Feasibility and Prognostic significance of ventricular-arterial coupling after myocardial infarction: the RIGID-MI cohort

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Tweet: ventriculo-arterial coupling, PWV, GLS, AMI

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ABSTRACTBackground. The clinical significance and feasibility of the recently described non-invasive parameters exploring ventricular-arterial coupling (VAC) remain uncertain.

Objectives. To assess VAC parameters for prognostic stratification in stable patients with LVEF ≥40% following myocardial infarction (MI).

Methods. Between 2018 and 2021, patients with LVEF ≥40% were evaluated 1-month following MI using transthoracic echocardiography (TTE) and arterial tonometry at rest and after handgrip test. VAC was studied via the ratio between arterial elastance (Ea) and telesystolic LV elastance (Ees) and between pulse wave velocity (PWV) and global longitudinal strain (GLS). Patients were followed for major adverse cardiovascular events (MACE): all-cause death, acute heart failure, stroke, AMI, urgent cardiovascular hospitalization.

Results. Among the 374 patients included, Ea/Ees and PWV/GLS were obtained at rest for 354 (95%) and 253 patients (68%) respectively. Isometric exercise was workable in 335 patients (85%). During a median follow-up of 32 months (IQR: 16-42), 41 (11%) MACE occurred. Patients presenting MACE were significantly older and had higher prevalence of peripheral arterial disease, lower GLS, higher Ea, PWV and PWV/GLS ratio. Ea/Ees ratio and standard TTE parameters during isometric exercise were not associated with MACE. After adjustment, PWV/GLS ratio was the only VAC parameter independently associated with outcome. ROC-curve analysis identified a PWV/GLS ratio >0.70 (Youden Index=0.37) as the best threshold to identify patients developing MACE: HR (95% CI) = 2.2 (1.14-4.27), P=0.02.

Conclusion. PWV/GLS ratio, assessed 1-month after MI, identifies a group of patients at higher risk of MACE providing additional value on top of conventional non-invasive parameters.

ABBREVIATIONS

MI = Myocardial Infarction

cf-PWV = carotido-femoral Pulse Wave Velocity

CI = Confidence Interval

ICCU = Intensive Cardiac Care Unit

DBP = Diastolic Blood Pressure

Ea = arterial elastance

Ees = end-systolic elastance

ESP = End-systolic Pressure

GLS = Global Longitudinal Strain

HF = Heart Failure

HR = Hazard Ratio

IQR = Interquartile Range

LV = Left Ventricle

LVEF = Left Ventricular Ejection Fraction

MBP = Mean Blood Pressure

MACE = Major Adverse Cardiovascular Events

PWV = Pulse Wave Velocity

SBP = Systolic Blood Pressure

SD = Standard Deviation

VAC = ventricular-arterial coupling

INTRODUCTION

In the past decade, several indexes obtained non-invasively by transthoracic echocardiography (TTE) at rest and/or during exercise have been described to finely assess left ventricle (LV) mechanics and ventriculo-arterial coupling (VAC). Parameters of myocardial deformation such as global longitudinal strain (GLS) and myocardial work (MW) may reveal a subclinical myocardial dysfunction and thus provide prognostic insight (1,2). In addition, the parameters exploring LV and the arterial system mechanics (i.e. arterial elastance (Ea), telesystolic LV elastance (Ees)) and their dialogue (i.e. VAC) have been identified as an independent prognostic marker in different cardiovascular diseases and can now be assessed non-invasively (2–4). Recently, the ratio between the reliable indexes of arterial stiffness (carotid-femoral pulsed wave velocity [cf-PWV]) and GLS has been proposed to characterize VAC and identify patients with greater severity of HF and worse functional capacity (5). Finally, the handgrip test, which significantly increases afterload (6), could be useful in detecting patients with maladaptive VAC.

Myocardial infarction (MI) is a public health concern. Although mortality has decreased in the recent years, it seems to have reached a "plateau" and MI is still associated with poor long-term prognosis (7,8). It is now established that this prognosis is mainly driven by myocardial damage consequences such as heart failure (HF) and sudden death (9). Therefore, an extensive and accurate assessment of the LV myocardial function after MI is of paramount importance to identify patients at higher risk for adverse outcome. While left ventricle ejection fraction (LVEF) has been successfully used for decades to stratify patient prognosis, this parameter is not predictive of prognosis in the large proportion of patients surviving MI without a frank alteration of LV function (i.e. LVEF superior to 40%) thanks to efficient reperfusion strategy.

To date, there is little data regarding the feasibility and clinical significance of the non-invasive ventricular mechanics and VAC parameters in patients with unaltered LVEF. Thus, the aim of the present study was to investigate the feasibility and prognostic value of VAC parameters, assessed at rest and during an isometric exercise (i.e. handgrip test), on top of conventional echocardiographic parameters to predict major adverse cardiovascular events (MACE) onset in patients with normal or mildly reduced LVEF (LVEF ≥40%) following MI.

METHODS

Study population

The study explored patients included in the RIGID-MI study (Impact of Peripheral Vascular Stiffness Assessment on Risk Prediction in Patients with Myocardial Infarction, NCT04058782) and with LVEF superior to 40% one month after MI as assessed by TTE.

RIGID-MI study is an ongoing prospective monocentric study including patients admitted in the intensive cardiac care unit (ICCU) in Lille University Hospital for MI, with or without ST elevation. MI was defined by the 2018 4th universal definition (10). All patients underwent coronary angiogram during their ICCU stay and were treated according to current ESC guidelines (11,12). Patients without any percutaneous coronary intervention, 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 year-old were excluded. Clinical and biological data at admission were collected. One month following MI, a thorough clinical examination, blood test, a 6-minutes walking test, a transthoracic echocardiography (TTE) and a VAC assessment at rest and during handgrip test were performed. Medical therapy was also collected. The local ethics committee approved the protocol and patients gave informed consent.

Cardiac Imaging

A comprehensive TTE was performed in all patients according to current guidelines using state-of-the-art echocardiographic ultrasound system (Vivid 9, Vivid 95, GE Healthcare, Little Chalfont, UK) (13,14). 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

(15). MW was analysed using specific vendor module by General Electric Healthcare (16). The software uses the theoretical ventricular pressure curve described by Russell et al.(17), adjusted 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; global 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.

Arterial properties and Ventricular-Arterial coupling

Arterial tonometry (SphygmoCor®, AtCor Medical Pty. Ltd., Sydney Australia) of the femoral, and carotid arteries was measured by experienced technicians according to international recommendations (18). The carotid pulse was measured using the tonometer while the femoral pulse was measured through pulsations in a cuff placed around the thigh. Augmented pressure was calculated as the difference between the second and the first systolic peak. Aortic augmentation index, which measures the contribution of pressure wave reflection to ascending aorta waveforms, was calculated as the ratio of augmented pressure to pulse pressure and normalized at a heart rate of 75 beats/min (AIx@75). Cf-PWV was calculated as the ratio of the surface distance between the 2 recording sites (straight-line distance * 0.80) and wave transit time. The travel distance was measured between recording sites using a non-stretchable medical tape measure and a caliper. The carotid-femoral distance was measured from the suprasternal notch to the site of femoral artery waveform measurement using a caliper to avoid effects of body size and/or shape. Three consecutive measurements were recorded, and the median value was considered. All measurements were recorded by the same nurse, trained for this evaluation.

VAC was calculated with 2 different methods. The first one was defined as the ratio of arterial stiffness (measured by cf-PWV) to myocardial performance evaluated by STE-derived GLS (i.e. cf-PWV/GLS ratio). The second one was calculated as the ratio of the arterial elastance (Ea) to end-systolic elastance (Ees), as described previously by Chen and al (4) with a measurement of the end-systolic pressure (ESP) by the SphygmoCor® (19).

Handgrip test

After TTE examination at rest, the patients were asked to grip a dynamometer with one third of their maximum strength for 8 minutes using either hand, and echocardiographic images were acquired between 3 and 8 minutes of the exercise. The dynamometer indicates a real-time grip strength, and dedicated medical staff was observing the grip strength, confirming that the patient was appropriately keeping the grip strength during the exercise.

Follow-up

Patients were followed 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 MACE were recorded: death (any cause), HF hospitalization, unplanned coronary revascularization, stroke, MI, and urgent cardiovascular hospitalization. Revascularization planned during the index hospitalization for MI (occurring therefore before the 1-month evaluation),non-coronary revascularization, and events occurring before the 1-month evaluation 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.

Statistical analysis

Continuous variables were described as mean +/- standard deviation (SD) or as median with interquartile range (IQR) as appropriate. Categorical variables were presented as absolute numbers and percentages.

Comparisons between patients with and without MACE 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, $\chi 2$ test for qualitative variables. Cox-proportional hazards regression backward model was used to determine variables associated with MACE onset. Variables with a P value <0.10 in univariate analysis were entered into the multivariable models. Time-related MACE were plotted with Kaplan–Meier curves and compared with log-rank tests.

A value of P <0.05 was considered statistically significant. Statistics were performed using Graphpad (GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA), MedCalc v16.4 (Olstead, Belgium), and R, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Between January 2018 and December 2021, 417 patients were included in the RIGID-MI cohort and 43 were excluded from the present analysis: 22 patients were lost to follow-up and 21 had a LVEF <40% at 1 month after MI (see flow chart in **Figure 1**). Baseline characteristics of the 374 patients considered in the study are summarized in **Table 1**. The median age was 59 [50;65] years. The population was composed of 76.5% of male, 17% had diabetes mellitus, 44% had hypertension, and 33% were obese. An ST-elevation MI occurred in 244 patients (68%). The ICCU characteristics are provided in Supplemental Table 1. At 1 month after MI, 20% of the population was symptomatic (NYHA ⩾II and none had angina) and the medical therapy was almost optimized: 96% had angiotensin-converting enzyme inhibitor (ACEi) or ARB, 96% had beta-blockers, 95% received dual antiplatelet therapy and 97% had statins. Median 6 min walking test was 482 m [415;550].

Echocardiographic and vascular parameters are summarized in **Table 2**. Median LVEF was 59% [53;64], while median GLS was slightly altered (17.1% [14.6;19.0]). The median left atrial volume index (LAVi) was 35 mL/m^2 [29;42], and median TAPSE was 23 mm [21;26]. Median MW parameters were 1839 mmHg% [1523; 2105] for global work index (GWI) and 93% [90;95] for global work efficiency (GWE).

Assessment feasibility of ventricular mechanics, arterial mechanics and their coupling parameters

Among the 374 patients, a SphymoCor® assessment was successfully performed in 354 (95%) and 335 (85%) were able to performed the handgrip test. The VAC index using arterial elastance and end-systolic ventricular elastance was successfully obtained in 354 (95%) patients at rest and for 319

(95%) of the patients who could realize the handgrip. The VAC index using the PWV/GLS ratio was successfully obtained in 253 patients (68%). Poor echogenicity was the reason for unavailable GLS. During handgrip, the PWV assessment is challenging, explaining the unavailable data for some patients.

On the vascular front, median PWV was 10.2 $m.s^{-1}$ [8.8; 12.0] and arterial elastance was 1.58 mmHg/mL [1.33; 1.88]. On the myocardial front, median Ees was 2.05 mmHg/mL [1.61;2.51]. Regarding VAC parameters, PWV/GLS ratio was 0.60 [0.50;0.77] and Ea/Ees was 0.76 [0.68;0.89].

Prognostic insights of VAC parameters at rest

Among the 396 included patients with LVEF ≥40%, 374 (94.4%) underwent a clinical follow-up (median of 32 months (IQR 16 to 42)). Altogether, MACE occurred in 41 patients: 14 deaths (8 from any cause and 6 from cardiovascular causes), 16 HF hospitalizations, 11 unplanned coronary revascularizations for recurrent MI, 3 strokes and 3 urgent cardiovascular hospitalizations for other reasons (1 syncope requiring programmed ventricular stimulation, 1 for sinus node dysfunction, 1 for acute pericarditis). Patients presenting MACE were older (64 [58;74] vs. 58 [50;65] years, P <0.001), had a higher prevalence of hypercholesterolemia (59 vs. 40%, P=0.03), and of peripheral arterial disease (17 vs. 4 %, P=0.001), more impaired functional capacities as assessed by 6MWT (P=0.005). They also displayed lower GLS (P=0.01), lower GWI (P=0.03), higher arterial elastance (P=0.04) one month after MI. The initial MI presentation (STEMI vs. NSTEMI), LVEF or Ees were not predictive for MACE occurrence. Patients developing MACE displayed higher PWV/GLS ratio (0.79 [0.59;1.24] vs 0.59 [0.49; 0.74], P <0.001), this observation was not shown regarding Ea/Ees ratio (P=0.75).

Using univariate Cox regression analysis (see **Table 3**), age (β ± SE: 0.04 ± 0.01, P=0.0002), LV GLS (-0.1 ± 0.1, P=0.006), Ea/Ees (0.2 ± 0.1, P=0.03) and PWV/GLS (2.2 ± 0.46, P<0.0001) were associated with MACE. After multivariable adjustment using Cox regression analysis with a backward selection of variables, PWV/GLS ratio [β ± SE: 2.9 ± 0.46, P<0.0001], was the only parameter independently associated with MACE occurrence. As displayed on Kaplan-Meier survival curves, patients with the highest PWV/GLS ratio tertile (PWV/GLS ratio > 0.70) had higher MACE incidence: HR (95% CI) = 2.2 (1.14 - 4.27), vs lowest tertile (PWV/GLS ratio ≤ 0.53, P=0.02 by Cox **Figure 2**). ROC-Curve analysis showed that a cut-off of 0.70 for PWV/GLS ratio had the higher discriminating power to predict MACE onset (Youden index=0.37 Sensitivity=65%, Specificity=72%, Area Under the Curve = 0.71, p=0.0005) (**Supplemental Figure 2**). The increment in Chi2 was higher when adding PWV/GLS ratio (model 4) than when adding, GLS (model 3), PWV (model 2) or age and 6MWT (model 1) (model 4: 19.5 vs. model 3: 10.4, P=0.003, **Figure 3**)

Handgrip test: feasibility and prognostic insight

Among the 374 patients, 335 (85%) completed the handgrip isometric exercise test. The VAC index using arterial elastance and end-systolic ventricular elastance was successfully obtained in 319 (95%). Patients who presented MACE showed higher arterial elastance (Ea) (2.15 [1.58; 2.49] vs. 1.79 [1.52; 2.1], P=0.03) and LV end-systolic elastance (Ees) (2.64 [2.04; 3.2] vs. 2.31 [1.86; 2.72], P=0.02), but no difference regarding Ea/Ees was observed between groups (0.76 [0.71;0.89] vs. 0.80 [0.71;0.89], P=0.50) (see **Table 2**).

Using univariate Cox regression analysis (see **Table 3**), arterial elastance (β ± SE: 0.04 ± 0.01, P=0.03) was associated with MACE but not Ees (0.02 ± 0.03, P=0.47), nor Ea/Ees (0.5 ± 0.3, P=0.07).

DISCUSSION

Exploring patients one month after MI, we showed that 1) the majority of parameters for VAC assessment described in the literature in the recent years were workable. Ea/Ees was feasible in 95%.

The PWV/GLS ratio was feasible in 68% of cases, the handgrip maneuver was doable in 85% (2) when feasible, a higher PWV/GLS ratio (but not Ea/Ees ratio) independently identifies a group of patients who were at higher risk of MACE and (3) in a post-MI population with LVEF ≥ 40% this ratio did better than either of its individual components and provides a significative and additional value in predicting MACE onset.

Evaluation of VAC

One of the unfinished quests in cardiovascular imaging is to provide a rapid, accurate and non-invasive assessment of myocardial function. Although providing no prognostic information in a mid-range or preserved LVEF population, LVEF remains the most used parameter in daily practice to assess myocardial function. Over the past decade, the parameters of myocardial deformation, more specifically GLS, have been shown to be superior to LVEF to detect early subclinical myocardial dysfunction and to predict MACE onset in many pathological situations (20,21). Additionally, measuring MW parameters, which considers afterload exerted on the LV by generating a surrogate of LV pressure over time using LV pressure non-invasively and echocardiography-derived valvular timing event, promising to provide an assessment of myocardial function less dependent on loading conditions. (2,22,23).

Nevertheless, it seems relevant to apprehend the cardiac function by integrating it into its global environment, considering its dialogue with the downstream arterial tree. Hence, increased arterial stiffness plays a significant role in the metabolic and hemodynamic abnormalities that characterize heart failure with preserved ejection fraction (HFpEF) patients at rest and during exercise (24). In this setting, there is a growing interest in assessing VAC in HF patients. VAC is defined as the ratio of arterial elastance (Ea) and Ees where Ea is derived from the end systolic pressure to stroke volume (SV) curve and provides a measure of overall afterload and Ees a marker of LV performance. These two parameters can be measured by the SphygmoCor®. Other authors have proposed to explore the VAC by calculating the ratio between PWV/GLS. This ratio is based on two parameters widely studied in the literature: the carotid-femoral PWV which has been linked to cardiovascular events and is consider the "gold standard" to measure aortic stiffness (25) and GLS a marker of subclinical LV contractile dysfunction. Noteworthy, the value of PWV found in our population was consistent with previous studies (5).

PWV corresponds to normal values of a population, which is 10 years older (26). In this work, Ees is at the lower normal range and so is Ea. The ratio Ea/Ees is half the way between maximal work and maximal efficiency, corresponding to a mildly decreased EF (27). The lower Ea may be attributable in part to of infarction and extensive medical therapy, resulting in lower pressure and lower heart rate. Ea is marginally significantly higher in the MACE group. Its main determinants (SVR and heart rate) only show a trend. As already explained by Chirinos and al., given the pulsatile nature of the left ventricle as a pump, arterial load varies over time, is complex and cannot be expressed as a single number.(28)

Ea/Ees was workable in 95% and PWV/GLS in 68%. This may be disappointing, as VAC analysis requires the use of an additional device to measure PWV (the Sphygmocor® in our study), it is time-consuming and sometimes laborious but we hope that the results shown in this work will incite the cardiology community to evaluate VAC in post-MI patients.

Even if the measurement of PWV and GLS, unlike the classical measurement of ventricular-arterial coupling (Ea/Ees), does not consider a formal measurement of the energies involved, we have shown that the PWV/GLS ratio can identify a subpopulation at higher risk of MACE following MI and provides additional prognostic value compared to conventional parameters.

PWV/GLS vs. Ea/Ees

In our cohort, the Ea/Ees was not associated with MACE, unlike the PWV/GLS ratio. Interestingly, Ikonomidis and al. (29) have already compared these 2 parameters in patients with systemic hypertension and shown that PWV/GLS ratio but not the Ea/Ees index was related to impaired carotid-intima media thickness, coronary-flow reserve and diastolic function. Besides, by exploring a large population of middle-aged individuals, Holm and al.(30) showed that these 2 methods were poorly correlated and proved that the PWV/GLS ratio should be preferably used to assess VAC. In their study, higher PWV/GLS ratio was significantly associated with cardiovascular factors regardless of age.

The lack of sensitivity of the Ea/Ees ratio when EF is preserved has been already demonstrated by Chirinos and Sweitzer in HF patients (28). Indeed, patients with HFpEF demonstrate normal energetic 'coupling' of the LV (Ees) and the arterial load (Ea), as the aortic stiffness leads to a higher LV stiffness. However, as already detailed in the literature, this approach allows us to understand the limited stroke volume reserve and increased blood pressure lability and preload sensitivity in this population (31). We need to emphasize that our population is at risk for HFpEF but is not a true HFpEF population.

PWV/GLS ratio after MI

To our knowledge, our study is the first to explore the clinical significance of the PWV/GLS ratio 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. Epidemiologic data have shown an increase in the incidence of HF over the past decades in parallel with the decrease in mortality after MI, thanks to advances in revascularization and better pharmacological treatments (32,33). In this context, the

PWV/GLS ratio has proved its importance in precisely differentiating patients at different stages across the entire cardiovascular continuum (5).

Handgrip test

The purpose of the handgrip test is to increase afterload and stress out the cardiovascular system without increasing preload or heart rate (6,34). This test can be easily performed in the echocardiography laboratory and allows a reproducible and quantifiable stress evaluation without the constraints of an ergometer (especially for the elderly). In our study, the maneuver did not appear to provide an additive value. Further studies are required to explore the interest of the handgrip test in this population.

Clinical implications

In our study, the PWV/GLS ratio seems to be the best non-invasive parameter to predict adverse outcomes after MI. It could be proposed in daily practice to adapt medical treatment, propose closer clinical monitoring, ensure painstaking therapeutic compliance and a correction of modifiable risk factors.

Strengths and Limitations

We chose to evaluate our patients 1 month after MI and after adaptation of the 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, an assessment of MW parameters 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 category. We did not perform inter/intra-observer comparison for VA coupling measurements. VA coupling was done by one nurse trained for this measure, 3 measures were performed each time for PWV evaluation. Moreover, the interobserver variation has already been studied elsewhere using the same device (Sphygmocor Xcel) and was reported to be good (35,36). The present findings provide real-world evidence, but these could have been affected by drug-related chronotropic incompetence. Missing data may have played a role in our results. Hence, NTproBNP levels were only available for a limited proportion of the population (n=104) precluding its use in the multivariable regression analysis. But when LVEF is > 40% at 1 month after MI, NtproBNP is not done in clinical routine in our center. In the selected group of patients with preserved or near normal LVEF included in our study, LVEF was not an independent prognostic factor. But it is precisely for this reason, that we are interested in other markers such as VAC to better predict MACE in this population. We need to emphasize that individual PWV measurements do not show perfect reproducibility and display fair overlap between MACE and non-MACE patients. Despite a strong statistical significance, we acknowledge further studies will be needed to explore VAC in larger and multicenter registries. Lastly, Zamani has demonstrated that in a large multi-ethnic population of adults free of clinically evident cardiovascular disease at baseline, reflection magnitude independently predicted all-cause mortality (37). Reflection magnitude (the ratio of the amplitude of the backward wave to that of the forward wave) is a composite index influenced by both central and peripheral arterial structure and function and may represent a marker of overall arterial health. Unfortunately, we didn’t measure this parameter and it should be studied in the future.

CONCLUSIONS

VAC evaluation is feasible in the majority of patients with unaltered LVEF after MI. PWV/GLS ratio identifies a group of patients who are at higher risk of MACE and provides additional value on top of conventional non-invasive parameters in predicting MACE onset.

Data Availability Statement

No new data were generated or analysed in support of this research.

Conflict of interest

Nothing to disclose

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FIGURE LEGENDS

Figure 1. Flow-Chart of the study

Flow-Chart of the study. Ea: arterial elastance, Ees: left ventricular end-systolic elastance, GLS: global longitudinal strain, LVEF: left ventricular ejection fraction, PWV: pulse wave velocity

Figure 2. Major events according to PWV/GLS tertiles

Kaplan Meier analysis of freedom from major events (ME) according to PWV/GLS ratio tertiles. GLS: Global Longitudinal Strain, PWV: pulse wave velocity.

Figure 3. Incremental value of PWV/GLS ratio to predict major events onset

The bar graphs show the $\chi 2$ value for the four models associated with major events (ME). The baseline model includes age and 6MWT. The addition of PVW/GLS ratio provides incremental prognostic information over the baseline model and models incorporating PWV and left ventricular GLS. 6MWT: 6 minutes walking test, GLS: Global Longitudinal Strain, PWV: pulse wave velocity.

Central Illustration. Prognostic significance of ventriculo-arterial coupling in patients following AMI

Table 1. Baseline characteristics of the study population

	Overall (n=374)	No MACE (n=333)	MACE (n=41)	p
Demographics				
Age, y	59 [50; 65]	58 [50; 65]	64 [58; 74]	**<0.001**
Male	286 (76.5)	257 (77)	29 (71)	0.47
BMI, kg/m²	27 [24; 30]	27 [24; 29]	26 [24;31]	0.449
Waist circumference, cm	97 [91; 106]	97 [90; 106]	98 [92; 106]	0.953
Obesity	123 (33)	108 (33)	15 (37)	0.75
Active smoking	268 (72)	240 (72)	28 (68)	0.72
STEMI	244 (68)	221 (70)	23 (56)	0.11
Clinical Evaluation				
NYHA				0.25
I	295 (80)	265 (80.8)	30 (73)	
II	67 (18.2)	58 (17.7)	9 (22)	
III	7 (1.9)	5 (1.5)	2 (5)	
IV	0(0)	0(0)	0(0)	
Systemic hypertension	163 (44)	141 (43)	22 (54)	0.25
Hypercholesterolemia	155 (42)	131 (40)	24 (59)	**0.03**
Stroke/TIA	12 (3)	9 (3)	3 (7)	0.27
Diabetes mellitus	65 (17)	54 (16)	11 (27)	0.14
Prior CAD[1]	36 (10)	27 (8)	9 (22)	**0.01**
CKD	11 (3)	8 (2)	3 (7)	0.207
PAD	19 (5)	12 (4)	7 (17)	**0.001**
6MWT, m	482 [415; 550]	490 [425 ;550]	429 [382 ;501]	**0.005**
Biology				
Total cholesterol, g/L	1.23 [1.00; 1.45]	1.23 [1.06; 1.43]	1.38 [1.19; 1.84]	0.115
HDL, g/L	0.38 [0.33; 0.47]	0.38 [0.33; 0.47]	0.41 [0.36; 0.46]	0.36
LDL, g/L	0.63 [0.50; 0.80]	0.62 [0.50; 0.79]	0.63 [0.49; 0.88]	0.54
Creatinine, mg/L	9.3 [8.1; 10.5]	9.3 [8.1; 10.5]	10.2 [8.0; 13.4]	0.16
Haemoglobin, g/dL	14 [13; 15]	14 [13; 15]	13 [11; 14.0]	**0.004**
NtProBNP, pg/mL (n=104)	447 [170; 1052]	434 [162; 948]	1633 [533; 1793]	0.10
Treatment				
Aspirin	360 (98)	319 (98)	41 (100)	0.59
Bi-antiaggregation	357 (95)	319 (98)	37 (90)	0.80
Betablocker	352 (96)	314 (96)	38 (93)	0.56
ACE inhibitor or ARBs	353 (96)	317 (97)	36 (88)	**0.02**
Statin	356 (97)	318 (98)	38 (93)	0.22

Data are median ± IQR or n (%) BMI: body mass index. NYHA: New York Heart Association. TIA: transient ischemic attack. CAD: coronary artery disease. CKD: chronic kidney disease. PAD: peripheral artery disease. 6MWT: 6 minutes walking test. HDL: high-density lipoprotein. LDL: low-density lipoprotein. ACE inhibitor: inhibitor of angiotensin converting enzyme. ARBs: angiotensin receptor blockers.

[1]: history of CAD before the acute coronary syndrome

Table 2. Cardiac and vascular characteristics

	Overall (n=374)	No MACE (n=333)	MACE (n=41)	p
Cardiac Imaging				
SBP, mmHg	127 [114; 141]	127 [114; 140]	126 [115; 145]	0.39
DBP, mmHg	70 [64; 78]	70 [65; 7]	72 [63. 78]	0.84
HR, bpm	61 [55; 69]	61 [54; 67]	65 [56; 74]	**0.05**
LVEF, %	59 [53; 64]	59 [53; 64]	57 [51; 64]	0.38
LVEDV, mL	118 [100; 140]	118 [100; 139]	122 [95; 147]	0.90
SV, mL	68 [59; 79]	68 [59; 80]	68 [54; 78]	0.44
GLS, %	17.1 [14.6; 19.0]	17.3 [14.8; 19.0]	15.4 [11.6; 18.8]	**0.01**
LVMi, g/m²	86 [72; 100]	85 [71; 99]	91 [79; 104]	0.09
LAVi, mL/m²	35 [29; 42]	34 [29; 41]	39 [33; 47]	**0.01**
E/e'	8.3 [6.7; 10.2]	8.1 [6.6; 9.8]	9.9 [8.0; 11.9]	**<0.001**
TAPSE, mm	23 [21; 26]	24 [21; 26]	23 [21; 25]	0.32
SPAP, mmHg	29 [25; 34]	29 [25; 33]	36 [26; 40]	0.07
GWI, mmHg%	1839 [1523 ; 2105]	1857 [1543 ; 2122]	1697 [1365. 1918]	**0.03**
GCW, mmHg%	1938 [1639 ; 2216]	1944 [1647 ; 2234]	1782 [1544. 2035]	**0.05**
GWW, mmHg%	114.0 [78.5. 163.5]	111 [78. 160]	148 [86. 176]	0.14
GWE, %	93 [90 ; 95]	93 [90 ; 95]	92 [87 ; 95]	**0.01**
Arterial properties and VAC				
Central SBP, mmHg	118 [107; 129]	118 [107; 129]	121 [108; 133]	0.38
Central DBP, mmHg	74 [67; 81]	74 [67; 81]	72 [65; 80]	0.47
Central PP, mmHg	44 [36; 51]	43 [36; 51]	48 [39; 54]	0.10
SVR, $dyne.s.cm^{-5}$	1828 [1520; 2172]	1805 [1513; 2164]	1904 [1562; 2333]	0.31
Aix at 75, %	0.32 [0.21; 0.52]	0.32 [0.21; 0.54]	0.32 [0.22; 0.41]	0.88
Carotid-femoral PWV, m/s	10.2 [8.8; 12.0]	10.1 [8.7; 11.6]	12.2 [9.8; 14.3]	**0.002**
Ea, mmHg/mL	1.58 [1.33; 1.88]	1.57 [1.33; 1.87]	1.75 [1.46; 2.05]	**0.04**
Ees, mmHg/mL	2.05 [1.61 ; 2.51]	2.02 [1.61 ; 2.45]	2.25 [1.62 ; 2.82]	0.11
Ea/Ees	0.76 [0.68. 0.89]	0.77 [0.68. 0.89]	0.74 [0.67. 0.93]	0.75
PWV/GLS, $m.s^{-1}. \%^{-1}$	0.60 [0.50. 0.77]	0.59 [0.49. 0.74]	0.79 [0.59. 1.24]	**<0.001**
Handgrip evaluation				
Ea, mmHg/mL	1.58 [1.33. 1.88]	1.79 [1.52. 2.1]	2.15 [1.58. 2.49]	**0.03**
Ees, mmHg/mL	2.05 [1.61. 2.51]	2.31 [1.86. 2.72]	2.64 [2.04. 3.2]	**0.02**
Ea/Ees	0.76 [0.68. 0.89]	0.80 [0.71. 0.89]	0.76 [0.71. 0.9]	0.50

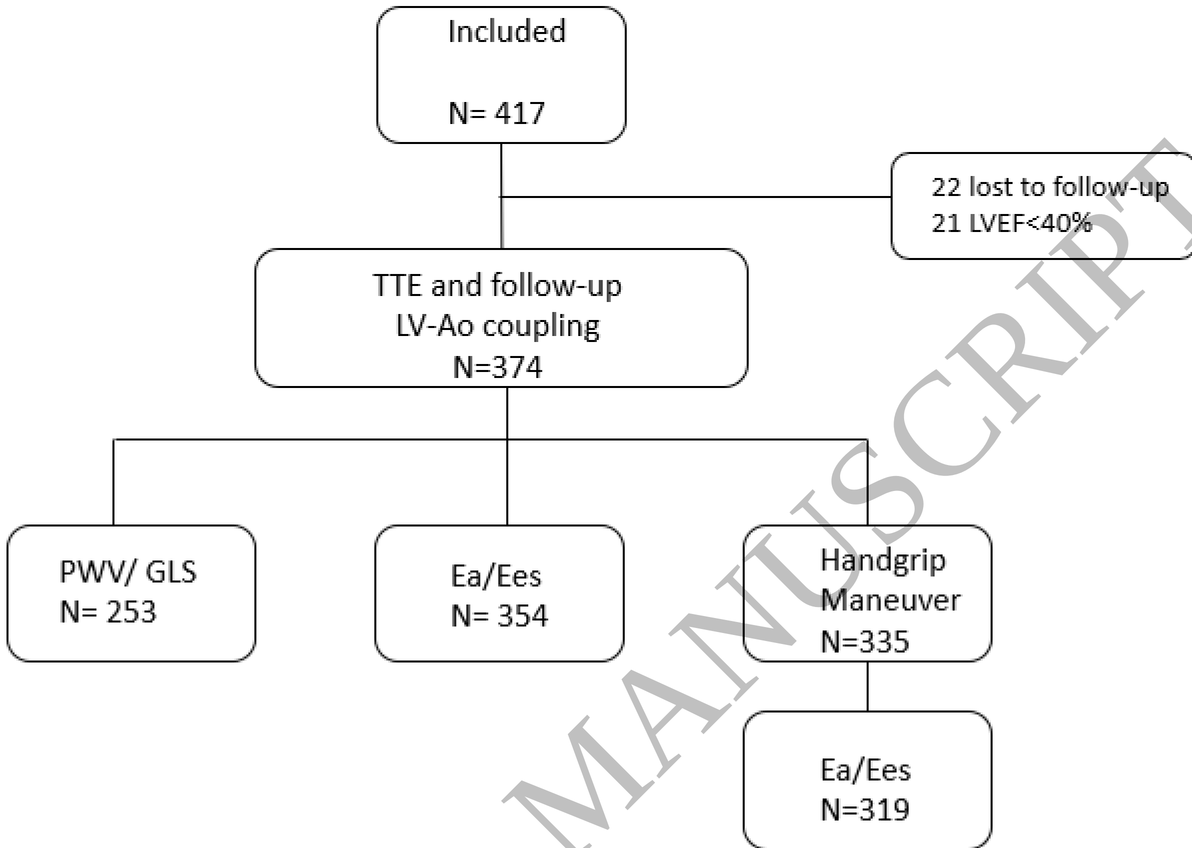
Data are median [IQR]. n (%). Aix: aortic augmentation index. DBP: diastolic blood pressure. Ea: arterial elastance. Ees: left ventricular end-systolic elastance. GCW: global constructive work. GLS: global longitudinal strain. GWE: global work efficiency. GWI global work index. GWW: global wasted work. HR: heart rate. LAVi: indexed left atrial volume. LVMi: indexed left ventricular mass. LVEDV: left ventricular end-diastolic volume. LVEF: left ventricular ejection fraction. SBP: systolic blood pressure. SPAP: systolic pulmonary arterial pressure. SV: stroke volume. SVR: systemic vascular resistance. TAPSE: tricuspid annular plane systolic excursion, VAC: ventricular-arterial coupling

Table 3. Cox regression analysis to assess determinants of MACE following AMI at 1 month

	Univariable		Multivariable	
	β ± SE	**p**	**β ± SE**	**p**
Age	0.04 ± 0.01	**0.0002**	--	--
Sex (male)	0.8 [0.4;1.5]	0.45		
BMI (kg/m²)	0.02 ± 0.03	0.55		
Systemic hypertension	1.5 [0.8;2.8]	0.20		
Hypercholesterolemia	2.1 [1.1;3.8]	**0.02**		
Diabetes	1.8 [0.9;3.6]	0.09		
STEMI	0.60 [0.33; 1.1]	0.11		
6MWT	-0.004 ± 0.001	**0.001**		
LVEF (%)	-2.3 ± 1.9	0.23		
LV SV (mL)	-0.003 ± 0.01	0.74		
LVEDV (mL)	0.002 ± 0.005	0.64		
LV GLS (%)	-0.1 ± 0.1	**0.006**	--	--
LVMi (g/m²)	0.01 ± 0.007	0.07		
E/E'	0.02 ± 0.01	0.21		
LAVi (mL/m²)	0.03 ± 0.01	**0.02**		
TAPSE (mm)	-0.03 ± 0.03	0.35		
GWI (mmHg%)	-0.0009 ± 0.0004	**0.02**		
GCW (mmHg%)	-0.0008 ± 0.0004	**0.04**		
GWW (mmHg%)	0.003 ± 0.002	0.21		
GWE (mmHg%)	-0.08 ± 0.03	**0.004**		
PWV (m/s)	0.1 ± 0.00	**<0.0001**		
Arterial elastance (mmHg/mL)	0.02 ± 0.07	0.83		
Ees (mmHg/mL)	0.007 ± 0.06	0.89		
Ea/Ees (n=357)	0.3 ± 0.1	**0.03**	--	--
PWV/GLS ($m.s^{-1}.\%^{-1}$)	2.2 ± 0.46	**<0.0001**	2.9 ± 0.69	**<0.0001**
HG Arterial elastance (mmHg/mL)	0.04 ± 0.01	**0.03**		
HG Ees (mmHg/mL)	0.02 ± 0.03	0.47		
HG Ea/Ees	0.5 ± 0.3	0.07		

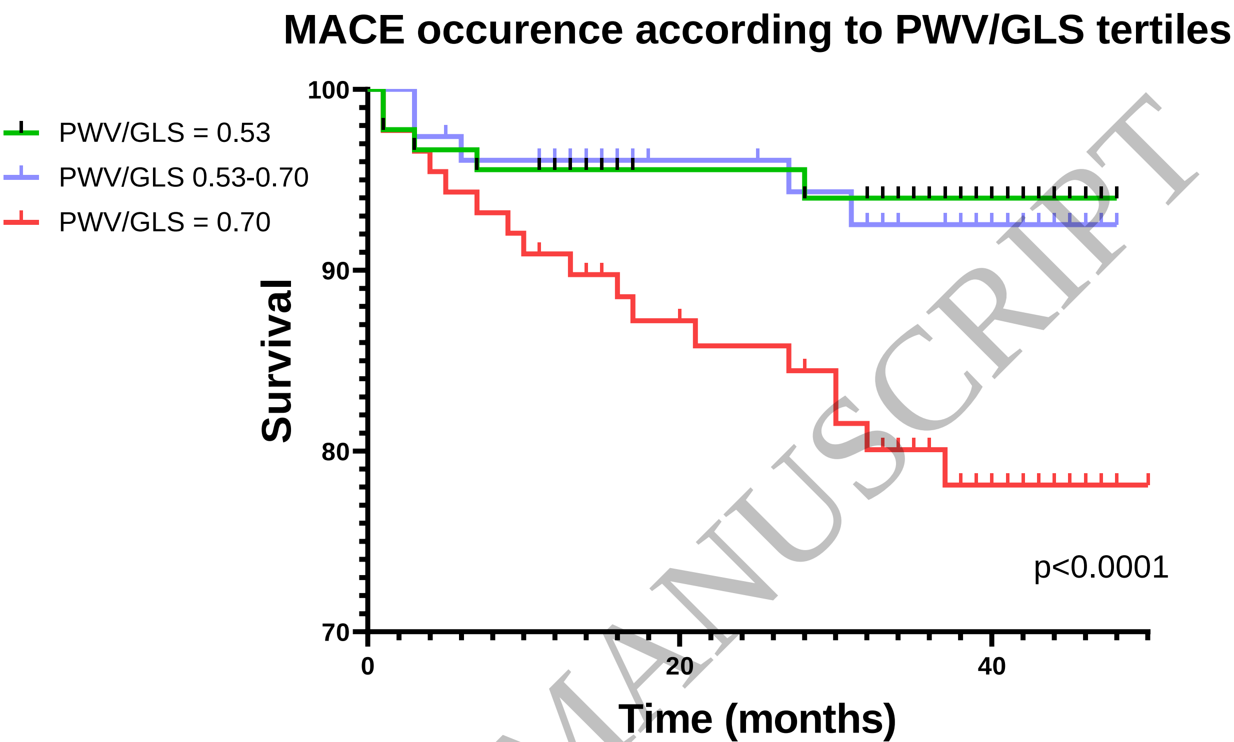
Data are β ± SE for quantitative data and HR for qualitative data. Unless specified, all parameters were assessed at rest. Adjustment for age, GLS, PWV/GLS, Ea/Ees (backward method). 6MWT: 6 minutes walking test, BMI: body mass index, Ees: left ventricular end-systolic elastance, GCW: global constructive work, GWE: global work efficiency, GWI: global work index, GWW: global wasted work, HG: hand grip, LAVi: indexed left atrial volume, LVEDV: left ventricular end-diastolic volume, LVEF left ventricular ejection fraction, LVMi: indexed left ventricular mass, PWV: pulsed wave velocity, TAPSE: tricuspid annular plane systolic excursion.

Figure 1. Flow-Chart



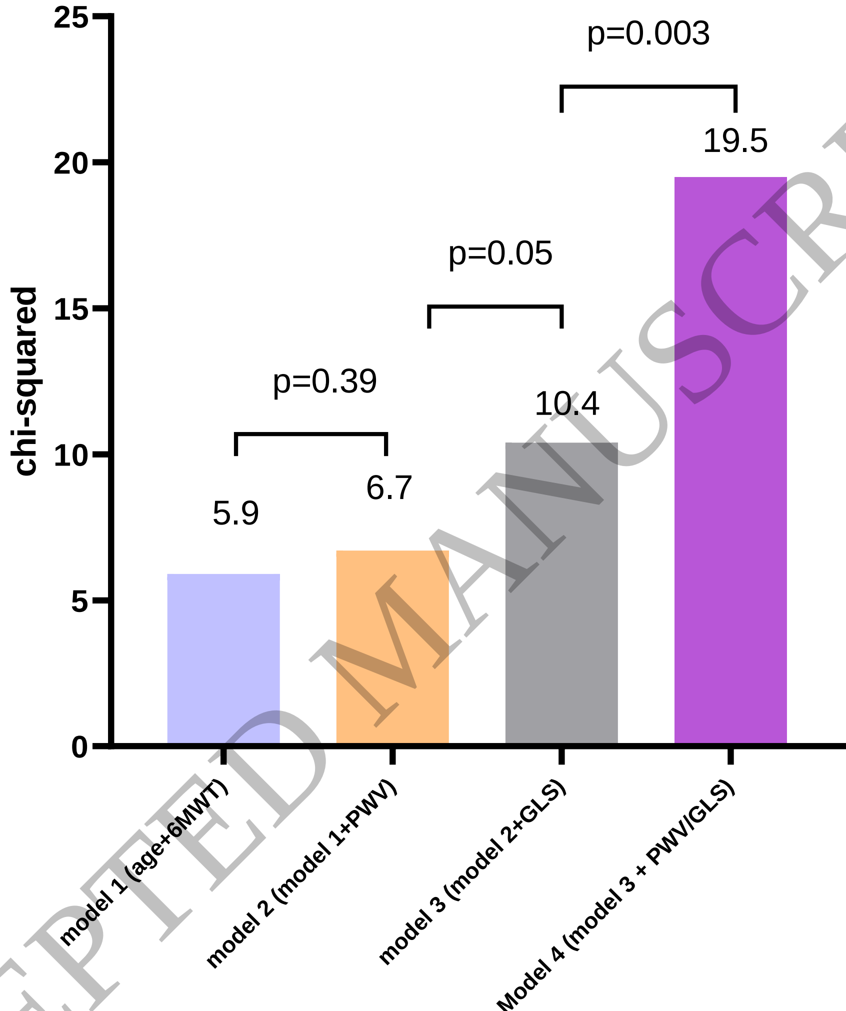
Ea: arterial elastance, Ees: left ventricular end-systolic elastance, GLS: global longitudinal strain, LVEF: left ventricular ejection fraction, PWV: pulse wave velocity.

Figure 2. Major Adverse Cardiovascular Events according to PWV/GLS tertiles



GLS: Global Longitudinal Strain, PWV: pulse wave velocity

Figure 3. Incremental value of PWV/GLS ratio to predict MACE onset



Model 1 = age + 6MWT; Model 2 = Model 1 + PWV; Model 3 =Model 2 + GLS; Model 4 = Model 3 + PWV/GLS ratio. 6MWT: 6 minutes walking test, GLS: Global Longitudinal Strain, PWV: pulse wave velocity

Central Illustration.