation between variables was assessed by Spearman's method. Performance of each echocardiographic speckle tracking strain–pressure loops parameters for predicting HFpEF hospitalization was evaluated by receiver-operating characteristics (ROC) analyses. The optimal cut-off value was defined as the value that maximizes the sum of sensitivity and specificity using the Youden test. Standard formulas calculated positive predictive value and negative predictive value. The Kaplan–Meier analysis and log-rank test were used to compare the cumulative incidence of clinical endpoints between groups. A one-sided log-rank test with an overall sample size of 58 subjects (29 patients in each group) achieves 85% power at a 0.05-significance level to detect a difference of 0.3 between 0.45 and 0.15—the proportions surviving in Groups 1 and 2, respectively. Cox proportional hazard regression method was used to test

the association between GWW and clinical outcomes; results are presented as hazard ratio (95% CI). A *P* value <0.05 was considered statistically significant. All analyses were performed using the Statistical Package for Social Sciences, version 25.0 (SPSS, PC version, Chicago, IL, USA).

Results

Clinical characteristics

From January 2017 to December 2019, 423 patients were admitted for *de novo* HFpEF in our Cardiology Unit, among whom 132 (31.2%) had a TTE performed at least 6 months before the hospitalization (*Figure 1*). Thus, the final study population consisted of 29 patients (age 79 [73.5–83], 48.3% male patients) and 29 matched subjects (age 80 [75.5–86.5], 48.3% male patients). Major reasons for exclusion were the absence of TTE prior to hospitalization, sub-optimal quality of images for speckle-tracking or absence of EKG tracing or blood pressure recording at the time of TTE (*Figure 1*). In the HFpEF group, the median time between baseline TTE and index HFpEF hospitalization and between TTE during index hospitalization and follow-up was 14 [IQR 9–21] months and 10 [IQR 7–21] months respectively (*Figure 1*). In the low likelihood of HFpEF group, the median time between TTE at baseline and at follow up was 31 [IQR 18–40] months. *Table 1* shows baseline clinical characteristics in both groups. The median age was 80 years [74–85], and 52% were female. Future HFpEF patients showed significantly higher BMI, higher H2FPEF score, and lower prevalence of CAD compared with the low likelihood of HFpEF group (all *P* < 0.05). The prevalence of cardiovascular risk factors, comorbidities, and atrial fibrillation were similar between the two study groups. Specifically, in the low likelihood of HFpEF group, coronary artery disease was observed in 41.4% of patients, of whom 4 (13.8%) had previous AMI and 10 (34.5%) previous PTCA, while peripheral arterial disease and chronic obstructive pulmonary disease were evident in 31% of these patients. A comparable proportion of patients in both groups took diuretics. However, future HFpEF patients vs. low likelihood of HFpEF subjects showed higher prescription of loop diuretics. Blood pressure, heart rate, and the clinical indication for baseline TTE were similar in both groups.

Echocardiographic characteristics: Baseline and follow-up

Table 2 shows baseline echocardiographic characteristics in both groups. Future HFpEF patients had significantly greater LV wall thickness, LV mass index, average E/e*ı*, LAVi, TR Vmax and prevalence of diastolic dysfunction compared with low

Table 1 Baseline clinical characteristics between the future HFpEF and the low likelihood of HFpEF group

	Total population $N = 58$	Future HFpEF group $N = 29$	Low likelihood of HFpEF group $N = 29$	P value
Female gender	30 (51.7)	15 (51.7)	15 (51.7)	0.99
Age, years	80 [74–85]	79 [73.5–83]	80 [75.5–86.5]	0.26
BMI, kg/m^2	26.7 [24.13–30.9]	29.6 [26.4–33.65]	25.5 [23.5–27.25]	0.001
BMI > 30	20 (34.5)	13 (44.8)	7 (24.1)	0.68
BSA, (m^2)	1.83 [1.72–2]	1.89 [1.75–2.07]	1.78 [1.64–1.92]	0.028
Cardiovascular risk factors				
Smoking habit	28 (48.3)	11 (37.9)	17 (58.6)	0.12
Hypertension	51 (87.9)	26 (89.7)	25 (86.2)	0.49
Dyslipidaemia	38 (65.5)	16 (55.2)	22 (75.9)	0.10
T2DM	17 (29.3)	10 (34.5)	7 (24.1)	0.39
Medical history				
Atrial fibrillation	21 (36.2)	13 (44.8)	8 (27.6)	0.17
Peripheral arterial disease	13 (22.4)	4 (13.8)	9 (31)	0.12
COPD	17 (29.4)	8 (27.6)	9 (31)	0.77
Pre-CVA/TIA	4 (6.9)	2 (6.9)	2 (6.9)	0.98
CAD	16 (27.6)	4 (13.8)	12 (41.4)	0.019
Pre-AMI	4 (6.9)	0 (0)	4 (13.8)	0.038
Pre-PTCA	12 (20.7)	2 (6.9)	10 (34.5)	0.01
CKD	15 (25.9)	7 (24.1)	8 (27.6)	0.76
Baseline medical therapy				
Antiplatelets	29 (50)	9 (31)	20 (69)	0.004
ASA	27 (46.6)	8 (27.6)	19 (65.5)	0.004
P2Y12-I	8 (13.8)	3 (10.3)	5 (17.2)	0.45
ACE-I	17 (29.3)	7 (24.1)	10 (34.5)	0.39
ARBs	15 (25.9)	8 (27.6)	7 (24.1)	0.76
Aldosterone blockers	18 (31)	12 (41.4)	6 (20.7)	0.09
Diuretics	50 (86.2)	25 (86.2)	25 (86.2)	0.99
Loop diuretics	24 (48)	18 (72)	6 (24)	
Thiazide	26 (52)	7 (28)	19 (76)	
Beta-blockers	36 (62.1)	15 (51.7)	21 (72.4)	0.10
Calcium-blocker	13 (22.4)	7 (24.1)	6 (20.7)	0.75
Anticoagulation	23 (39.7)	15 (51.7)	8 (27.6)	0.57
Statins	40 (69)	16 (55.2)	24 (82.8)	0.023
Ezetimibe	7 (12.1)	2 (6.9)	5 (17.2)	0.23
Clinical characteristics				
H2FPEF score	4 [3–6]	6 [4–6.5]	3 [3–4]	0.001
SBP, (mmHg)	140 [130–160]	140 [124–151]	140 [130–160]	0.27
DBP, (mmHg)	80 [70–80]	80 [70–80]	80 [70–80]	0.64
HR, (bpm)	71 [66–84]	75 [66–85]	69 [67–80]	0.76
Clinical presentation				0.43
Angina	9 (15.5)	3 (10.3)	6 (20.7)	
Dyspnoea	20 (34.5)	13 (45)	7 (24.1)	
Routine screening	20 (34.5)	9 (31)	11 (38)	
Others (palpitations, syncope)	9 (15.5)	4 (13.7)	5 (17.2)	

Continuous variables are presented as median (interquartile range); categorical ones as *n* (%).
ACE-I, angiotensin-converting-enzyme inhibitors; AMI, acute myocardial infarction; ARBs, angiotensin II receptor blockers; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; CKD, chronic kidney disease (EGFR <60 mL/min); COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DBP, diastolic blood pressure; HR, heart rate; P2Y12-I, P2Y12 inhibitors; PTCA, percutaneous transluminal coronary angioplasty; SBP, systolic blood pressure; T2DM, type 2 Diabetes Mellitus; TIA, transient ischemic attack.

likelihood of HFpEF group (all *P* < 0.05). *Table 3* shows baseline speckle-tracking parameters in both groups. The future HFpEF vs. the low likelihood of HFpEF group showed significantly lower reservoir and contractile LAS, LV GLS and all the indices of MW except for GWW, which was significantly higher (all *P* < 0.05). The median N-terminal pro brain natriuretic peptide (NT-proBNP) levels for the future HFpEF group at the moment of hospitalization were 2885 [1915–8515] ng/L. No significant correlations were observed between baseline MW parameters and clinical H2FPEF score (all *P* values >0.05) as well as MW parameters assessed at the time of

hospitalization and NT-proBNP in the future HFpEF group (all *P* values >0.05). *Figure 2* shows individual examples of patients with future HFpEF and a low likelihood of HFpEF patient. In the future HFpEF group, we observed a significant reduction of GWE between baseline and hospitalization due to the decrease in GCW and the increase in GWW, while GWE showed partial recovery at follow-up (*Figure 3A,A'*). In contrast, no significant changes in any of the MW parameters in the low likelihood of HFpEF group were observed (*Figure 3B,B'*). LARS and LV GLS did not change significantly between examinations in any study group.

Table 2 Baseline echocardiographic indices in the future HFpEF and the low likelihood of HFpEF group

	Total population N = 58	Future HFpEF group N = 29	Low likelihood of HFpEF group N = 29	P value
LVEDDi, (mm)	26 [23–28]	25 [23–27]	26 [24–28]	0.22
LVEDVi, (mm)	54 [47–61]	53 [45–62]	56 [47–63]	0.58
IVS, (mm)	11 [10–12]	12 [11–13]	11 [9–12]	0.001
PWT, (mm)	9 [9–10]	10 [9–11]	9 [8–9]	0.001
RWT	0.38 [0.35–0.46]	0.41 [0.36–0.48]	0.38 [0.35–0.41]	0.11
LVMi	93 [84–107]	102 [89–112]	87 [75–98]	0.003
2D LVEF, (%)	55 [55–60]	55 [55–59]	55 [55–60]	0.13
TAPSE, (mm)	19 [17–22]	19 (17–21)	21 [18–23]	0.05
E wave, (m/s)	0.83 [0.65–1.1]	1 [0.8–1.2]	0.73 [0.64–0.97]	0.02
E/A, (ratio)	0.9 [0.7–1.3]	1.02 [0.8–1.5]	0.8 [0.7–1.1]	0.05
e/ septal, (m/s)	0.06 [0.05–0.07]	0.05 [0.05–0.06]	0.06 [0.05–0.07]	0.06
e/, lateral, (m/s)	0.8 [0.07–0.10]	0.08 [0.07–0.10]	0.09 [0.07–0.10]	0.28
e/, average, (m/s)	0.07 [0.05–0.09]	0.06 [0.05–0.08]	0.08 [0.06–0.09]	0.09
E/e/ average	12 [9.3–16.4]	14 [10.1–23.4]	10 [8.4–13.4]	0.009
TR V max, (m/s)	2.8 [2.5–3.2]	3 [2.7–3.3]	2.7 [2.5–3]	0.006
TR gradient, (mmHg)	38 [30–45.3]	45 [35–50]	35 [30–40]	0.001
LAVi, (mL/m^2)	39 [28–54.7]	48 [33–61]	33 [25–45]	0.003
E/e/ > 14	19 (32.8)	14 (48.3)	5 (17.2)	0.012
e/ sep. <0.07 or e/ lat. <0.1 m/s	44 (75.9)	25 (86.2)	19 (65.5)	0.07
LAVi > 34 mL/m^2	35 (60.3)	22 (75.9)	13 (44.8)	0.016
TR vel. > 2.8	27 (46.6)	19 (65.5)	8 (27.6)	0.04
Diastolic dysfunction	19 (32.8)	15 (51.7)	4 (13.8)	0.02
Indeterminate	23 (39.7)	10 (34.5)	13 (44.8)	0.42
Normal diastolic function	16 (27.6)	4 (13.8)	12 (41.4)	0.019

Continuous variables are presented as median (interquartile range); categorical ones as *n* (%).
2D LVEF, two-dimensional left ventricular ejection fraction; IVS, interventricular septum; LAVi, left atrium volume index; LVEDD, left ventricular end-diastolic diameter indexed to BSA; LVEDVi, left ventricular end-diastolic volume indexed to BSA; LVMi, left ventricular mass indexed to BSA; PWT, posterior wall thickness; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Table 3 Baseline speckle tracking indices between the future HFpEF and the low likelihood of HFpEF group

	Total population N = 58	Future HFpEF group N = 29	Low likelihood of HFpEF group N = 29	P value
LV GLS, (%)	15 [17–12]	13 [16–11]	15 [18–14]	0.012
LV GWI, (mmHg%)	1589 [1168–1855]	1309 [951–1619]	1681 [1576–1955]	<0.001
LV GWE, (%)	90 [86–92]	87 [81–90]	91 [88–95]	0.002
LV GCW, (mmHg%)	2110 [1864–2388]	1977 [1554–2284]	2218 [1933–2435]	0.036
LV GWW, (mmHg%)	210 [151–309]	272 [198–398]	165 [106–221]	<0.001
LARS, (%)	17 [12–22]	16 [11–20]	20 [16–25]	0.011
LASct, (%)	8 [0–12]	5 [0–9]	11 [7–14]	0.01
LAScd, (%)	10 [8–13]	10 [8–13]	10 [8–13]	0.92

Continuous variables are presented as median (interquartile range); categorical ones as *n* (%).
LARS, left atrial reservoir strain; LASc, left atrial contraction strain; LAScd, left atrial conduit strain; LV GCW, left ventricular global myocardial constructive work; LV GWE, left ventricular global myocardial work efficiency; LV GWI, left ventricular global myocardial work index; LV GWW, left ventricular global wasted myocardial work; LVGLS, left ventricular global longitudinal strain.

Performance of myocardial work indices to predict future heart failure with preserved ejection fraction hospitalization

Among different MW indices, GWW had the highest diagnostic performance to predict first HFpEF hospitalization [area under the receiver-operating characteristics curve (AUC) = 0.80, 95% CI 0.69–0.91, *P* < 0.001] and its combination with cardiovascular death (AUC = 0.80, 95% CI 0.66–0.90, *P* < 0.001) and all-cause mortality (AUC = 0.79, 95% CI 0.62–0.88, *P* = 0.001) (*Figure 4*). The optimal cut-off of GWW was 170 mmHg%, with 90% sensitivity, 55% specificity, 67% positive predictive value, and 84% negative predictive value. During whole follow-up, a total of 15 (25.9%) out of 58 patients died, 9 (31%) in the HFpEF group, and 6 (21%) in the low likelihood of HFpEF group. Patients with GWW > 170 mmHg% showed significantly shorter event-free survival than patients with lower GWW both for MAE and MACE (15 months vs. 49 months, log-rang *P* < 0.01) (*Figure 5*). In the Cox regression analysis, a value of GWW > 170 mmHg% was associated with more than four-fold increase of MACE (HR = 4.5, 95% CI 1.59–13.12, *P* = 0.005) and almost three-fold higher risk of MAE (HR 2.9, 95% CI 1.24–6.6, *P* = 0.014).

Figure 2 Individual example of MW indices in a patient with future heart failure with preserved ejection fraction (HFpEF) (A,A' baseline vs. hospitalization) and a low likelihood of HFpEF patient (B,B', baseline vs. follow-up).
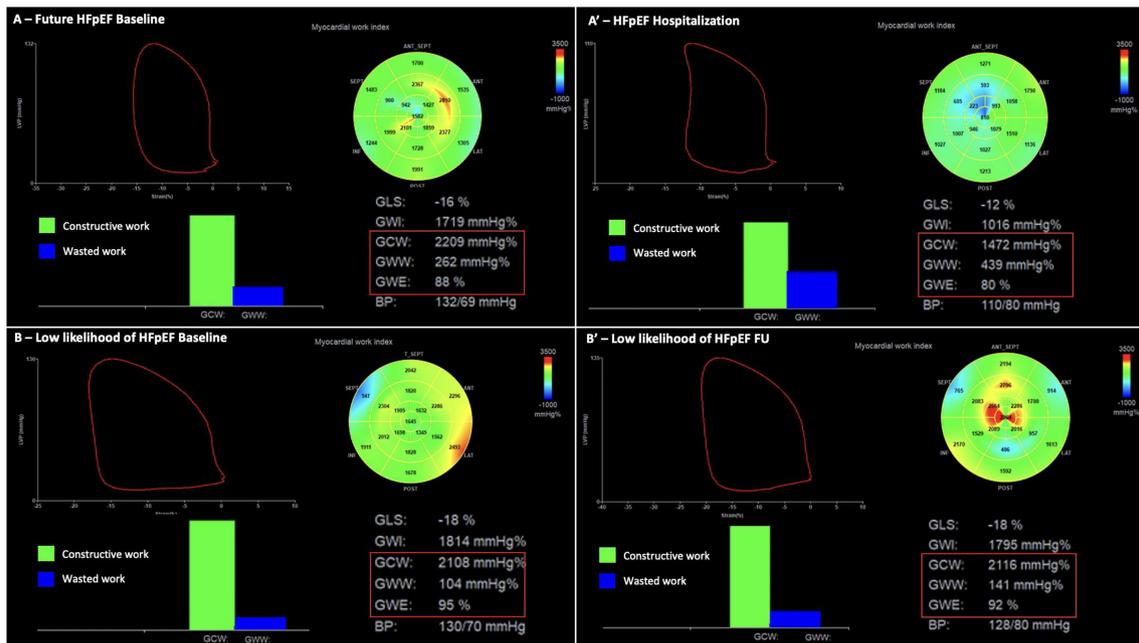
Reproducibility

Intra-observer and inter-observer variability was assessed by two operators in 15 randomly selected patients in each group. Repeated calculations of GWI, GWE, GCW and GWW by the same observer revealed a mean difference of 46.3 mmHg%, 1.2%, 22.8 mmHg% and 8.4 mmHg%, respectively (*Table 4*). Intra-observer ICC was 0.97 (95% CI 0.89–0.99), 0.99 (95% CI 0.96–0.99), 0.97 (95% CI 0.89–0.99), 0.97 (95% CI 0.92–0.99) and 0.96 (95% CI 0.93–0.98) for GLS, GWI, GWE, GCW, and GWW indicating good reproducibility. The ICC between the two observers was 0.96 (95% CI 0.56–0.99), 0.97 (95% CI 0.76–0.99), 0.98 (95% CI 0.94–0.99), 0.97 (95% CI 0.86–0.99), and 0.98 (95% CI 0.95–0.99) for GLS, GWI, GWE, GCW, and GWW, respectively. Thus, both intra-observer and inter-observer ICCs indicate good or excellent reliability for all parameters.

Discussion

The present study is the first to evaluate the clinical usefulness of MW analysis in risk and prognostic stratification of HFpEF patients. The main findings can be summarized as follows: (i) compared with low likelihood of HFpEF subjects, future HFpEF patients showed significant impairment in all the indices of MW at baseline, which further deteriorated at the moment of HFpEF admission. In contrast, no significant difference was observed in the low likelihood of HFpEF group over time; (ii) among the echo-derived parameters, GWW showed the highest performance to predict future hospitalization for *de novo* HFpEF and its combination with cardiovascular or all-cause mortality; (iii) GWW was a superior prognostic indicator compared with EF and GLS; (iv) no significant correlations were observed between GWW, H2FPEF score, and NT-proBNP levels.

Gap in knowledge of the standard two-dimensional-echocardiographic tools

Compared with previous data, we found in cohort higher percentage of diastolic dysfunction and indeterminate diastolic function.[4,5] One possible explanation for this difference might be due to the baseline patients' characteristics because our patients exhibited a worse cardiovascular risk profile and more comorbidities than patients of other studies. Specifically, compared with referred studies' patients, our cohort was significantly older, with higher prevalence of hypertension, pre-existing diabetes, obesity, and dyslipidaemia. Therefore, considering the clinical and echocardiographic characteristics, it is plausible that these patients could also have pre-clinical diastolic dysfunction, although not fulfilling yet all the echocardiographic criteria recommended in the 2016 guidelines.

Although HFpEF is characterized by a diastolic dysfunction that leads to elevated LV filling pressure, it is often associated

Figure 3 Serial changes of LARs, LV GLS, GWI, GWE, GCC, and GWW in the future HFpEF (Panels A,A') and the low likelihood of heart failure with preserved ejection fraction (HFpEF) group (Panels B,B') between baseline (T0), at the moment of hospitalization (T1) (only for the future HFpEF group) and during follow-up (T2). Future HFpEF group: median time between T0 and T1 was 14 [IQR 9–21] months, and the median time between T1 and T2 was 10 [IQR 7–21] months. Low likelihood of HFpEF group: median time between T0 and T2 was 31 [IQR 18–40] months. ** is for statistical significance (*P* < 0.05). Abbreviations: GCC, global constructive work; GLS, left ventricular global longitudinal strain; GWE, global work efficacy; GWI, global work index; GWW, global waste work; IQR, interquartile range; LARS, left atrial reservoir strain.
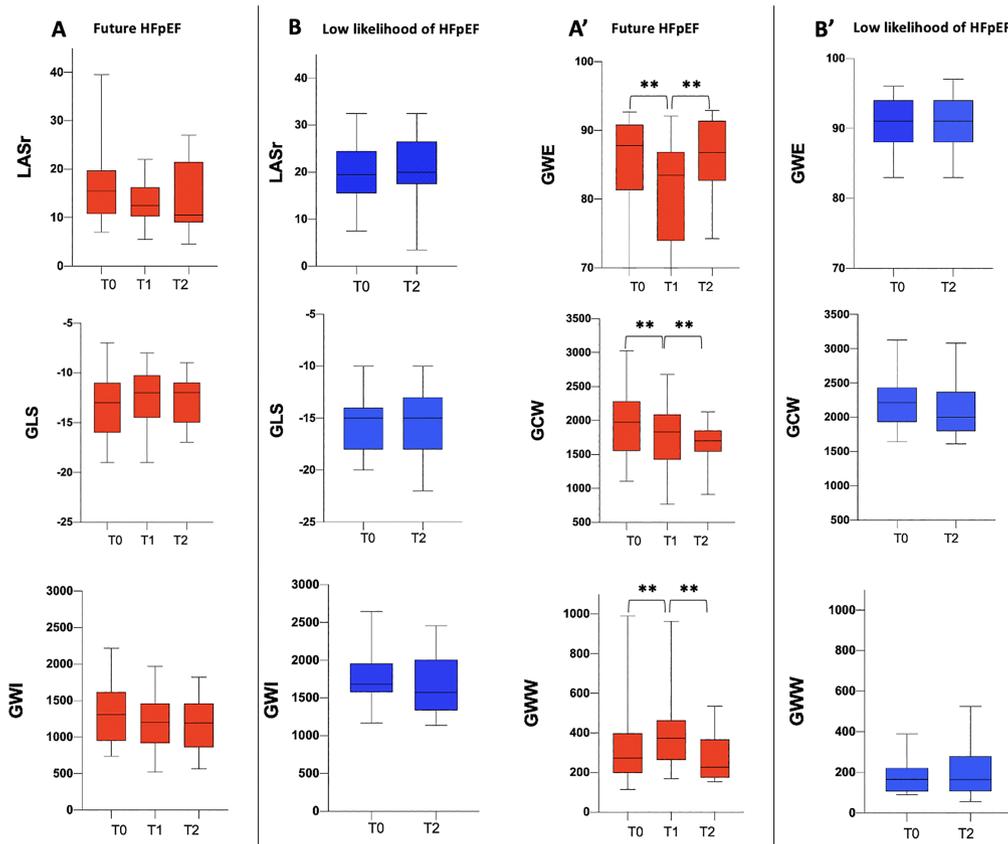
with subtle abnormalities of LV systolic function and metabolic alterations.[12] Previous studies demonstrated that 2D speckle tracking echocardiography could enrich traditional echocardiographic assessment of LV function and overall prognosis in HFpEF patients.[26] In fact, the LV longitudinal deformation not only contributes to the ejection phase but also reflects disturbances in the twisting physiology, thereby compromising cardiac haemodynamics and generating HFpEF phenotype.[27,28] LV GLS enables detection of subclinical LV dysfunction and its extent in the earlier phase of disease.[12,29] Nevertheless, GLS is an afterload-dependent parameter and may not adequately reflect myocardial contractility, mainly in patients with changing afterload conditions affecting clinical usefulness during the longitudinal follow-up. Consequently, in the presence of changing afterload, the unrestricted reliance on strain may cause misinterpretation of LV contractile state and lead to inaccurate clinical interpretation.

Myocardial work and clinical implications in heart failure with preserved ejection fraction

Stroke work evaluation has been used for several decades for heart failure characterization and treatment optimization. Traditionally, stroke work is calculated as the area of the LV pressure–volume loops derived from invasive LV catheterization. Myocardial work reflects both stroke work and myocardial oxygen consumption.[30] However, the clinical value of LV pressure–volume evaluation is limited by the invasive nature of LV catheterization. Russell *et al*. introduced non-invasive myocardial work evaluation based on the pressure–strain area derived from speckle tracking echocardiography and non-invasive brachial artery cuff pressure.[31] The pressure–strain method showed a robust correlation with invasive LV myocardial work assessment and allowed evaluation of wasted work and subsequent MW efficacy.[14] Thus, non-invasive MW is a validated index of LV systolic per-

Figure 4 Receiver-operating characteristics (ROC) curve for the predictive performance of two-dimensional speckle tracking echocardiography (2D-STE)-derived indices of left ventricular (LV) systolic function for future heart failure with preserved ejection fraction (HFpEF) hospitalization, major adverse cardiovascular events (MACE) and major adverse events (MAE).

HFpEF Hospitalization	AUC	SE	P-value	95% CI
LASr	0.307	0.07	0.012	0.170 − 0.443
GLS	0.691	0.07	0.013	0.554 − 0.828
GWI	0.231	0.062	< 0.001	0.091 − 0.335
GCW	0.339	0.072	0.036	0.199 − 0.480
GWW	0.801	0.057	< 0.001	0.689 − 0.912

MACE	AUC	SE	P-value	95% CI
LASr	0.297	0.07	0.008	0.160 − 0.434
GLS	0.717	0.067	0.005	0.587 − 0.848
GWI	0.208	0.058	< 0.001	0.073 − 0.300
GCW	0.296	0.068	0.008	0.162 − 0.429
GWW	0.797	0.060	< 0.001	0.664 − 0.900

MAE	AUC	SE	P-value	95% CI
LASr	0.259	0.067	0.002	0.127 − 0.391
GLS	0.735	0.066	0.003	0.607 − 0.864
GWI	0.223	0.055	< 0.001	0.075 − 0.290
GCW	0.322	0.070	0.023	0.185 − 0.459
GWW	0.793	0.065	< 0.001	0.622 − 0.876

Figure 5 Kaplan–Meier survival curves for MAE (Panel A) and MACE (Panel B) prediction by GWW > or ≤170 mmHg%. Abbreviations: GWW, global waste work; MAE, major adverse events; MACE, major adverse cardiac events.
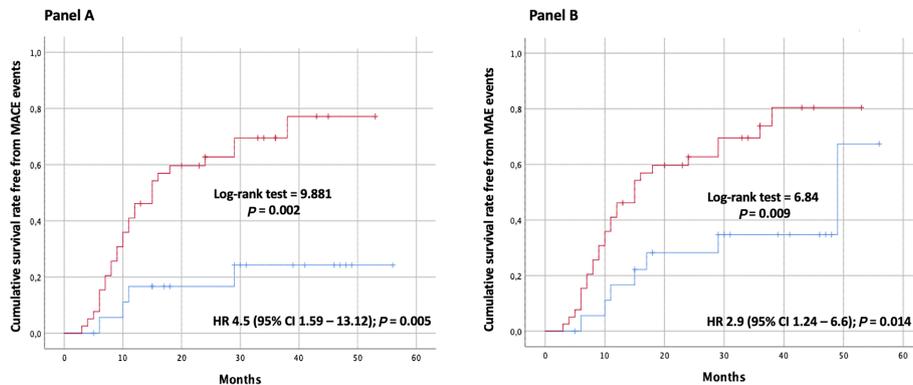
Table 4 Intra-observer and inter-observer variability

	Intra-observer variability			Inter-observer variability		
	ICC (95% CI)	Bias	Limits of agreement	ICC (95% CI)	Bias	Limits of agreement
GLS, %	0.97 (0.89–0.99)	0.53 ± 0.99	−1.41 to 2.5	0.96 (0.56–0.99)	0.93 ± 0.799	−0.63 to 2.49
GWI, mmHg%	0.99 (0.96–0.99)	−46.3 ± 63	−169.58 to 77	0.97 (0.76–0.99)	−88.13 ± 91.5	−267.47 to 91.21
GWE, %	0.97 (0.89–0.99)	−1.2 ± 1.93	−4.98 to 2.58	0.98 (0.94–0.99)	−0.53 ± 1.69	−3.84 to 2.78
GCW, mmHg%	0.97 (0.92–0.99)	−22.8 ± 154.7	−325.9 to 280.3	0.97 (0.86–0.99)	−82.13 ± 115.89	−309.27 to 145.01
GWW, mmHg%	0.96 (0.93–0.98)	8.4 ± 51.1	−91.8 to 108.6	0.97 (0.94–0.98)	−6 ± 47.8	−99.7 to 87.7

CI, confidence interval; GCW, left ventricular global myocardial constructive work; GLS, left ventricular global longitudinal strain; GWI, left ventricular global myocardial work index; GWE, left ventricular global myocardial work efficiency; GWW, left ventricular global wasted myocardial work.

formance, referring to the amount of work performed by the LV during mechanical systole and incorporates afterload. It can be obtained both bedside and offline. Accordingly, it shows less load dependency than conventional indices such as LVEF and GLS.[25]

The added clinical value of LV MW has been demonstrated in patients with hypertension or in aiding the prognostic stratification in patients with cardiac amyloidosis and ST-segment elevation myocardial infarction.[32,33] Furthermore, in the HFpEF setting, Przewlocka-Kosmala et al. demonstrated that GCW is a better determinant of exercise capacity than GLS and that improvement in functional capacity during follow-up is associated with increment of GCW.[34] Using longitudinal MW analyses, the current study is the first to point out at the role of MW in the risk stratification of HFpEF patients and its association with clinical outcomes. In addition, our findings provide side by side evaluation of MW analyses with other imaging parameters utilized in HFpEF assessment. While GLS, LAS and MW values in the future HFpEF group were reduced, the latter showed the highest accuracy to predict *de novo* hospitalizations and composite MACE and MAE endpoints. These findings are pivotal as loading conditions in many patients with HFpEF with preserved LV function may fluctuate over time, undermining the performance of load-dependent indices. Moreover, MW integrates both mechanic and energetic-metabolic components, that is, stroke work and myocardial oxygen consumption, offering additional insight into the pathophysiology of individual cardiac-level phenotype. In fact, MW analysis allows estimating energy waste of the LV and its efficacy (GWE). The waste energy is measured as myocardial work consumed during segmental lengthening (negative work) that does not turn into segmental contraction (positive work), being named wasted work.[17] The activity of the myocardium is strongly linked to the oxidation of the substrates that affect the production of energy necessary for determining heart rate, contractile capacity, and load. However, not all the energy generated by oxidative metabolism is used and converted into effective work.

According to our data, an interesting hypothesis could be that in these patients with fibrosis and abnormalities in both myocardial active relaxation and passive stiffness, due to the associations of multiple cardiovascular risk factors and co-morbidities, more energy is needed (i) to contract cardiomyocytes that are not completely relaxed, (ii) to compensate for the reduction of one or more components (longitudinal and/or circumferential) of the LV contraction, and (iii) to overcome the increased cardiac and aortic stiffness and resistance (patients with uncontrolled arterial hypertension). Thus, in these patients a greater cardiomyocytes energy demand corresponds to a greater energy used, which is however wasted and not transformed into an effective stroke volume. Indeed, a reduced mechanical efficiency was already demonstrated in HFpEF patients with coexisting LVH.[35] The

observation that the lost work increases at the time of hospitalization is consistent with the mechano-energetic un-coupling hypothesis of HFpEF. In a normal heart, the percentage of the global waste work is not more than 10%, which means that almost all the energy generated during systolic contraction is utilized for stroke volume. More than 10% of the energy developed by the myocardium of patients who experienced *de novo* HFpEF hospitalization was dissipated and is not transformed into effective work in the present study. This supports the notion that HFpEF patients with greater wasted energy as assessed by GWW are more susceptible to future clinical deterioration. It is also of note that clinical score or NT-proBNP admission did not correlate with GWW, conversely to HFrEF.[36] Likewise, based on the current findings, the values greater than 170 mmHg% might identify patients at risk of future events. This hypothesis generating findings should be further evaluated.

Study limitations

Following study limitations should be considered. First, this is a single-centre and retrospective study on relatively small sample size, even though all these patients were well characterized aiming to exclude other causes of diastolic dysfunction, with HFpEF patients selected according to the occurrence of hospitalization. Thus, our data provide preliminary hypothesis-generating findings requiring further prospective validation in a larger cohort. Consequently, given the low number of events recorded, we were unable to adjust for all potential confounders potentially affecting clinical outcomes. Furthermore, non-invasive MW analysis is provided only by one vendor, and thus the established cut-off values in our study cannot be directly adapted to other vendor platforms.

Conclusion

Heart failure with preserved ejection fraction is a severely underdiagnosed condition, and as such, its detection is often delayed. Longitudinal routine assessment of non-invasive MW might be clinically helpful for early identification of ambulatory patients with dyspnoea, preserved LVEF, and risk factors, who need prompt and tailored treatment optimization to reduce incidence of HF decompensation and to plan a closer outpatient visit. As LV performance depends on contractile properties, variations in afterload, and energetic-metabolic profile, non-invasive MW provides additional granularity in the clinical evaluation of patients at risk for HFpEF. In this setting, GWW appears to provide superior prognostic performance than GLS in identifying patients at higher risk of HFpEF hospitalization. Prospective multicentre studies are needed to validate the clinical and prognostic value of GWW.

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