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Clinical significance of myocardial work parameters after acute myocardial infarction

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Aims

To investigate the additional prognostic value of myocardial work (MW) parameters following acute myocardial infarction (AMI).

Methods and results

Between 2018 and 2020, 244 patients admitted in the cardiac intensive care unit in Lille University Hospital for AMI were included. One-month following AMI, comprehensive transthoracic echocardiography (TTE) was performed to assess parameters of myocardial function. Patients were then followed for major events (ME): cardiovascular death, heart failure, and unplanned coronary revascularization. At 1-month, half of the population was symptomatic (NYHA \geq II), and medical therapy was almost optimized (angiotensin-converting enzyme inhibitor/angiotensin 2 receptor blocker in 95.5%, beta-blockers in 96.3%, DAPT in 94.7%, and statins in 97.1%). After a median follow-up of 681 (interquartile range: 538–840) days, ME occurred in 26 patients (10.7%). Patients presenting ME were older (65.5 ± 14.2 vs. 58.1 ± 12.1 years, $P = 0.005$) with a higher prevalence of hypertension (65.4 vs. 36.2% , $P = 0.004$), more impaired left ventricular (LV) function as assessed by LV ejection fraction ($P = 0.07$), global longitudinal strain ($P = 0.03$), or MW parameters [$P = 0.01$ for global work efficiency (GWE)], and greater LV and left atrium dilatations ($P = 0.06$ for left ventricular end-diastolic volume index and $P = 0.03$ for left atrial volume index). After adjustment, GWE was the only TTE parameter independently associated with long-term occurrence of ME ($P = 0.02$). A GWE value $< 91\%$ was selected to identify patients at higher ME risk (hazard ratio: 95% confidence interval) = 2.94 (1.36–6.35), $P = 0.0041$).

Conclusion

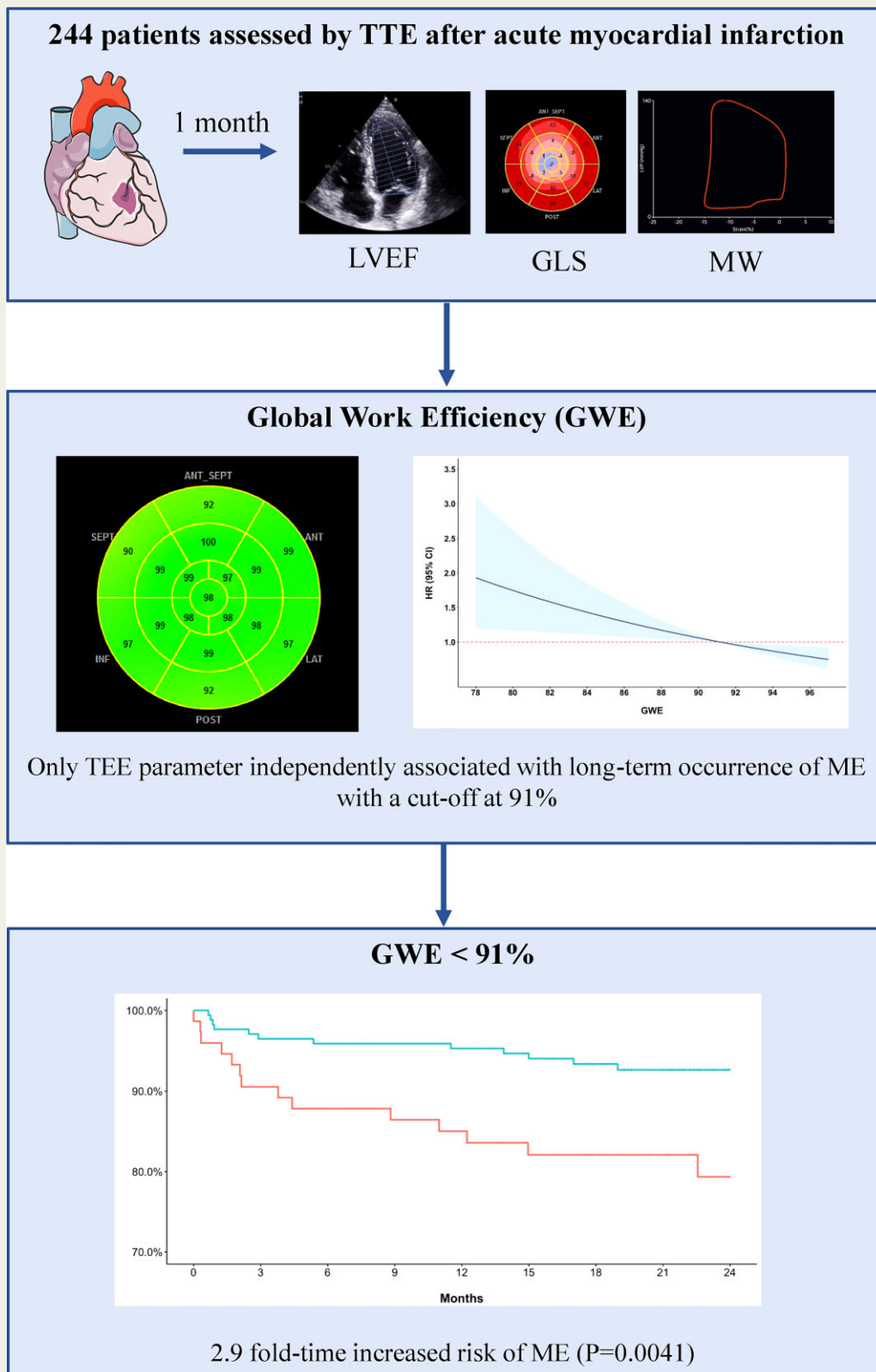
Lower GWE at 1 month after AMI is independently associated with higher ME rates. A GWE $< 91\%$ can improve the post-AMI patient risk stratification.

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Graphical Abstract



Flow chart summarizing the prognostic value of global work efficiency (GWE) 1-month after myocardial infarction (MI). GWE < 91% was independently associated with adverse events.

Keywords

Myocardial work • Global work efficiency • Myocardial infarction

Introduction

Acute myocardial infarction (AMI) is a public health concern. Although mortality decreased by more than 50% since 1995 thanks to advances in percutaneous coronary intervention (PCI), early care, and pharmacological treatments, AMI is still associated with poor long-term prognosis.¹ Noteworthy, this prognosis is mainly driven by myocardial damage with heart failure (HF) as the second cause of death, after sudden death and before MI recurrence.²

Therefore, an extensive and accurate assessment of the left ventricular (LV) myocardial function after MI is of paramount importance to identify patients at higher risk of HF and worse outcome. In this setting, several well-established transthoracic echocardiographic (TTE) parameters such as LV ejection fraction (LVEF) and global longitudinal strain (GLS) have been identified to predict adverse outcome.^{3,4} Myocardial work (MW) has been recently proposed to assess myocardial function through the integration of myocardial deformation and afterload, estimated by left ventricular pressure during a cardiac cycle, and using timing of valvular events and systolic brachial artery pressure.⁵

To date, there is little data regarding the clinical significance of MW parameters after a stable period following AMI. We hypothesized that MW parameters assessed 1 month after an AMI provide incremental value in addition to conventional TTE parameters to stratify the risk of major events (ME). Thus, the aim of the present study was to investigate the additional prognostic value of MW parameters to predict ME onset in patients following AMI, both with non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI).

Methods

Study population and design

Patients from the RIGID-MI study (Impact of Peripheral Vascular Stiffness Assessment on Risk Prediction in Patients with Myocardial Infarction, NCT04058782) were included. This study was a prospective monocentric study including patients admitted in the cardiac intensive care unit (CICU) in Lille University Hospital for AMI management, with or without ST elevation. Acute myocardial infarction was defined by the 2018 4th universal definition.⁶ All patients underwent coronary angiogram during their CICU stay and were treated according to current ESC guidelines.^{7,8} Patients with iatrogenic infarction, non-coronary troponin elevation (e.g. myocarditis, Takotsubo cardiomyopathy, sepsis), moderate to severe valvular heart disease, atrial fibrillation (AF), or younger than 18 years old were excluded. Clinical and biological data at admission were collected. The local ethics committee approved the protocol and patients gave informed consent.

One-month evaluation

At 1-month following AMI, a comprehensive TTE was performed during routine visits according to current guidelines using state-of-the-art echocardiographic ultrasound system (Vivid 95, GE Healthcare, Little Chalfont, UK).^{9,10} Medical therapy was also collected. Data were analysed offline on workstation EchoPac™ (EchoPAC version 203, General Electric Healthcare, Horton, Norway). LVEF and LV end-diastolic and end-systolic volumes were assessed on four-chamber and two-chamber apical views using biplane Simpson method. GLS was calculated from the two-dimensional greyscale images acquired in the apical

four-, three-, and two-chamber views, at a frame rate of 60–70 frames/s as previously described and given as absolute value.¹¹ MW was analysed using specific vendor module by General Electric Healthcare.¹² Valvular events were timed on pulsed-Doppler acquisitions. The software uses the theoretical ventricular pressure curve described by Russell *et al.*,⁵ adjusted for every patient on valvular events and peak systolic blood pressure, measured with an arm cuff immediately prior to the TTE. Using values of longitudinal strain and peak arterial pressure, the software builds a pressure–strain curve segment by segment and then derives four segmental indices: work index (in mmHg%) which is the area under the pressure–strain curve; constructive work (CW, in mmHg%) is the sum of the work of the segment that shortens during systole and lengthens during isovolumic relaxation; wasted work (WW, in mmHg%) is the work of the segments that lengthens during systole and/or shortens during isovolumic relaxation; work efficiency (WE, in %) represents the proportion of the spent energy that is useful for the pump function and is calculated by the ratio of the CW on the sum of constructive and WW. Each parameter is reported as 'global' corresponding to the mean of all 17-segmental values.¹³

Follow-up

Patients were followed-up by direct patient interviews and clinical examinations, telephone calls with the physicians, patients, or next of kin, or a review of the autopsy records and death certificates. The following ME were recorded: cardiovascular death, HF, and unplanned coronary revascularization. Revascularization planned during the index hospitalization for AMI and non-coronary revascularization were not considered. All clinical events were adjudicated by two investigators blinded to each other. A third investigator joined the adjudication in case of disagreement according to pre-specified definitions. A consensus was then reached.¹⁴

Statistical analysis

Continuous variables were described as mean \pm standard deviation (SD) or as median with interquartile range (IQR). Categorical variables were presented as absolute numbers and percentages. Linear regressions were used to explore the correlation between MW parameters and LVEF and GLS. To determine the intra-observer and inter-observer agreement of MW parameters, intraclass correlations, and their 95% confidence intervals (CIs) were calculated in 20 randomly selected patients. Comparisons between patients with and without ME during the follow-up (unpaired univariate analysis) were performed using Student *t*-test for normal or lognormal distribution quantitative variables, Mann–Whitney for non-normal distribution, χ^2 test for qualitative variables. Cox-proportional hazards regression stepwise model was used to determine variables associated with ME onset. Variables with a *P* value <0.10 on univariate analysis were entered into the multivariable models. We tested each model for log-linearity and proportionality assumptions. Time-related ME were plotted with Kaplan–Meier curves and compared with log-rank tests. Reclassification of patients using GWE as predictor was compared with the performance of LVEF with the category-free net reclassification improvement index. A value of *P* <0.05 was considered statistically significant. Statistics were performed using STATA 14.2 software (STATA Corporation, College Station), MedCalc v16.4 (Olstead, Belgium), and R, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

Between January 2018 and March 2020, 297 patients were included in the RIGID-MI cohort and 53 were excluded from the present analysis: 48 patients had too poor echogenicity, two patients were lost to follow-up, two patients had AF, and one had a significant pericardial effusion at 1-month TTE (see flow chart in [Figure 1](#)). Altogether, 244 patients were included in the final analysis. The baseline characteristics of these patients are summarized in [Table 1](#). The mean age was 59 ± 13 years. The population was composed of 81% of male, 13% had diabetes mellitus, and 40% had hypertension. An ST elevation MI occurred in 173 patients (71%) and most of the patients were Killip I class at admission (87%). The peak of hs-troponin T was 2016 (669; 4786) ng/L and 185 patients (76%) displayed a wall motion abnormality at admission. Coronary angiography findings are provided in [Supplemental Table 1](#).

One-month evaluation

At 1 month, half of the population was symptomatic (NYHA \geq II) and the medical therapy was almost optimized (95.5% had angiotensin-converting enzyme inhibitor (ACEi) or ARB, 96.3% had beta-blockers, 94.7% received dual antiplatelet therapy and 97.1% had statins). Mean LVEF was subnormal ($54.5 \pm 8.8\%$), while mean GLS was altered ($15.8 \pm 3.7\%$). The mean left atrial volume index (LAVi) was 37.7 ± 10.4 ml/m², and mean TAPSE was 23.3 ± 3.3 mm ([Table 2](#)). Mean MW parameters were 1731 ± 509 mmHg% for GWI, 1844 ± 510 mmHg% for GCW, 131 ± 73 mmHg% for GWW, and $91.2 \pm 6.6\%$ for GWE. Correlations between MW parameters were significant but only fair to moderate with LVEF (*r* values

ranging from 0.24 to 0.61) and fair to substantial with GLS (*r* values ranging from 0.39 to 0.81) ([Supplemental Figure 1](#)).

Reproducibility of myocardial work parameters

Intra-observer agreements were good for all MW parameters: 0.994 (95% CI: 0.986–0.998) for GWI, 0.991 (95% CI: 0.977–0.996) for GCW, 0.904 (0.770–0.960) for GWW and 0.990 (95% CI: 0.973–0.996) for GWE. Intra-observer agreement for GLS was 0.993, 95% CI 0.982–0.997. Likewise, inter-observer agreements were good for all MW parameters: 0.961 (95% CI: 0.904–0.984) for GWI, 0.974 (95% CI: 0.935–0.990) for GCW, 0.936 (95% CI: 0.846–0.974) for GWW, and 0.983 (95% CI: 0.935–0.990) for GWE. Intra-observer agreement for GLS was 0.978, 95% CI: 0.945–0.991. The Bland–Altman plot agreement for intra and inter-observer variability is provided in [Supplemental Figure 2](#).

Global work efficiency is independently associated with outcomes

After a median follow-up of 681 (IQR: 538–840) days, ME occurred in 26 patients (10.7%). Cardiovascular death occurred in four patients (1.6%), HF in 10 patients (4.1%), and 12 (4.9%) underwent unplanned coronary revascularization including five recurrent acute coronary syndromes.

Patients presenting ME were older (65.4 ± 14.2 vs. 58.1 ± 12.1 years, $P=0.005$), with higher prevalence of hypertension (65.4 vs 36.2% , $P=0.004$), more impaired LV function as assessed by LVEF ($P=0.07$), GLS ($P=0.003$), or MW parameters ($P=0.08$ for GWI, $P=0.09$ for GCW, and $P=0.01$ for GWE) and greater indexed LV end-diastolic volume (LVEDVi: 70.2 ± 16.8 vs. $64.4 \pm$

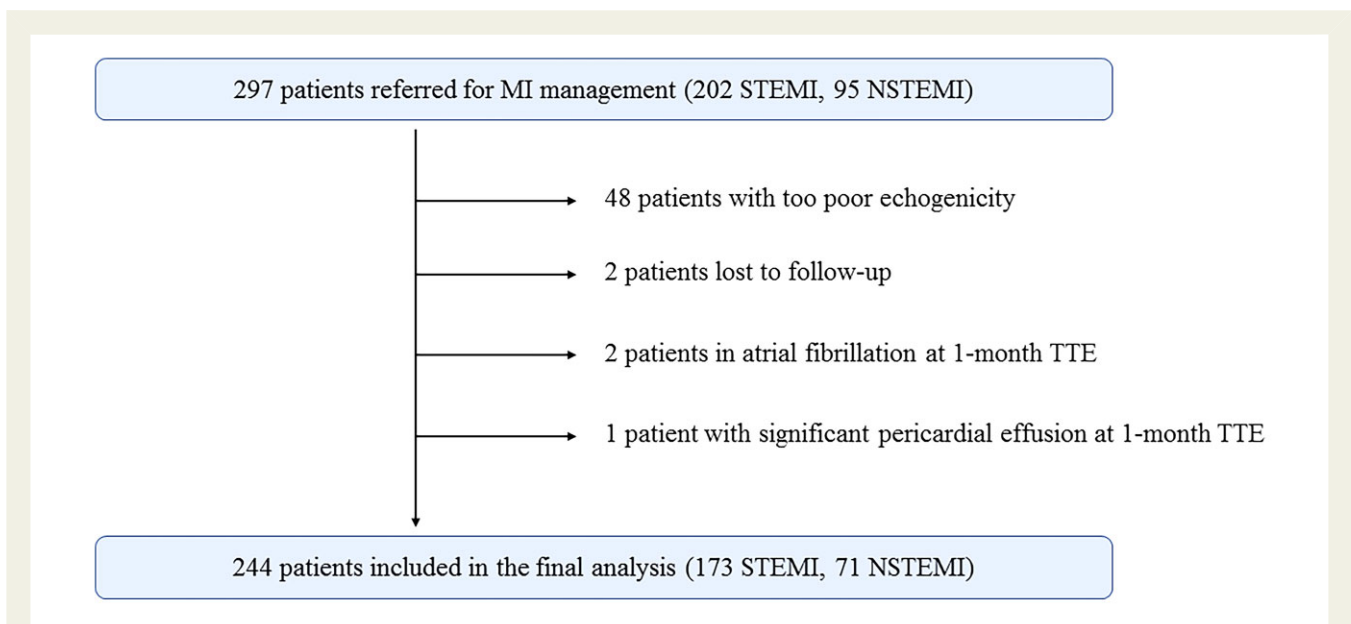


Figure 1 Flow diagram. Two hundred and ninety-seven patients were referred and 53 were excluded. Forty-eight patients for too poor echogenicity, two patients were lost to follow-up, two patients had atrial fibrillation, and one had a significant pericardial effusion at 1 month transthoracic echocardiography. Finally, 244 patients were analysed.

Table 1 Baseline characteristics at acute myocardial infarction admission

	All patients (n = 244)	No ME (n = 218)	ME (n = 26)	
Age (years)	58.8 ± 12.6	58.1 ± 12.1	65.5 ± 14.2	0.005
Gender women	51 (20.9)	45 (20.6)	6 (23.1)	0.77
BMI (kg/m ²)	27.4 ± 4.5	26.9 ± 5.5	27.3 ± 7.32	0.70
Diabetes mellitus	31 (12.7)	26 (11.9)	5 (19.2)	0.29
Hypertension	96 (39.3)	79 (36.2)	17 (65.4)	0.004
Active smoking	175 (71.7)	156 (71.6)	19 (73.1)	0.87
Stroke	6 (2.5)	4 (1.8)	2 (7.7)	0.07
ST elevation MI	173 (70.9)	158 (72.5)	15 (57.7)	0.12
Chronic kidney disease	6 (2.5)	6 (2.8)	0 (0)	0.39
Killip Class				0.03
I	213 (87.0)	195 (89.4)	18 (69.2)	
II	3 (1.2)	2 (0.9)	1 (3.8)	
III	5 (2.0)	1 (0.5)	4 (15.4)	
IV	23 (9.4)	20 (9.2)	3 (11.5)	
Haemoglobin (g/dL)	14.3 (13.2; 15.3)	14.4 (13.4; 15.3)	13.5 (12.7; 15.0)	0.05
Creatinine (mg/L)	9 (7–10)	9 (7–10)	9 (8–12)	0.03
Troponin T hs peak (ng/L)	2016 (669; 4786)	2119 (687; 4828)	820 (491; 3604)	0.25
LVEF (%)	50.4 ± 10.7	50.7 ± 10.5	47.7 ± 12.1	0.17
LV dilatation	19 (7.8)	16 (7.3)	3 (11.5)	0.46
Wall motion abnormality	185 (75.8)	165 (75.7)	20 (76.9)	0.92
Hospitalization length (days)	6.7 ± 4.1	6.7 ± 4.2	6.7 ± 2.8	0.99

Data are mean ± SD, median (interquartile) or n (%). BMI, body mass index; LV, left ventricle; ME, major event; MI, myocardial infarction.

14.4 ml/m², $P=0.06$) and LA dilations (LA volume index: 42.1 ± 12.0 vs. 37.2 ± 10.1 ml/m², $P=0.03$) (Tables 1 and 2). No difference was found regarding the initial presentation (STEMI vs. NSTEMI), hs-troponin peak. Similarly, there was no difference at admission regarding LVEF and the existence of a wall motion abnormality as assessed by TTE.

After multivariable adjustment using Cox regression analysis with a stepwise selection of variables, the existence of hypertension [HR (95% CI): 2.72 (1.20–6.19), $P=0.02$], prior stroke [HR (95% CI): 5.63 (1.28–24.7), $P=0.04$], the Killip Class [HR (95% CI): 1.41 (1.01–1.96), $P=0.04$], and GWE ($\beta \pm SE$; -0.05 ± 0.02 , $P=0.02$) were the only parameters independently associated with long-term ME occurrence. Based on the predicted HR for ME (Figure 2), a GWE value $<91\%$ was used to define a reduced GWE associated with an increased adverse event risk ($HR > 1$). As displayed on Kaplan–Meier survival curves, patients with GWE $<91\%$ had lower event-free survivals [HR (95% CI) = 2.94 (1.36–6.35), $P=0.0041$] (Figure 3). Additional Kaplan–Meier survival curves analysis based on the GWE median showed that patients with GWE $<93\%$ had lower event-free survivals [HR (95% CI) = 2.66 (1.16–6.11), $P=0.01$] (Supplemental Figure 3). Compared with LVEF, reclassification of patients using GWE resulted in a category-free Net Reclassification Improvement of 0.184 with a 12.2% net proportion of events assigned a higher risk and a 6.2% net proportion of non-events assigned a lower risk.

Discussion

Exploring patients 1 month after AMI (both NSTEMI and STEMI), our results showed that (i) reproducibility of MW parameters was good and (ii) a reduced GWE, defined as GWE $<91\%$, was the only TTE parameter independently associated with long-term occurrence of ME.

Evaluation of myocardial function

For a long time, cardiovascular imaging has dreamed of being able to provide a fast, accurate, and non-invasive assessment of myocardial function. Being easily accessible, LVEF remains the most used parameter in daily practice. However, it has been showed over the past decade that the analysis of GLS was superior to LVEF to detect early subclinical myocardial dysfunction and to predict ME onset in many pathological situations.^{15,16} However, the load-dependent limitation of these two parameters¹⁷ can be partially erased by measuring MW, which considers afterload exerted on the LV by generating a surrogate of LV pressure over time using LV pressure non-invasively (estimated using peripheral blood pressure synchronized) and echocardiography-derived valvular timing event. Interestingly, the area of this combined non-invasive LV pressure–strain loop is correlated with invasive MW¹⁸ and metabolism.⁵ Beyond the assessment of the total amount of work performed by the ventricle, this new

Table 2 One-month evaluation after myocardial infarction

	All Patients (n = 244)	No ME (n = 218)	ME (n = 26)	
NYHA Class				0.07
I	124 (50.8)	112 (51.6)	12 (46.2)	
II	71 (29.1)	67 (30.7)	4 (15.4)	
III	43 (17.6)	35 (16.1)	8 (30.8)	
IV	6 (2.5)	4 (1.8)	2 (7.7)	
SBP (mmHg)	127.3 ± 20.8	127.5 ± 20.8.5	126.3 ± 20.9	0.79
Heart rate (bpm)	63.3 ± 12.3	63.0 ± 12.1	66.2 ± 13.7	0.21
LVEF (%)	54.4 ± 8.8	54.8 ± 8.5	51.4 ± 10.8	0.07
GLS (%) *	15.8 ± 3.7	16.0 ± 3.5	14.3 ± 4.6	0.03
GWI (mmHg%)	1731 ± 509	1751 ± 488	1563 ± 648	0.08
GCW (mmHg%)	1844 ± 510	1863 ± 494	1685 ± 617	0.09
GWW (mmHg%)	131 ± 73	130 ± 72	144 ± 74	0.33
GWE (%)	91.2 ± 6.6	91.6 ± 6.1	88.1 ± 9.3	0.01
LVEDVi (mL/m ²)	65.1 ± 14.8	64.4 ± 14.4	70.2 ± 16.8	0.06
LVESVi (mL/m ²)	29.2 ± 12.5	28.5 ± 11.8	34.4 ± 16.6	0.02
LA volume (mL/m ²)	37.7 ± 10.4	37.2 ± 10.1	42.1 ± 12.0	0.03
TR velocity (m/s)	2.59 ± 0.35	2.59 ± 0.35	2.56 ± 0.34	0.79
E/e'	8.8 ± 3.4	8.6 ± 3.3	10.1 ± 4.1	0.04
TAPSE (mm)	23.3 ± 4.4	23.3 ± 4.5	23.5 ± 4.2	0.82
ACEi or ARB	233 (95.5)	210 (96.3)	23 (88.5)	0.07
MRA	31 (12.8)	26 (12.0)	5 (19.2)	0.30
Beta-blockers	235 (96.3)	211 (96.8)	24 (92.3)	0.25
Statins	237 (97.1)	211 (96.8)	26 (100)	0.35
Dual antiplatelet therapy	236 (94.7)	210 (96.3)	26 (100)	0.32
Anticoagulant	21 (8.6)	18 (8.3)	3 (11.5)	0.63

Data are mean ± SD, median (interquartile) or n (%). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin 2 receptor blocker; GCW, global constructive work; GWE, global work efficiency; GWI, global work index; GWW, global wasted work; LA volume, left atrium volume; LVEF, left ventricular ejection fraction; LVEDVi, indexed left ventricular end-diastolic volume; LVESVi, indexed left ventricular end-systolic; ME, major event; MRA, mineralocorticoid receptor blocker; NYHA, New York Heart Association; SBP, systolic blood pressure; TR, tricuspid regurgitation. * absolute value

Table 3 Cox regression analyses to assess determinants of major events following myocardial infarction

	Univariable			Multivariable		
	P	HR (95% CI)	β ± SE	P	HR (95% CI)	β ± SE
Age	0.0046		0.04 ± 0.02	-	-	-
Hypertension	0.006	3.12 (1.39–7.01)		0.02	2.72 (1.20–6.19)	
Stroke	0.06	4.05 (0.95–17.5)		0.04	5.63 (1.28–24.7)	
Killip Class	0.03	1.42 (1.04–1.93)		0.04	1.41 (1.01–1.96)	
NYHA Class	0.06	1.51 (0.99–2.31)		-	-	-
LVEF (%)	0.05		-0.04 ± 0.02	-	-	-
GLS (%) *	0.017		-0.12 ± 0.05	-	-	-
GWI (mmHg%)	0.049		-0.0008 ± 0.0004	-	-	-
GCW (mmHg%)	0.07		-0.0007 ± 0.0004	-	-	-
GWE (%)	0.006		-0.05 ± 0.02	0.02		-0.05 ± 0.02
LVEDVi (mL/m ²)	0.048		0.02 ± 0.01	-	-	-
LVESVi (mL/m ²)	0.015		0.03 ± 0.01	-	-	-
LA volume (mL/m ²)	0.02		0.04 ± 0.02	-	-	-
E/e'	0.03		0.07 ± 0.03	-	-	-
ACEi or ARB	0.08	0.35 (0.10–1.15)		-	-	-
Haemoglobin (g/dL)	0.007		-0.23 ± 0.09	-	-	-

Data are mean ± SD, median (interquartile) or n (%). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin 2 receptor blocker; GCW, global constructive work; GWE, global work efficiency; GWI, global work index; LA volume, left atrium volume; LVEF, left ventricular ejection fraction; LVEDVi, indexed left ventricular end-diastolic volume; LVESVi, indexed left ventricular end-systolic; ME, major event; NYHA, New York Heart Association. * absolute value. P value by Cox-proportional hazards regression stepwise model

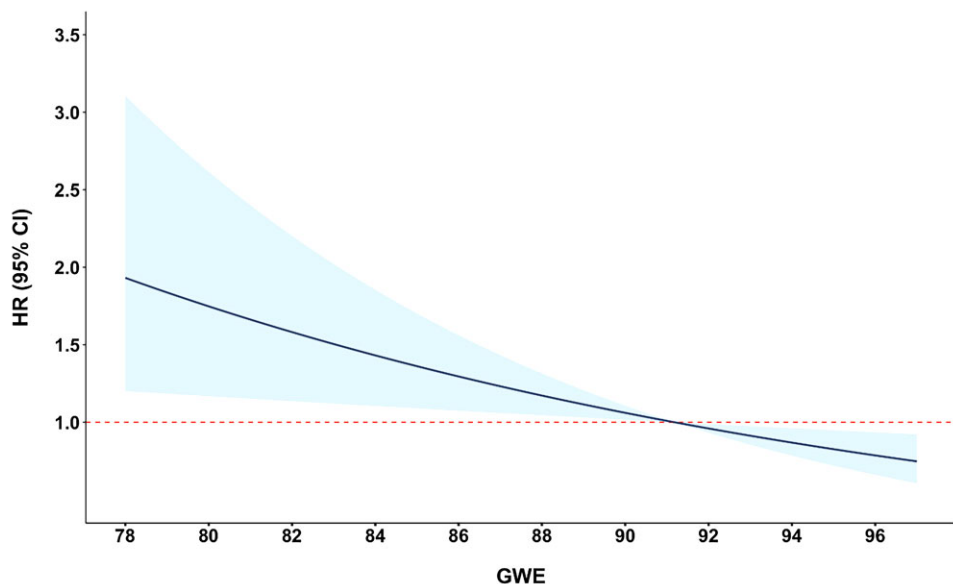
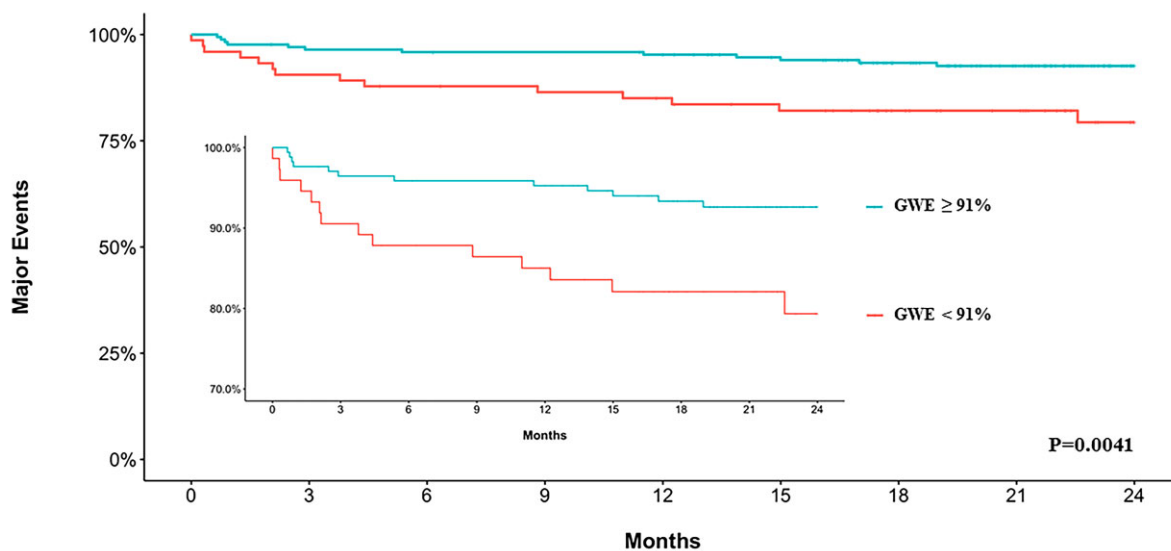


Figure 2 Predicted hazard ratio for major events according to increasing values of global work efficiency after myocardial infarction. CI, confidence interval; HR, hazard ratio.



	0	3	6	9	12	15	18	21	24
GWE < 91%	74	67	64	62	59	55	46	41	26
GWE ≥ 91%	170	163	162	161	159	148	133	113	69

Figure 3 Long-term prognostic impact of global work efficiency following acute myocardial infarction. Kaplan–Meier survival curves depicting time to major events. Data are shown according to global work efficiency (GWE) < or ≥ 91%. The inset shows the same date on an enlarged y axis. P value by log-rank test.

tool can assess the inhomogeneous pattern of work among different myocardial segments, which seems promising in cardiac resynchronization therapy¹⁹ and ischaemic cardiomyopathy.²⁰

Myocardial work in patients with myocardial infarction

Recently, several studies explored the usefulness of MW parameters in patients with AMI. Exploring 93 patients with STEMI treated by PCI, Meimoun *et al.*²¹ found that GCW was the best parameter to predict local and regional recovery, as well as in-hospital complications.²¹ Lustosa *et al.*²² showed that a GWE <86% within 48 h of admission in 507 STEMI patients was associated with worse long-term survival.²² To our knowledge, our study is the first to explore the clinical significance of MW parameters in patients with both NSTEMI and STEMI. In addition, we choose to assess these parameters 1 month after MI, which is the delay recommended to avoid early MI-related complications, optimize medical therapy, and allow a myocardial healing period.²³ The slight difference in GWE thresholds between our study and that of Lustosa *et al.* (respectively 91% and 86%) can thus be explained by the time when the GWE was analysed after AMI and by medical therapy optimization. Noteworthy, MW parameters were also able to identify acute coronary occlusion in patients with NSTEMI²⁴ or to detect significant coronary artery disease while combined to treadmill exercise stress test.

In our study, GWE seems to be the best non-invasive parameter of myocardial function to predict adverse outcomes after AMI. It could be used to adapt medical treatment, propose closer clinical monitoring, ensure painstaking therapeutic compliance and a correction of modifiable risk factors, and possibly propose screening for residual subclinical myocardial ischaemia.

Strengths and limitations

Even if it is debateable, we chose to evaluate our patients 1 month after MI and after adaptation of medical treatment so that our results can be extrapolated in daily practice for most cardiologists. Although medical treatment on admission and at discharge was not available, the medical therapy was optimized in most patients at 1 month. Similar to other TTE parameters, a correct evaluation of MW is not possible in patients with poor-quality images, and we excluded patients with AF and more than moderate valvular heart disease as MW parameters are less reliable in this setting. Despite a strong statistical significance, we acknowledge the cut-off of 91% of GWE is fragile and further studies will need to explore this threshold in larger and multicentre registries.

Conclusion

GWE is highly reproducible and lower GWE 1 month after AMI is independently associated with higher ME rates. A GWE <91% can improve the post-AMI patient risk stratification.

Lead author biography



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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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