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Reviews in Cardiovascular Medicine

Original Research

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DOI:10.31083/j.rcm2204178

Submitted: 3 September 2021 Revised: 29 October 2021 Accepted: 11 November 2021 Published: 22 December 2021

Increased aortic pulse wave velocity (PWV) has been proved as a strong predictor of major adverse cardiovascular events (MACE) in patients after myocardial infarction (MI). Due to the various technical approaches the level of high PWV values show significant differences. We evaluated the cut-off PWV values for MACE prediction using cardiac magnetic resonance imaging (CMR) and oscillometric methods for validating the prognostic value of high PWV in post-infarcted patients. Phase contrast imaging (PCI) and oscillometric based Arteriograph (AG) were compared in this 6 years follow-up study, including 75 consecutive patients of whom 49 suffered previous ST-elevation myocardial infarction (STEMI). Patients received follow-up for MACE comprising all-cause death, non-fatal MI, ischemic stroke, hospitalization for heart failure and coronary revascularization. An acceptable agreement and significant correlation (rho: 0.332, $p < 0.01$) was found between AG and CMR derived PWV values. The absolute values, however, were significantly higher for AG (median (IQR): 10.4 (9.2–11.9) vs 6.44 (5.64–7.5) m/s; $p < 0.001$). Totally 51 MACE events occurred during the 6 years follow-up period in post-infarcted patients. Kaplan-Meier analysis in both methods showed significantly lower event-free survival in case of high PWV (CMR: >6.47 m/s, AG: >9.625 m/s, $p < 0.001$, respectively). Multivariate Cox regression revealed PWV as a predictor of MACE (PWV CMR hazard ratio (HR): 1.31 (CI: 1.1–1.7), PWV AG HR: 1.24 (CI: 1.0–1.5), $p < 0.05$, respectively). Increased PWV derived by AG and CMR methods are feasible for MACE prediction in post-infarcted patients. However, adjusted cut-off values of PWV are recommended for different techniques to improve individual risk stratification.

Keywords

Pulse wave velocity; Cut-off value; Arteriograph; Cardiac magnetic resonance imaging; MACE prediction; Post-infarcted patients

1. Introduction

Early risk stratification of patients surviving myocardial infarction (MI) is crucial for the assessment of prognosis and to maintain proper secondary prevention treatment [1]. Increased aortic stiffness has been shown to be a strong predictor of mortality in the general population and in patients after MI [1–5]. Elevated pulse wave velocity (PWV), as the most accepted measure of arterial stiffness, was found to be an independent predictor of major adverse cardiovascular events (MACE) and it has suggested as a prognostic parameter for risk stratification in patients after ST-elevation myocardial infarction (STEMI) [2–6]. High PWV was also associated with elevated cardiac biomarkers and altered post-infarcted left ventricular (LV) hemodynamics [7, 8].

The new European cardiovascular prevention guideline suggests the use of arterial stiffness for future cardiovascular disease risk prediction, however, measurement difficulties and substantial publication bias argue against widespread use [9]. Recent guidelines recommended assessment of carotid-femoral (cf) PWV in clinical practice with a cut-off value of 10 m/s to evaluate cardiovascular risk focused mainly on healthy populations [10, 11]. Latest metaanalysis supports such recommendations even for high-risk populations based on cfPWV and brachial-ankle (ba) PWV measurements [12]. However, several other non-invasive techniques suitable for clinical routine have been developed to measure PWV, although they differ according to their physical basis: applying Doppler or high fidelity pressure measuring devices [13, 14]. The advantages of these inherently different techniques are their quick and relatively easily done, user friendly method, however, they have distinct disadvantages. The various non-invasive technical approach show significant differences in the calculated PWV values mainly due to the different length estimation of the pulse wave travel distance [15, 16]. Cardiac magnetic resonance imaging (CMR) provides accurate non-invasive measurements of aortic length, and phase-contrast imaging (PCI) is a validated method for measuring pulse wave transit time and thus allowing accurate calculation of PWV [14, 17, 18]. Also CMR imaging represents the gold-standard technique in post-infarcted patients for the assessment of LV function and structure as well as infarct size by late gadolinium enhancement (LGE). PCI with a slight adjustment to the routine protocol can be performed during the same CMR scan. However, in clinical practise the use of CMR for PWV

assessment is not widespread, due to high financial requirements and need of specifically trained operators.

In this prospective study we investigated the role of PWV for the prediction of MACE in post-infarcted patients assessed by two different non-invasive methods. We compared a CMR based PCI technique and an invasively validated, user friendly oscillometric based method (Arteriograph - AG) for calculating PWV. We aimed to evaluate the cut-off PWV values for each method, while MACE predict and validate the prognostic value of high PWV in post-infarcted patients in a 6-years follow-up.

2. Material and methods

2.1 Study population

Seventy-five consecutive patients (56 men and 19 women, average age mean $\pm$ SD: 55 $\pm$ 11 years) were included in whom routine CMR examination was performed on a clinical indication: assessment of LV function and infarct size with a history of coronary artery disease (CAD) or suspected cardiomyopathy for no CAD patients. Exclusion criteria were the presence of any cardiac arrhythmia, significant valvular heart disease, renal dysfunction with an estimated glomerular filtration rate $<$30 mL/min per 1.73 m^2, hemodynamically unstable condition and contraindications for CMR (pacemaker, claustrophobia, cerebral aneurysm clip, and known contrast agent allergy to gadolinium). All patients had simultaneous measurements of PWV by AG device and PCI CMR. Medical history, current medications and presence of any cardiovascular risk factors were assessed using personal medical documentary.

Subjects were recruited and categorized into two groups based on their history of CAD. The patients of post-infarcted group have history of previous ST-elevated myocardial infarction (STEMI), any previous coronary artery revascularisation (percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass surgery (CABG)) and typical ischaemic-pattern of late gadolinium enhancement (LGE). The control group has no CAD and no CMR evidence for cardiomyopathy.

Patients received a median follow-up of 6 years for MACE comprising all-cause death, including cardiovascular death, non-fatal myocardial infarction, hospitalization for heart failure, coronary revascularization and ischemic stroke.

2.2 Oscillometric analysis

The invasively validated Arteriograph device (AG) (TensioMed, Budapest, Hungary) measures aortic PWV based on an oscillometric method analysing arterial pressure curves registered in the upper arm. The algorithm has been described in detail previously [13, 19]. All measurements were performed in a supine position after 5 minutes of rest. A tape measure was used for compute the distance between the jugulum and the symphysis, two characteristic anatomical points [19, 20]. The distance travelled by the pulse wave divided by the difference in time, called as "return time" (RT) in milliseconds between the beginning of the first and second (reflected) waves defines the aortic PWV in m/s. Two separate measurements were performed and for statistical analysis, the mean PWV values of the two measurements were used.

2.3 Phase contrast CMR

CMR was performed in all participants on a 1.5 T MRI scanner (Magnetom Avanto, Siemens, Erlangen, Germany). In the course of CMR imaging first pre-contrast images were acquired. 3D aortic angiography was carried out during the administration of 0.15 mL/body weight in kgs gadobutrol contained contrast agent (Gadovist, 1.0 M, Bayer Pharma AG, Berlin, Germany) followed by a 20 mL saline flush, both administered at a rate of 2 mL/s. LGE imaging was performed 10 minutes after the contrast agent injection using inversion-recovery gradient echo sequences with the inversion time set to null viable myocardium.

Velocity encoded PCI was applied to measure the through-plane flow at two predefined locations in the ascending aorta and at the middle zone of the abdominal aorta. The first plane was positioned cross-sectional to the aortic arch above the sinus Valsalva, at the level of the pulmonary bifurcation, thus intersected the proximal segment of the descending aorta as well. The second plane was placed perpendicular to the longitudinal axis of the abdominal aorta, immediately proximal to the renal arteries.

Imaging parameters included the following: echo time of 1.15 ms, repetition time of 32.52 ms, flip angle 55 degrees, slice thickness of 8 mm, field of view at 325 $\times$ 400 mm, image resolution 256 $\times$ 256. The temporal resolution was optimised to ensure that 100 phases per cardiac cycle were obtained. Velocity encoding was set to 150 cm/s for through plane flow quantification, which was adjusted in the case of aliasing artefacts.

The aortic path lengths among the planes of the flow measurements were determined along the centreline of the aorta within the 3D aortic angiography image using the software package of MASS analytical software (MASS, v2020 EXP, Leiden University Medical Center, Leiden, The Netherlands). For quantitative flow curves, automatic vessel segmentation was performed in magnitude images guided by PC images with manual correction where needed. With the new module of MASS analytical software the flow curves from the two predefined planes were delineated simultaneously with a real time shift. For the time delay calculation, the time-to-max-upslope approach was applied as this has been seemed like the most reliable method and the less subject to sampling error [21]. The max-upslope of the flow waveforms at each location was calculated and a regression line was fitted to the maximum upslope of each of the flow curves intersecting the baseline tangent. The difference between the baseline intersection points determined the time delay in milliseconds. The PWV (expressed in m/s) was calculated automatically by dividing the aortic length between the measurement planes by the transit time calculated as the temporal shift between the max-upslopes of the ascending part of the flow waveforms.

LV volumes and function were calculated on short-axis cine images by using the semi-automated QMassMR method with a special algorithm for trabeculation detection - MassK mode technique (QMassMR, version 7.6, Medis Medical Imaging Systems, Leiden, the Netherlands). The typical ischemic (subendocardial or transmural) pattern of hyperenhancement was visually assessed on LGE images. The volume of MI as then quantified with a semiautomatic approach using the threshold of 5 standard deviations (SD) above the average of the normal myocardium [22]. Infarct size as a percentage of LV myocardium was then calculated. LV scar score (LVSS) was calculated according to the transmural extension of MI using a 3-point scale for each segment on a 16-segment model (0 = no hyperenhancement, 1 $\leq$ 50%, 2 $\leq$ 50%) [23]. Visual semi quantitative assessment of regional wall motion and thickening for wall motion score index (WMSI) was also performed using the 16-segment model [24].

2.4 Statistical analysis

Statistical analysis was carried out using SPSS Statistics for Windows (Version 27.0, IBM Corp, Armonk, NY, USA). Data were expressed as median(IQR) or mean $\pm$ SD according to the distribution of variables. The comparison between oscillometry and PC CMR technique was tested by the Spearman correlation coefficient, Mann-Whitney analysis and Bland-Altman with 95% limits of agreement. Bland-Altman test was performed using MedCalc Statistical Software (version 20.014, MedCalc Software bv, Ostend, Belgium). Mann-Whitney analysis or independent-samples *t*-test were performed for testing of statistically significant differences between the different groups. Stepwise multivariate linear regression analysis was carried out to compare how PWV measurements were related to physiological variables. Kruskal–Wallis test was used for testing whether the LGE transmurality (TM) had any influence on PWV values according to the 3-point scale of LVSS (no LGE, <50% of TM and >50% of TM).

Receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cut-off points for the prediction of MACE. Outcome functions were expressed by Kaplan-Meier graphs, and groups were compared using the log-rank test. Univariate and multivariate Cox regression analysis was performed to identify outcome predictors.

p-values of less than 0.05 were considered statistically significant.

3. Results

CMR were performed in 75 patients of whom 71 had analysable data from pulse wave analysis using the AG device. Forty-nine patients were classified as post-MI patients of whom thirty-four showed ischaemic LGE pattern. Baseline characteristics of the participants are listed in Table 1.

In comparison of the two methods, PWV measurements by AG and CMR were significantly correlated (Spearman's rho: 0.332, $p = 0.005$). Absolute PWV values were significantly higher for AG compared with CMR measurements (mean $\pm$ SD: 10.35 m/s $\pm$ 1.77 m/s vs 6.73 m/s $\pm$ 1.59 m/s; median (IQR): 10.4 m/s (9.2–11.9 m/s) vs 6.44 m/s (5.64–7.5 m/s); $p < 0.001$). Bland Altman plot was created to test for methods' agreement. The bias showed that in general the mean difference between the two measures was 3.6 m/s (upper and lower limit of agreement: –0.2 and 7.5 m/s). The coefficient of variation was 43.9% (Fig. 1).

PWV data derived by both methods yielded a significant correlation with age and systolic blood pressure (CMR - age r = 0.567, $p < 0.001$; SBP r = 0.341, $p < 0.005$, AG – age r = 0.243, $p < 0.05$; SBP r = 0.239, $p < 0.05$), however, we did not find any gender-related differences. Multivariate linear regression analysis showed that age, BMI and heart rate had a predictive value for PWV derived by CMR ($p < 0.05$, respectively). In the case of using AG, only age was significantly related to PWV values as an independent factor ($p < 0.05$).

Post-MI group and patients without CAD did not differ in average age, actual systolic and diastolic blood pressure and heart rate. In post-MI patients significantly higher PWV values were measured by AG and MRI, (median (IQR) AG: 11.0 m/s (9.7–12.2 m/s) vs 9.05 m/s (7.3–10.1 m/s), MRI: 6.85 m/s (5.9–8.1 m/s) vs 5.79 m/s (4.9–6.5 m/s), $p < 0.001$, respectively) as data were compared to control (non-CAD) patients.

Significantly lower ejection fraction (EF), stroke volume index (SVi) and cardiac output index (COi) were assessed in post-MI patients compared to non-CAD patients ($p < 0.05$, respectively) (Table 1). In all patient cohort we found a significant correlation between AG-PWV and ESVi (r = 0.266, $p < 0.05$), SVi (r = –0.287, $p = 0.015$) and EF (r = –0.384, $p < 0.001$), however, CMR-PWV did not show any correlations with LV volumetric and functional data.

Typical ischaemic pattern of LGE was found in 69% (34/49) of post-MI patients. In patients with LGE significantly lower EF ($p = 0.001$) and significantly higher indexed end-systolic, end-diastolic volumes (ESVi, EDVi) ($p < 0.001$, respectively) and LV mass index ($p < 0.05$) were measured compared to post-MI patients without LGE. PWV values assessed by both methods did not show significant difference regarding the presence of LGE in the post-MI group. However, if we compared patients with LGE to non-CAD patients, then significantly higher PWV values were measured by both methods in the attendance of MI (AG $p < 0.001$, CMR $p < 0.05$).

Infarct size as the percentage of LV myocardium with a threshold limit of 5 SD showed strong positive correlation with LVSS, WMSI (rho: 0.82; 0.63, both $p < 0.001$) and ESVi, EDVi (rho: 0.52; 0.35, $p < 0.001$ and $p < 0.05$, respectively) along with a strong negative correlation with EF (rho: –0.59, $p < 0.001$). However, neither the AG, nor the MRI derived PWV values correlated with the infarct size. Furthermore, according to the 3-point scale of LVSS (no LGE, <50% of TM and >50% of TM) no significant differences were found between AG and CMR PWV values and TM ex-

Table 1. Baseline characteristics and descriptive parameters of all patient cohort and after stratification for post-infarcted and non-CAD control groups.

	All patients (n: 75)	Post-MI (n: 49)	Non-CAD (n: 26)	*p*-value
Baseline characteristic				
Age, years	55.2 ± 10.8	57.3 ± 8.5	51.3 ± 13.5	0.080
Male, n (%)	56 (75)	37 (75)	19 (73)	0.818
Body weight, kg	84.3 ± 18.2	85.0 ± 17.8	82.9 ± 19.1	0.529
Body height, cm	172.1 ± 8.3	171.3 ± 8.7	173.6 ± 7.3	0.213
BMI, kg/m²	28.3 ± 4.7	28.7 ± 4.3	27.3 ± 5.2	0.367
SBP, mmHg	132.2 ± 14.1	133.9 ± 14.1	129.0 ± 13.9	0.231
DPB, mmHg	76.8 ± 9.1	76.8 ± 9.1	76.9 ± 9.4	0.920
Heart rate, bpm	69.0 ± 9.9	68.5 ± 9.2	69.8 ± 11.3	0.684
Active smoking, n (%)	22 (29)	16 (33)	6 (23)	0.386
Hypertension, n (%)	52 (70)	43 (88)	9 (34)	**<0.001****
T2DM, n (%)	19 (25)	16 (32)	3 (12)	0.036*
CAD, n (%)	49 (65)	49 (100)	0 (0)	**<0.001****
Medications				
ACE-inhibitor/ARB, n (%)	46 (61)	38 (78)	8 (31)	**<0.001****
Beta-blockers, n (%)	50 (67)	42 (86)	8 (31)	**<0.001****
Calcium antagonist, n (%)	15 (20)	11 (23)	4 (15)	0.760
Statin, n (%)	41 (55)	38 (78)	3 (12)	**<0.001****
Antiplatelet, n (%)	50 (67)	41 (84)	9 (35)	**<0.001****
Laboratory results				
Serum glucose level, mmol/L	6.29 ± 1.8	6.46 ± 1.8	5.79 ± 1.8	0.052
HgbA1c, mmol/L	6.35 ± 1.0	6.35 ± 0.9	6.36 ± 1.4	0.937
Cholesterin, mmol/L	4.67 ± 1.2	4.61 ± 1.2	4.84 ± 1.1	0.927
LDL, mmol/L	2.89 ± 1.1	2.87 ± 1.2	2.96 ± 0.8	0.935
TG, mmol/L	1.68 ± 0.9	1.70 ± 1.0	1.64 ± 0.7	0.723
HDL, mmol/L	1.18 ± 0.4	1.14 ± 0.4	1.30 ± 0.5	0.297
Aortic stiffness				
AG PWV, m/s (IQR)	10.4 (9.2–11.9)	11.0 (9.7–12.2)	9.05 (7.3–10.1)	**<0.001****
CMR PWV, m/s (IQR)	6.44 (5.6–7.5)	6.85 (5.9–8.1)	5.79 (4.9–6.5)	**<0.001****
CMR derived parameters				
EDVi, mL/m^2	68.2 (57.4–83.1)	67.2 (55.7–83.3)	68.4 (60.7–83.2)	0.551
ESVi, mL/m^2	24.1 (18.6–41.3)	28.3 (19.5–42.7)	21.9 (18.5–30.6)	0.161
SVi, mL/m^2	40.6 (34.6–45.1)	38.5 (34.3–44.5)	44.5 (40.4–49.8)	**0.003***
COi, L/(m^2*min)	2.7 (2.5–3.5)	2.7 (2.5–3.0)	3.3 (2.61–4.17)	**0.007***
EF, %	60.8 (50.3–69.6)	54.8 (46.9–67.4)	66.2 (57.7–71.7)	**0.008***
LVMassi, g/m^2	66.1 (59.8–78.4)	66.0 (59.9–78.6)	66.1 (59.4–77.8)	0.898
Ischaemic pattern of LGE, n (%)	34 (45)	34 (69)	0 (0)	**<0.001****

MI, myocardial infarction; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; LGE, late gadolinium enhancement; ACE, angiotensin converter enzyme; ARB, angiotensin receptor blocker; HgbA1c, glycated haemoglobin; LDL, low-density lipoprotein; TG, triglyceride; HDL, high-density lipoprotein; AG PWV, pulse wave velocity derived by Arteriograph; CMR PWV, pulse wave velocity derived by CMR; EDVi, end-diastolic volume index; ESVi, end-systolic volume index; SVi, stroke volume index; COi, cardiac output index; EF, ejection fraction; LVMassi, left ventricular mass index; IQR, interquartile range. Data are represented as mean ± SD or median (IQR). *: $p < 0.05$, **: $p < 0.001$.

pansion using Kruskal-Wallis test (CMR PWV *p*: 0.224; AG PWV *p*: 0.297).

During the median follow-up of 6 years, totally 51 MACE events occurred at 31 post-MI patients. 14 patients had only 1, the other 17 patients suffered 2 or more MACE events. Baseline characteristics of the post-MI study cohort and their relation with MACE are summarized in Table 2. Patients underwent MACE were older (60.2 ± 6.9 vs 52.7 ± 5.5 years, $p < 0.05$), and had higher calculated PWV values derived by both methods (CMR: 6.98 (6.5–8.6) vs 6.20 (5.69–7.39) m/s, AG: 11.5 (9.95–12.63) vs 10.1 (9.23–11.18) m/s, $p < 0.05$ respectively). Moreover, significantly higher ESVi (31.46 (19.73–42.22) vs 20.75 (17.84–31.33) mL/m^2, $p < 0.05$) and lower EF (53.7 (46.7–63.9) vs 66.3 (47.9–70.3) %, $p < 0.05$) was detected in patients with MACE events. However, no statistically significant differences were found for sex, BMI,

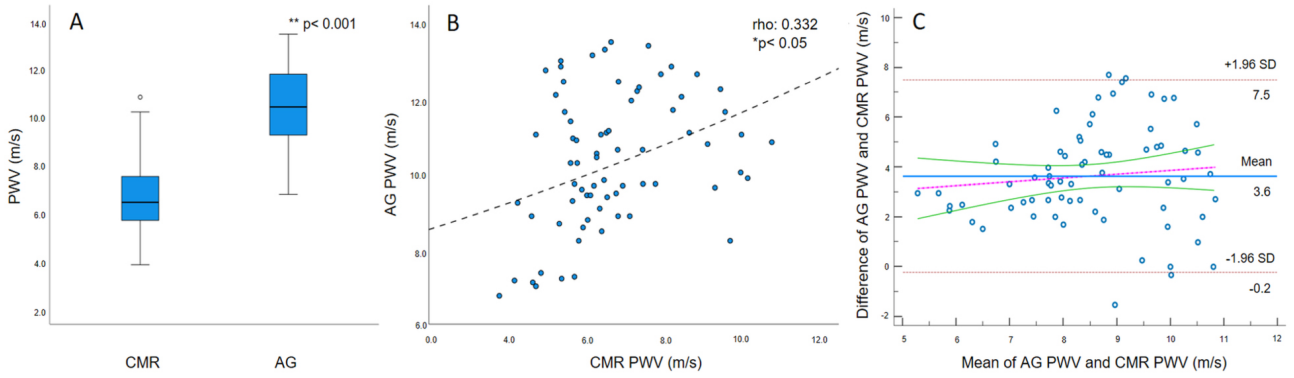


Fig. 1. Comparision of PWV measured by AG and CMR; absolute median PWV values (A), Spearman correlation (B) and Bland-Altman analysis (C). PWV, pulse wave velocity; CMR, cardiac magnetic resonance imaging; AG, Arteriograph.

mean diastolic blood pressure and heart rate, history of DM and smoking, infarct size or other volumetric CMR parameters between patients with and without MACE. Table 3 shows all cardiovascular events during the follow-up period.

For predicting the MACE-free survival in post-MI patients receiver operating characteristic (ROC) analysis was performed and optimized PWV cut-off values were calculated (CMR: 6.47 m/s; area under the curve (AUC) of 0.697, 95% confidence interval (CI) 0.57–0.82); AG: 9.625 m/s; AUC: 0.682, 95% CI: 0.56–0.81) (Fig. 2). The MACE events occurred significantly more often in post-MI patients with high PWV (CMR PWV >6.47 m/s 24 patients, 49% versus 7 patients, 14%; AG PWV >9.625 m/s 22 patients, 48% versus 6 patients, 13%; $p < 0.005$ respectively) during the 6 years follow-up (Table 3). According to Kaplan-Meier analysis, the MACE-free survival time counted till the first MACE occured, was significantly shorter in patients with high PWV derived by both methods (mean survival time (95% CI) CMR: 2.99 (2.16–3.83) vs 4.60 (3.90–5.39) years, AG: 3.22 (2.47–3.97) vs 5.05 (4.32–5.76) years, $p < 0.001$, respectively) (Fig. 2).

Univariate and multivariable regression analysis for predictors of MACE are shown in Table 4. Univariate Cox regression indicated age, history of hypertension, HF, left ventricle volumetric and functional parameters (EDVi, ESVi, EF, LGE) and PWV absolute values derived by both methods as predictors of MACE. Multivariable Cox regression analysis including PWV by both methods together with age, sex, mean arterial blood pressure, BMI, smoking revealed CMR and AG PWV as an independent predictor of MACE ($p < 0.05$).

4. Discussion

Measurement of aortic PWV is the gold-standard technique to assess aortic stiffness [10, 14]. Recently, high aortic PWV, measured by CMR, was proved as an independent predictor of MACE after STEMI [6]. However, PWV values show significant differences according to the applied various non-invasive technical approaches. In the present study, two valid, non-invasive technique were compared for the assessment of aortic PWV in post-infarcted patients: oscillometric based AG device and CMR PCI method. We found a good correlation between AG and CMR measurements. Agreement between the two methods was acceptable, Bland-Altman plot showed good agreement in the lower range, whereas in the upper range a scatter was observable (Fig. 1). This increasing discrepancy by higher PWV value was also found comparing AG to other commercially used non-invasive methods [25, 26]. According to previous studies the absolute PWV values were significantly lower assessed by PCI CMR measurements compared to other user friendly, non-invasive methods in healthy population and post-STEMI patients [27, 28]. Both techniques use the "transit-time" method for PWV calculation, which was described in detail previously. However, the applied travel distance measurements are different. While AG used an estimated travel distance from the sternal notch to the upper edge of the pubic bone, in CMR technique a precise aortic centreline distance measurements could be acquired, therefore an accurate PWV value could be assessed [29]. Rezai *et al.* [30] suggested that differences in PWV values originated from the altered distance measurements derived by the two methods in a healthy men-only population. According to their results differences in PWV by CMR and the AG device were primarily because of differences between the AG external surface estimate of aortic root to bifurcation length and that measured by CMR. In our patient cohort the use of the CMR length with the AG transit time to calculate PWV significantly reduced the mean difference (3.6 m/s versus 1.4 m/s, $p < 0.05$). However, the recalculated AG PWV using CMR measured length was still higher comparing to CMR PWV. Several other factors could influence the PWV agreement between the two methods. Differences in the transit time calculation: wave-peak detection by AG versus max-upslope of the flow waveforms measurements used for CMR. Also AG apply simultaneous approach to transit time measurement contrary to ECG gated CMR sequential records flow waveforms. However, in our study cohort the mean difference in tran-

Table 2. Baseline characteristics and descriptive parameters of the post-infarcted patients after stratification for MACE and no MACE groups.

Variable	Patients with MACE (n: 31)	No MACE (n: 18)	*p*-value
Age, years	60.2 ± 6.9	52.7 ± 5.5	**0.043***
Female, n (%)	6 (19)	6 (33)	0.273
BMI, kg/m^2	28.5 ± 4.5	29.2 ± 4.2	0.663
MAP, mmHg	97.6 ± 10.1	92.6 ± 8.6	0.097
Heart rate, bpm	68.7 ± 10.5	68.1 ± 6.6	0.827
Hypertension, n (%)	28 (90)	15 (83)	0.472
T2DM, n (%)	10 (32)	6 (33)	0.719
HF, n (%)	2 (6)	0 (0)	0.272
Active smoking, n (%)	8 (26)	8 (44)	0.180
ACE-inhibitor/ARB, n (%)	24 (77)	14 (78)	0.844
Beta-blockers, n (%)	26 (84)	16 (89)	0.424
Calcium antagonist, n (%)	6 (19)	5 (28)	0.464
Statin, n (%)	24 (77)	14 (78)	0.844
Antiplatelet, n (%)	26 (84)	15 (83)	0.877
EF, %	53.7 (46.7–63.9)	66.3 (47.9–70.3)	**0.043***
ESVi, mL/m^2	31.5 (19.7–42.2)	20.7 (17.8–31.3)	**0.023***
Ischaemic pattern of LGE, n (%)	22 (71)	12 (67)	0.925
Infarct size, %	16.0 (8.0–21.0)	17.0 (9.0–25.5)	0.608
AG PWV, m/s (IQR)	11.5 (9.9–12.6)	10.1 (9.2–11.2)	**0.045***
CMR PWV, m/s (IQR)	6.98 (6.5–8.6)	6.20 (5.7–7.4)	**0.038***

MI, myocardial infarction; MACE, major adverse cardiovascular events; BMI, body mass index; MAP, mean arterial pressure; T2DM, type 2 diabetes mellitus; HF, heart failure; ACE, angiotensin converter enzyme; ARB, angiotensin receptor blocker; EF, ejection fraction; LGE, late gadolinium enhancement; AG PWV, pulse wave velocity derived by Arteriograph; CMR PWV, pulse wave velocity derived by CMR; IQR, interquartile range. Data are represented as mean ± SD or median (IQR). *: $p < 0.05$.

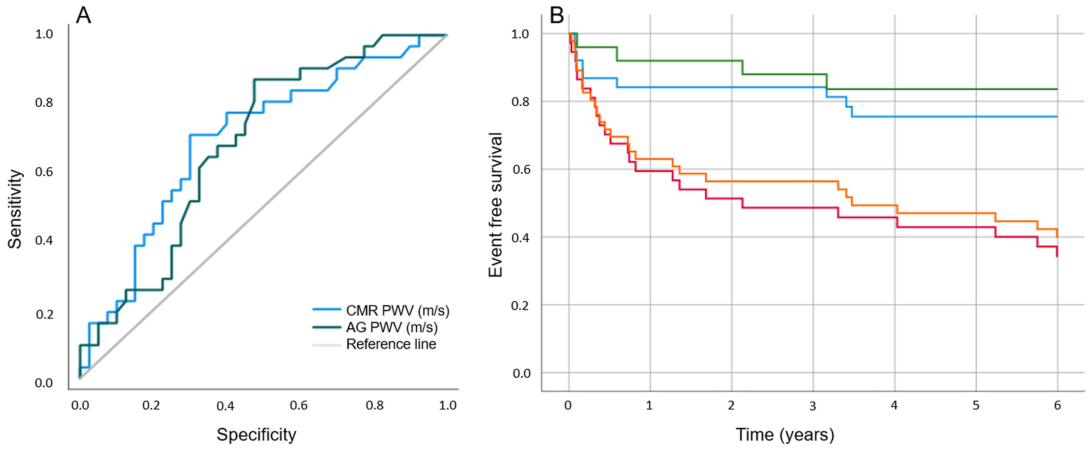
Table 3. The incidence of major adverse cardiovascular events (MACE) in all post-infarcted patients cohort and after grouping patients by the PWV cut-off values derived by each methods, during the 6 years follow-up.

MACE events in post-infarcted patients	All post-MI (n: 49)	CMR PWV (n: 49)		AG PWV (n: 46)	
		<6.47 m/s	≥6.47 m/s	<9.625 m/s	≥9.625 m/s
Number of patients with MACE, n (%)	31 (63)	7 (14)	24 (49)	6 (13)	22 (48)
Total number of MACE, n	51	10/51	41/51	8/48	40/48
All cause death, n (%)	8 (15)	0	8 (20)	1 (12.5)	7 (17.5)
Cardiovascular death, n (%)	3 (6)	0	3 (7)	0	3 (7.5)
Non-fatal myocardial infarction, n (%)	6 (12)	0	6 (15)	1 (12.5)	5 (12.5)
Hospitalisation for coronary revascularisation, n (%)	28 (55)	9 (90)	19 (46)	5 (62.5)	20 (50)
Hospitalisation for heart failure, n (%)	6 (12)	1 (10)	5 (12)	1 (12.5)	5 (12.5)
Ischemic stroke, n (%)	3 (6)	0	3 (7)	0	3 (7.5)

sit time measured by AG was not significant to that calculated by MRI. Finally measurement conditions such as inconvenient temperature, noise and light may influence patients' emotions in the scanner resulting in variation between the two methods.

Other non-invasive devices applying direct body surface distance measurements overestimate real anatomic pathway [29]. Several methodological considerations were published according to pulse wave travel distance calculations (such as the 80 % method or the subtraction methods), although this topic has remained highly controversial [29, 31]. Sugawara *et al.* [32] indicated the application of a simple conversion factor providing less estimation errors and similarly reliable and equivalent cfPWV values obtained with both accepted travel distance calculating methods. According to the above mentioned findings and our recent results, we emphasize that PWV values derived by different non-invasive methodologies show good agreements and similar trends, but the data are not interchangeable in the same patient.

Corresponding to several studies, we found significantly higher PWV values in post-infarcted patients [6, 8, 28, 29]. High aortic stiffness results in an early pulse-wave reflection, which shifts towards the reflected pulse from diastole to systole. The reflection wave augments systolic blood pressure and increases LV afterload and myocardial wall stress. These hemodynamic alterations result in impaired coronary



	Cut-off (m/s)	AUC	95 % CI	Sensitivity (%)	Specificity (%)
CMR PWV	6.47	0.697	0.57-0.82	0.710	0.300
AG PWV	9.625	0.682	0.56-0.81	0.871	0.475

Fig. 2. ROC analysis of PWV derived by AG and CMR for the prediction of MACE (A) and Kaplan-Meier curves for the occurrence of MACE stratified by PWV (B). PWV cut-off values calculated by ROC analysis. ROC, reciever operating characteristic; PWV, pulse wave velocity; AG, Arteriograph; CMR, cardiac magnetic resonance imaging; MACE, major adverse cardiovascular events; AUC, area under curve; CI, confidence interval.

perfusion. In the present study an association between aortic stiffness and ESVi, and impaired CO was found as described previously by Hirsch *et al.* [7]. High aortic PWV is associated with adverse effects on LV myocardium related to hemodynamic biomarkers in post-infarcted patients. Aortic PWV independently predict high-sensitivity cardiac troponin T concentrations [33] and directly associated with high plasma levels of biomarkers of myocardial wall stress, such as natriuretic peptides and adrenomedullin [8]. In post-infarcted patients, the impact of the infarct size on cardiac remodelling and remaining LV dimensions and function has been broadly investigated [34, 35]. In the present study, we also aimed to focus the pathophysiological impact of high aortic stiffness on the injured LV myocardium and infarct size. Impaired vascular stiffness was linked to CAD severity in patients after MI [36], however, some studies did not find any significant correlation between the individual coronary lesion SYNTAX score and regional arterial stiffness parameters in patients with verified CAD [37, 38]. In our study, PWV derived by either methods did not correlate neither with the infarct size, nor with any LV function indicating parameter in neither of groups. Feistritzer *et al.* [39], similarly to our results, did not find significant correlation for PWV and LV EF, EDSVi, LVMassi and infarct size. We could conclude that although impaired arterial function and higher PWV values were found in patients with CAD and/or with LGE, our results suggest that arterial stiffness parameters cannot provide any additional information about the expansiveness of the MI and vice versa.

Previous meta-analyses have provided evidence on the predictive value of PWV for cardiovascular events and all-cause mortality [12, 40]. However, defining the threshold values for PWV calculation is challenging. PWV cut-off values may differ depending on the applied methods and on the nature and risk factors of the examined population cohort. An expert consensus recommended a cut-off value of 10 m/s for cfPWV as a fixed threshold focused mainly on healthy population [3]. A recent systematic review and meta-analysis of non-invasive cfPWV studies demonstrated the importance of arterial stiffness as an indicator of cardiovascular risk even in high-risk populations [12]. The cut-off points based on cfPWV and baPWV studies ranged between 9.9 and 13 m/s for cardiovascular mortality, and from 9.9 to 11.8 m/s for all-cause mortality. cfPWV is the recommended arterial stiffness measurement technique according to the recent guidelines due to the large amount of longitudinal data from cohort studies [10, 14]. New instrumental solutions that allow the PWV assessment in clinical routine, such as CMR or oscillometric (AG) methods emerge. Beside the high accuracy of cfPWV methods the measuring easiness of oscillometric PWV, since the latter only requires the wrapping of blood pressure cuff on one upper arm, presenting this method as an applicable tool for PWV assessment in daily clinical practice. However, the various emerging non-invasive technical approach show significant differences in the calculated PWV values mainly due to the different length estimation of the pulse wave travel distance [15, 16]. CMR provides accurate non-invasive measurements of aortic length, and phase-contrast imaging is a validated method for measuring pulse wave transit time and thereby allowing accurate calculation of PWV.

We evaluated the optimized cut-off PWV values for each applied methods for predicting MACE-free survival and support the prognostic value of high PWV in post-infarcted pa-

Table 4. Univariate and multivariate Cox regression analysis for the prediction of MACE.

Univariate Cox regression		
	HR (95% CI)	*p* value
Age, ys	1.06 (1.02–1.10)	**0.002***
Sex, female, n (%)	0.59 (0.243–1.43)	0.240
BMI, kg/m^2	1.04 (0.96–1.11)	0.358
MAP, mmHg	1.03 (0.99–1.06)	0.152
Heart rate, bpm	0.99 (0.96–1.03)	0.671
CMR PWV, m/s	1.35 (1.10–1.65)	**0.004***
AG PWV, m/s	1.26 (1.03–1.54)	**0.025***
CMR PWV $\geq$6.47 m/s	3.53 (1.63–7.61)	**0.001***
AG PWV $\geq$9.625 m/s	4.95 (1.73–14.18)	**0.003***
Hypertension, n (%)	5.43 (1.66–17.82)	**0.005***
T2DM, n (%)	1.38 (0.66–2.90)	0.395
HF, n (%)	7.69 (2.21–26.79)	**0.001****
Active smoking, n (%)	0.71 (0.32–1.57)	0.396
EF, %	0.95 (0.93–0.98)	**<0.001****
EDVi, mL/m^2	1.02 (1.00–1.03)	**0.046***
ESVi, mL/m^2	1.03 (1.01–1.05)	**<0.001****
Ischemic LGE, n (%)	2.94 (1.42–6.08)	**0.004***
Multivariate Cox regression		
	HR (95% CI)	*p* value
CMR PWV, m/s	1.31 (1.07–1.66)	**0.010***
Age, ys	1.17 (1.00–1.09)	**0.048***
Sex, female, n (%)	0.55 (0.21–1.45)	0.229
BMI, kg/m^2	1.01 (0.93–1.09)	0.895
MAP, mmHg	1.00 (0.97–1.04)	0.920
Active smoking, n (%)	0.82 (0.36–1.89)	0.632
AG PWV, m/s	1.24 (1.01–1.53)	**0.037***
Age, ys	1.05 (1.00–1.10)	**0.028***
Sex, female, n (%)	0.50 (0.18–1.38)	0.180
BMI, kg/m^2	1.00 (0.91–1.09)	0.932
MAP, mmHg	1.01 (0.97–1.05)	0.544
Active smoking, n (%)	0.66 (0.28–1.58)	0.353

BMI, body mass index; MAP, mean arterial pressure; CMR PWV, pulse wave velocity derived by CMR; AG PWV, pulse wave velocity derived by Arteriograph; T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; HF, heart failure; EF, ejection fraction; EDVi, end-diastolic volume index; ESVi, end-systolic volume index; LGE, late gadolinium enhancement; HR, hazard ratio; CI, confidence interval. Bold font is used for statistically significance data; *: $p < 0.05$, **: $p < 0.001$.

tients. During the 6-years follow-up period 51 MACE events were observed in post-MI patients, which is in line with data from literature [40]. In our study, ROC analysis revealed a 6.47 m/s and a 9.625 m/s PWV cut-off values for predicting MACE by CMR and AG methods. Both the AUC values and the sensitivity, specificity of the calculated cut-off values indicate weaknesses in the test accuracy, although they may be reasonable, due to the high discrepancy of the measures. Feistritzer *et al.* [6] calculated a comparable, 7.3 m/s cut-off PWV value derived by PCI CMR with a similar AUC value of 0.68 (95% CI 0.56–0.79) for predicting MACE in post-STEMI patients. However, in their findings the association between PWV and MACE was mostly driven by the occurrence of new congestive heart failure. In our study, the hospitalisation for coronary revascularisation exposed the majority of MACE events (Table 3). It is important to emphasize, that in our post-infarcted patient cohort high aortic PWV, non-invasively assessed by both CMR and AG methods is associated with reduced MACE-free survival at 6 years of follow-up. PWV is an independent predictor of MACE for both non-invasive methods even after adjustment for age, sex, mean arterial blood pressure, BMI and active smoking.

Our AG derived PWV results support the recommendations for high-risk populations, as the cut-off point in the current study was a 9.625 m/s representing the increased risk for post-infarcted patients. In the study of Accus *et al.* [41] a PWV cut-off value of 10.15 m/s was calculated to predict MACE in a good agreement with our results. All these findings emphasize the clinical relevance for the future measurement of aortic PWV might contribute to improved risk stratification after MI, which is crucial for the assessment of prognosis and guidance of secondary prevention treatment.

5. Conclusions

In summary, the present study confirmed a good agreement between oscillometric and CMR methods in PWV calculation. Although the oscillometric method could overestimate PWV compared to CMR, it is easy to apply and cost effective advantage makes this technique suitable for everyday clinical routine. Using CMR, an accurate PWV could be derived and precise volumetric and infarct size assessments could be performed. Hence, in the course of routine CMR examination, an additional arterial stiffness information could improve individual risk stratification. Therefore, our results confirm recent guidelines suggestions using either of these methods to assess PWV, however, due to the different range of absolute values, adjusted cut-off values are recommended for different techniques to improve individual risk stratification [9]. Nevertheless, the role of PWV calculation in outcome prediction is not debateable, however, further studies are needed to investigate the thorough task of arterial stiffness and PWV-guided treatment strategies in post-infarcted patients.

6. Limitations

Several methodological aspects of our study require consideration. The most accepted technique for the assessment of cfPWV was not performed in this study, however, a good agreement between the applied methods with invasive validation measurements were reported previously. We involved patients consecutively during CMR scanning, besides the exclusion criteria no selection or healthy control group was assessed. The insufficient number of patients was another deficiency to obtain objective data, as well as the limited number of adverse events. 71 of 75 patients had analysable pulse wave curves for PWV assessment by AG device. At the

remaining 4 patients we could not calculate PWV even manually, because of technical difficulties. In the course of MRI postprocessing we did not assess the influence of microvascular obstruction and myocardial oedema or peri-infarct zone in the infarct size determination and in LV function. Consequently, the findings of the present study should be confirmed with larger studies in the future.

Author contributions

ZM—conducted the data analysis, created the tables and figures and wrote the main part of the manuscript; NF—provided her expertise in the statistical analysis; RJVDG—provided his technological expertise for inventing the novel model of MASS analytical software; TS and BG—provided professional assistance and factual review and helped write and edit the manuscript.

Ethics approval and consent to participate

The present study was performed in conformity with the ethical guidelines of the Declaration of Helsinki. The study was approved by the local institutional ethics committee (approval number 316-3254). Written informed consent was obtained from all patients before study inclusion.

Acknowledgment

We would like to thank all the individuals for participating in our research and all the authors for their expertise and assistance throughout every aspects of our study and for their help in writing the manuscript. We would like to express our gratitude to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

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