ORIGINAL RESEARCH

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Prognostic Value of Aortic Stiffness in Patients After ST-Elevation Myocardial Infarction

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***Background*—**High aortic stiffness has been shown to be a strong predictor of morbidity and mortality in the general population and several patient cohorts. However, in patients after ST-elevation myocardial infarction, the prognostic value of high aortic stiffness is unknown so far.

***Methods and Results*—**This prospective observational study included 160 consecutive patients with first acute ST-elevation myocardial infarction. Aortic pulse wave velocity (PWV) was measured 2 (interquartile range 2-4 days) days after infarction using cardiac magnetic resonance imaging. The primary end point was defined as a composite end point of major adverse cardiac and cerebrovascular events (MACCE) comprising death, nonfatal myocardial reinfarction, new congestive heart failure, and stroke. During a median follow-up of 1.2 years (interquartile range 1.0-3.1 years), 19 (12%) MACCE events occurred. Kaplan-Meier analysis showed a significantly lower MACCE-free survival in patients with high PWV (PWV >7.3 m/s, log-rank P=0.003). Multivariable Cox regression analysis revealed PWV >7.3 m/s to be an independent predictor of MACCE after adjustment for age, sex, mean blood pressure, N-terminal pro–brain natriuretic peptide levels, presence of multivessel disease, and left ventricular stroke volume (hazard ratios ≥3.5; 95% confidence interval 1.4-13.3; all P≤0.018). In reclassification analysis the addition of PWV to a risk model comprising major clinical prognostic parameters led to a net reclassification improvement of 0.11 (95% confidence interval 0.06-0.17; P<0.001).

***Conclusions*—**Increased aortic stiffness is an independent predictor of MACCE after acute ST-elevation myocardial infarction. Moreover, the assessment of aortic stiffness in addition to classical risk factors significantly improved early risk stratification.
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Key Words: aortic stiffness • cardiac magnetic resonance • prognosis • pulse wave velocity • ST-elevation myocardial infarction

In patients after ST-elevation myocardial infarction (STEMI), early risk stratification is crucial for the assessment of prognosis as well as to guide adequate secondary prevention treatment.[1]

In recent years, aortic stiffness has attracted attention as a potentially useful parameter for risk stratification of patients with myocardial infarction. High aortic pulse wave velocity (PWV), a surrogate for aortic stiffness, was linked to increased plasma levels of natriuretic peptides in the acute and chronic stage after STEMI.[2,3] Moreover, aortic stiffness was associated with increased levels of high-sensitivity cardiac troponin T (hs-cTnT) concentrations 1 year after STEMI.[4] Pathophysiologically, the relation between aortic stiffness and natriuretic peptides as well as hs-cTnT levels might be due to hemodynamic alterations. At first, high aortic stiffness results in early wave reflection of the aortic pulse wave and thereby causes increased left ventricular (LV) afterload.[5] LV afterload, again, is a major determinant of myocardial wall stress and natriuretic peptide release.[6] Second, early pulse wave reflection results in a reduction of diastolic blood pressure and consequently impaired coronary perfusion, which might trigger subclinical myocardial injury and hs-cTnT release.[7] In patients with chronic infarcts, retrospective data from Hirsch et al suggest an impact of high aortic stiffness on LV end-systolic volume.[8]

These data suggest a potential prognostic relevance of PWV in patients surviving myocardial infarction. However, the current data regarding PWV and postinfarction clinical outcome are insufficient.[9]

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Clinical Perspective

What Is New?

- For the first time, this study revealed increased aortic stiffness as an independent outcome predictor in a well-defined cohort of patients with ST-elevation myocardial infarction.

What Are the Clinical Implications?

- In the present study assessment of aortic stiffness significantly improved early risk stratification after acute ST-elevation myocardial infarction, which may be important for the assessment of prognosis and guidance of secondary prevention treatment.

Cardiac magnetic resonance (CMR) imaging represents the gold-standard technique for the assessment of LV function and structure as well as infarct size. Phase-contrast CMR, which provides an accurate and reproducible method for the determination of aortic PWV, can be performed during the same CMR scan.[10]

In the present study we aimed to prospectively investigate the promising role of aortic stiffness, assessed noninvasively by means of CMR imaging–derived aortic PWV, for the prediction of major adverse cardio- and cerebrovascular events (MACCE) after reperfused STEMI.

Methods

Study Population

Patients admitted with first STEMI and no prior cardiac events treated with primary percutaneous coronary intervention to the coronary care unit of University Hospital of Innsbruck were consecutively screened for participation in this single-center, prospective, observational study. Eligibility criteria were diagnosis of first STEMI according to the redefined European Society of Cardiology/American College of Cardiology committee criteria[11] and primary percutaneous coronary intervention within 24 hours of symptom onset. Exclusion criteria were renal dysfunction with an estimated glomerular filtration rate <30 mL/min per 1.73 m^2, Killip class >2, and contraindications for CMR (pacemaker, claustrophobia, orbital foreign body, cerebral aneurysm clip, and known contrast agent allergy to gadolinium).

Initially, 225 STEMI patients were screened for study participation. CMR scans were available in 192 patients. Of those, 16 patients were excluded because of poor image quality (10 with incorrect ECG triggering; 3 with incorrect position of the transverse imaging slice through the aortic arch; 1 with incorrect position of the oblique sagittal slice along the aorta; 2 with aliasing artifacts). Finally, 16 patients were excluded because of missing follow-up data despite at least 4 separate attempts to contact them. Thus, 160 patients were included in the final analysis (Figure 1).

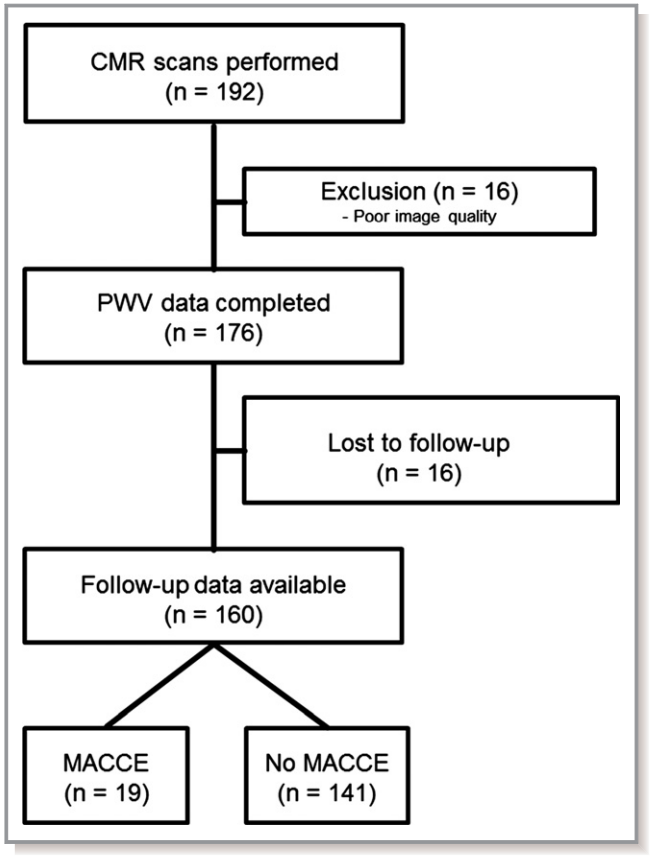

Figure 1. Flow diagram of the study cohort. CMR indicates cardiac magnetic resonance; MACCE, major adverse cardiac and cerebrovascular events; PWV, pulse wave velocity.

Demographic data and medical history were acquired by means of a standardized questionnaire during hospitalization. Presence of cardiovascular risk factors was defined as described previously.[12] Presence of multivessel disease was defined as the presence of >70% stenosis in >1 large epicardial coronary artery according to coronary angiography during primary percutaneous coronary intervention.

The present study was performed in conformity with the ethical guidelines of the Declaration of Helsinki. The study was approved by the local ethics committee of the Medical University of Innsbruck. Written informed consent was obtained from all patients before study inclusion.

Study End Points

Follow-up data were obtained through telephone contact with the patient or a close relative using a standardized questionnaire by trained personnel blinded to PWV data. Corresponding medical records were carefully reviewed to check the declared end points. The primary end point of the present

study was the incidence of MACCE, defined as a composite of death, nonfatal myocardial reinfarction, new congestive heart failure, and stroke. Death was defined as all-cause mortality. Myocardial reinfarction was defined in accordance with the redefined Eurorean Society of Cardiology/American College of Cardiology committee criteria.[13] New congestive heart failure was defined as a first episode of cardiac decompensation requiring intravenous diuretic therapy. Stroke was defined as ischemic or hemorrhagic stroke with an episode of neurological dysfunction due to focal cerebral infarction according to the updated stroke criteria.[14] The secondary end point was defined as each individual end point of the composite end point. The most severe end point was selected for primary end point analysis if >1 MACCE end point occurred during follow- up (death > new congestive heart failure > stroke > myocardial reinfarction).

Cardiac Magnetic Resonance Imaging

CMR scans were performed at a median of 2 days (interquartile range [IQR] 2-4 days) after infarction. All scans were performed on a 1.5-T MR imaging unit (AVANTO_fit; Siemens, Erlangen Germany). Details on the applied sequence were described previously.[4] We used a velocity-encoded phase-contrast sequence with velocity encoding set to 150 cm/s. The same velocity encoding (150 cm/s) was used for all CMR scans. As stated above, aliasing artifacts occurred in 2 patients. Reconstruction matrix was 256×208, and the voxel size was 1.33×1.33×8 mm. Acquisition was retrospectively ECG gated, and 128 calculated phases were obtained.

To measure aortic through-plane flow, acquisition planes were set to the ascending and abdominal aorta as described in detail previously[4] (Figure 2). Manual delineation of aortic contours on the velocity-encoded images was performed using standard software (ARGUS, Siemens, Erlangen, Germany). Subsequently, the velocity values were depicted in a flow-time diagram. The onset of the systolic upstroke was defined as the arrival of the pulse wave at the respective level of measurement. The distance between aortic acquisition levels at the ascending and abdominal aorta was measured along the aortic luminal midline on an oblique sagittal slice. In the "transit-time" method, aortic PWV was subsequently calculated as the ratio of the distance between the ascending and abdominal aorta and the travel time of the pulse wave.[4]

To measure local aortic stiffness at the level of the ascending, descending thoracic, and abdominal aorta, distensibility coefficients were calculated. In brief, the distensibility coefficient is calculated as the ratio of the relative aortic

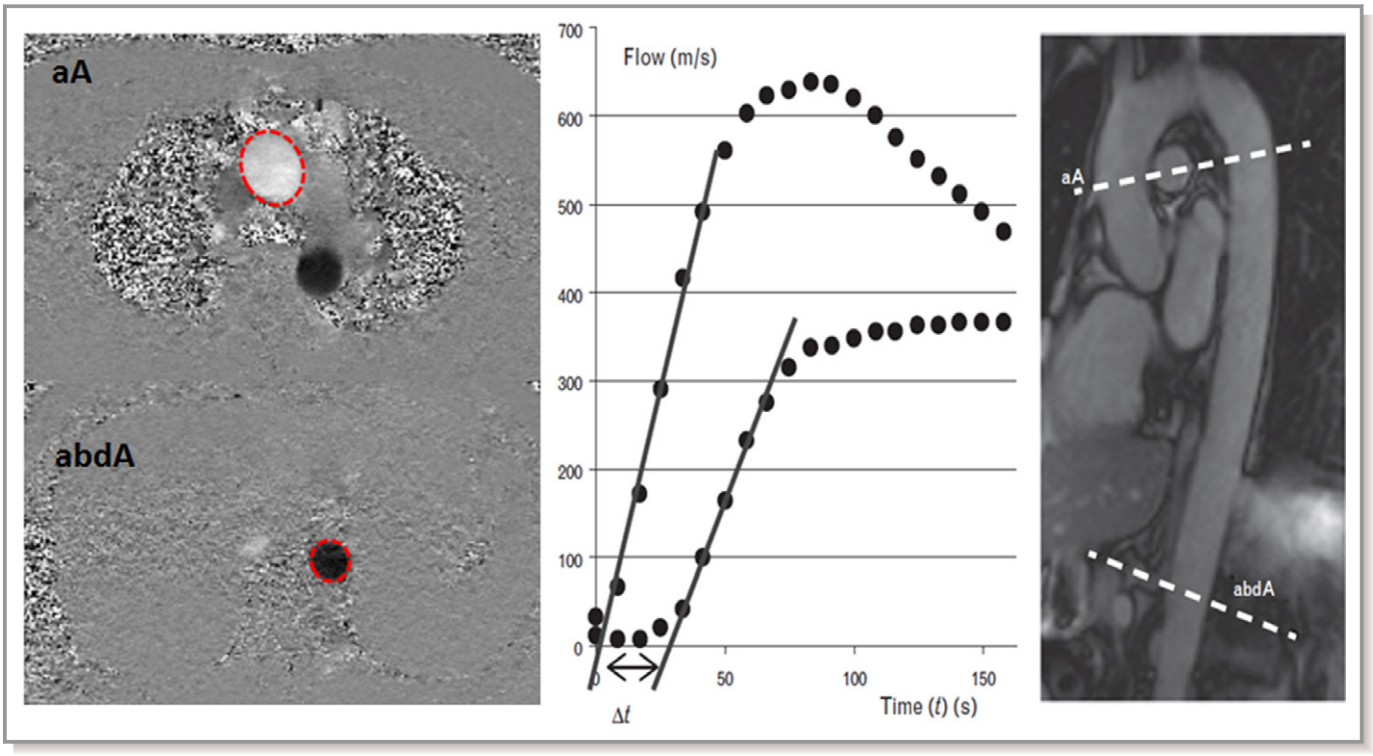

Figure 2. Assessment of aortic pulse wave velocity. Blood flow was measured at the level of the ascending (aA) and abdominal (abdA) aorta. Distance between those levels was measured along the luminal midline of the aorta on an oblique sagittal slice. aA indicates ascending aorta; abdA, abdominal aorta.

lumen change during systole derived from the magnitude images of the velocity-encoded sequences.[15]

LV function and structure as well as infarct size were determined during the same CMR scan as described in detail previously.[10]

Biomarkers

All biomarkers were analyzed immediately after collection from heparinized plasma samples at the central laboratory of University Hospital of Innsbruck by personnel blinded to PWV and clinical data. N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations were measured using a commercially available proBNP II assay as described in detail previously (Roche Diagnostics, Vienna, Austria).[2] The analytical limit of detection of this assay is 5 ng/L, and the limit of quantification is 50 ng/L. Cardiac troponin T concentrations were measured using a fifth-generation high-sensitivity assay (Roche Diagnostics, Vienna, Austria). Creatine kinase and high-sensitivity C-reactive protein concentrations were measured as previously described.[16]

NT-proBNP concentrations were measured on admission and subsequently once daily from day 1 to day 4 after infarction or discharge. hs-cTnT levels were measured 3 times during the first 24 hours and subsequently once daily from day 1 to day 4 or discharge. Peak biomarker concentration was defined as the highest level in the concentration time course.

Statistical Analysis

For statistical analysis SPSS 22.0 (IBM, Armonk, NY) and R 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria) were used. To test for normal distribution, the Shapiro-Wilk test was applied. Normally distributed continuous variables are expressed as mean±standard deviation, not normally distributed distributed continuous variables as median with corresponding IQR. Categorical variables are expressed as number and percentage. The Pearson test was used for calculation of correlations of continuous variables if normally distributed; otherwise Spearman rank correlation coefficients were calculated. To test for differences in continuous variables between groups, Student t test, ANOVA, and Mann-Whitney U test were applied. For comparison of categorical variables between groups, the χ^2 test was used. Outcome functions were expressed by Kaplan-Meier graphs, and groups were compared using the log-rank test. Univariable and multivariable Cox regression analysis was performed to identify outcome predictors. Variables with a $P<0.05$ in univariable analysis and possible confounders of PWV were entered in a multivariable model together with PWV. As previously discussed, due to the limited number of MACCE events, a maximum of 2 variables were entered in each model.[17] Together with presence of multivessel disease, PWV, age, mean blood pressure, NT-proBNP concentrations, and LV stroke volume were used as dichotomized variables for outcome analysis to allow for an adequate comparison of hazard ratios. Dichotomization was performed according to optimized cutoff values for MACCE prediction (PWV 7.3 m/s; age 60 years; mean BP 95 mm Hg; NT-proBNP 1736 ng/L; LV stroke volume 73 mL) calculated by receiver operating characteristic analysis as previously described.[12] Furthermore, a risk score adding PWV to major clinical prognostic determinants of MACCE (age, NT-proBNP, multivessel disease) was developed. As described in a previous study, 1 point was given for each of these parameters when they were above the optimal cutoff value derived from receiver operating characteristic analysis.[18] This resulted in a score ranging from 0 to 4 points. Subsequently, we formed risk classes for the occurrence of MACCE: low (0-1 point), intermediate (2-3 points), and high (4 points). Categorical and continuous net reclassification improvement was calculated with R package PredictABEL to evaluate the additive prognostic value of PWV over established prognostically relevant clinical markers. All statistical tests were 2-tailed, and a $P<0.05$ was considered statistically significant.

Results

Patient Characteristics

Baseline characteristics of the study cohort and their relation with MACCE are summarized in Table 1. In the total study cohort, PWV was 6.8 m/s (IQR 5.9-8.3 m/s). PWV was significantly correlated with age ($r=0.661$, $P<0.001$) and peak NT-proBNP concentrations ($r=0.302$, $P<0.001$) (Figure 3). Furthermore, an inverse correlation was found between PWV and LV stroke volume ($r=-0.235$, $P=0.003$). No significant correlations were detected between PWV and admission ($r=0.098$, $P=0.223$) and peak ($r=0.065$, $P=0.412$) hs-cTnT levels, as well as mean blood pressure ($r=0.024$, $P=0.768$). PWV was significantly higher in females compared to males (7.9 m/s, IQR 6.6-10.1 m/s versus 6.7 m/s, IQR 5.7-8.0 m/s; $P=0.009$). Patients with hypertension (7.3 m/s, IQR 6.2-8.8 m/s versus 6.3 m/s, IQR 5.6-7.5 m/s; $P=0.012$) and nonsmokers (7.2 m/s, IQR 6.3-8.8 m/s versus 6.4 m/s, IQR 5.3-7.8 m/s; $P=0.001$) showed significantly higher PWV. Moreover, PWV was significantly higher in patients with multivessel versus 1-vessel disease (7.2 m/s, IQR 6.2-8.8 m/s versus 6.6 m/s, IQR 5.5-7.8 m/s; $P=0.030$).

The mean follow-up period was 1.8±1.3 years with the median being 1.2 years (IQR 1.0-3.1 years). During

Table 1. Baseline Characteristics of the Study Cohort and After Stratification for the Occurrence of MACCE

	Overall Cohort (n=160)	No MACCE (n=141)	MACCE (n=19)	*P* Value
Baseline characteristics				
Age, y	58±12	57±12	65±10	0.003*
Female sex, n (%)	27 (17)	23 (16)	4 (21)	0.532
Body mass index, kg/m^2	26 (25-29)	27 (25-29)	26 (24-26)	0.099
CKD, n (%)	20 (13)	19 (14)	1 (5)	0.471
Mean BP, mm Hg	95 (84-106)	94 (84-105)	96 (82-116)	0.690
Cardiovascular risk factors				
Hypertension, n (%)	91 (57)	77 (55)	14 (74)	0.142
Diabetes mellitus, n (%)	19 (12)	14 (10)	5 (26)	0.054
Current smoker, n (%)	85 (53)	77 (55)	8 (42)	0.336
Hyperlipidemia, n (%)	86 (54)	76 (54)	10 (53)	0.999
Family history for AMI, n (%)	43 (27)	40 (29)	3 (16)	0.285
Pain-to-balloon time, min	201 (135-355)	206 (135-352)	177 (123-641)	0.669
Time from STEMI to CMR, d	2 (2-4)	2 (2-4)	3 (1-4)	0.812
Infarct-related artery				0.213
Right coronary artery, n (%)	67 (42)	60 (43)	7 (37)	0.632
Left anterior descending artery, n (%)	71 (45)	59 (42)	12 (63)	0.090
Left circumflex coronary artery, n (%)	17 (11)	17 (12)	0 (0)	0.226
Ramus intermedius, n (%)	3 (2)	3 (2)	0 (0)	0.999
Multivessel disease, n (%)	70 (44)	56 (40)	14 (74)	0.007*
Peak CK, U/L	1907 (943-3359)	1847 (982-3290)	2169 (931-5633)	0.569
Peak hs-cTnT, ng/L	4411 (2001-8384)	4385 (1959-8157)	6035 (2101-14 980)	0.380
Peak NT-proBNP, ng/L	802 (264-2060)	702 (227-1463)	2159 (741-3378)	0.012*
hs-CRP, mg/dL	2.1 (1.0-4.5)	2.1 (0.9-4.5)	2.9 (1.7-4.5)	0.155
LVSV, mL	78±18	79±18	65±11	<0.001*
LV muscle mass, g	133 (117-159)	134 (119-159)	122 (103-164)	0.237
IS, % muscle mass	15 (7-25)	15 (7-26)	15 (8-21)	0.905
DC aA, 10^{-3} mm Hg^{-1}	2.9 (2.2-4.3)	3.0 (2.2-4.6)	2.3 (1.2-2.8)	0.006*
DC dA, 10^{-3} mm Hg^{-1}	3.1 (2.1-4.3)	3.2 (2.1-4.5)	2.5 (1.9-3.6)	0.184
DC abA, 10^{-3} mm Hg^{-1}	4.7 (3.4-6.8)	4.7 (3.4-6.8)	5.0 (3.2-6.8)	0.967
DC mean, 10^{-3} mm Hg^{-1}	3.7 (2.7-4.9)	3.9 (2.7-5.0)	3.4 (2.6-4.5)	0.240
PWV, m/s	6.8 (5.9-8.3)	6.7 (5.7-8.2)	8.0 (7.0-9.3)	0.013*

aA indicates ascending aorta; abA, abdominal aorta; AMI, acute myocardial infarction; BP, blood pressure; CK, creatine kinase; CKD, chronic kidney disease; CMR, cardiac magnetic resonance; dA, descending thoracic aorta; DC, distensibility coefficient; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; IS, infarct size; LVSV, left ventricular stroke volume; MACCE, major adverse cardiac and cerebrovascular events; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PWV, pulse wave velocity; STEMI, ST-elevation myocardial infarction.
*indicates statistical significance (P<0.05).

follow-up the primary end point MACCE occurred in 19 (12%) patients, including 6 (4%) deaths, 6 (4%) events of new congestive heart failure, 6 (4%) cases of nonfatal myocardial reinfarction, and 4 (3%) strokes. One patient (0.6%) suffered 2, and 1 patient (0.6%) suffered 3, MACCE events.

Primary End Point

Patients suffering from MACCE were older (65±10 years versus 57±12 years; P=0.003), showed significantly higher peak NT-proBNP concentrations (2159 ng/L, IQR 741-3378 ng/L versus 702 ng/L, IQR 227-1463 ng/L;

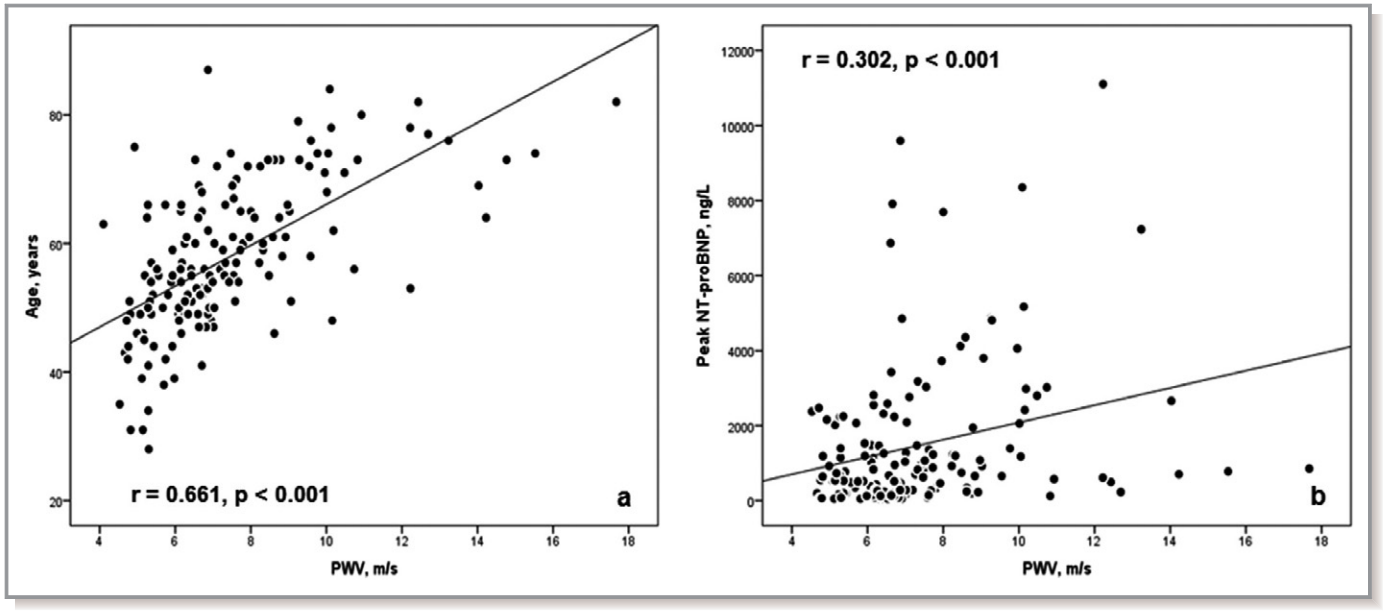

Figure 3. Linear correlation between PWV and age (A) and NT-proBNP concentrations (B). NT-proBNP indicates N-terminal pro-B-type natriuretic peptide; PWV, pulse wave velocity.

P=0.012), and had higher PWV (8.0 m/s, IQR 7.0-9.3 m/s versus 6.7 m/s, IQR 5.7-8.2 m/s; *P*=0.013) (Table 1). Moreover, patients developing MACCE were more likely to exhibit multivessel disease (n=14, 74% versus n=56, 40%; *P*=0.007). LV stroke volume was significantly lower in patients with MACCE (65±11 versus 79±18; *P*<0.001). No statistically significant differences between patients with and without MACCE were detected for sex, mean arterial blood pressure, LV muscle mass, or infarct size (all *P*>0.200) (Table 1).

In receiver operating characteristic analysis, aortic PWV with the optimal cutoff value of 7.3 m/s showed an area under the curve of 0.68 (95% confidence interval 0.56-0.79) for the prediction of MACCE (Figure 4). The primary end point occurred significantly more often in patients with PWV >7.3 m/s (14 events, 22% versus 5 events, 5%; *P*=0.002) (Figure 5). According to Kaplan-Meier analysis, MACCE rate was significantly higher in patients with high PWV (PWV >7.3 m/s, log-rank *P*=0.003), high age (age >60 years, log-rank *P*=0.005), high NT-proBNP concentrations (NT-proBNP >1736 ng/L, log-rank *P*<0.001), presence of multivessel disease (log-rank *P*=0.020), and low LV stroke volume (log-rank *P*<0.001) (Figure 6).

Different models of multivariable Cox regression analysis including PWV together with age, sex, mean arterial blood pressure, peak NT-proBNP concentrations, presence of multivessel disease, and LV stroke volume revealed PWV >7.3 m/s as an independent predictor of MACCE (hazard ratios ≥3.5, 95% confidence interval 1.4-13.3; all *P*≤0.018) (Table 2).

In reclassification analysis, applying the calculated risk levels of 0% to <4%, 4% to <14%, 14% to <60%, and ≥60%, the addition of PWV to a clinical risk model comprising age, NT-proBNP, and mulitvessel disease led to a net reclassification improvement of 0.11 (95% confidence interval 0.06-0.17; *P*<0.001). The continuous net reclassification improvement was 0.83 (95% confidence interval 0.40-1.27; *P*<0.001).

Secondary End Points

During follow-up, 6 (4%) patients died; 4 (3%) patients died from cardiovascular causes, whereas 2 (1%) patients died from noncardiovascular causes. Age (*P*=0.086), presence of multivessel disease (*P*=0.120), LV stroke volume (*P*=0.096), and infarct size (*P*=0.158) trended to show an association with mortality. No significant association was detected between death and NT-proBNP concentrations (*P*=0.231). Although infarct size was associated with the occurrence of new congestive heart failure (*P*=0.004), no significant associations were detected between infarct size and the risk for myocardial reinfarction (*P*=0.425) or stroke (*P*=0.201). New congestive heart failure occurred significantly more often in patients with PWV >7.3 m/s compared to patients with PWV <7.3 m/s (n=5, 8% versus n=1, 1%; *P*=0.035) (Figure 7A). No significant differences between patients with PWV above and below 7.3 m/s were detected regarding the occurrence of stroke (n=3, 5% versus n=1, 1%; *P*=0.301) (Figure 7B), myocardial reinfarction (n=3, 5% versus n=3, 3%; *P*=0.681) (Figure 7C), or death (n=4, 6% versus n=2, 2%; *P*=0.213) (Figure 7D).

Discussion

This is the first study prospectively investigating the prognostic impact of aortic PWV in patients after acute STEMI. The

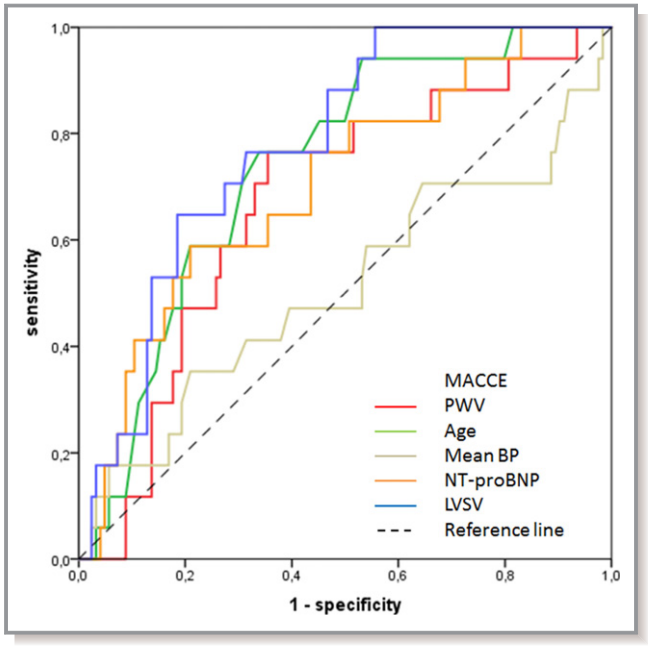

Figure 4. ROC analysis of PWV (AUC=0.68, 95% CI 0.56-0.79), age (AUC=0.74, 95% CI 0.63-0.85), mean BP (AUC=0.51, 95% CI 0.34-0.68), peak NT-proBNP concentrations (AUC=0.71, 95% CI 0.58-0.84), and LVSV (AUC=0.78, 95% CI 0.68-0.87) for the prediction of MACCE. AUC indicates area under the curve; BP, blood pressure; CI, confidence interval; LVSV, left ventricular stroke volume; MACCE, major adverse cardiac and cerebrovascular events; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PWV, pulse wave velocity; ROC, receiver operating characteristics.

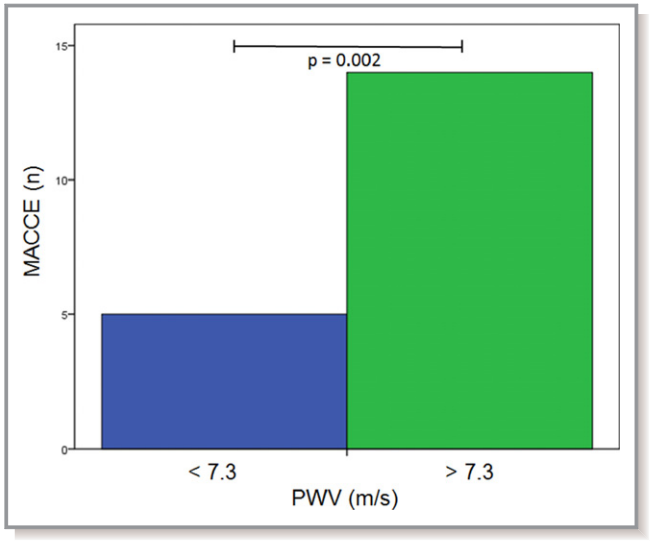

Figure 5. Numbers of MACCE in patients with PWV above and below 7.3 m/s. MACCE indicates major adverse cardiac and cerebrovascular events; PWV, pulse wave velocity.

major findings of the present study are these: (1) high aortic PWV, noninvasively assessed by CMR early after STEMI, is associated with reduced MACCE-free survival at long-term follow-up; (2) PWV is an independent predictor of MACCE even after adjustment for age, sex, mean arterial blood pressure, NT-proBNP concentrations, presence of multivessel disease, and LV stroke volume; and (3) the addition of PWV to a risk model comprising major clinical prognostic determinants of MACCE significantly improved early risk stratification.

Aortic Stiffness and Hemodynamics

Measurement of aortic PWV is the gold-standard technique to assess aortic stiffness in vivo. In the study presented in this article, aortic PWV was measured using the CMR-derived "transit-time" method, which was described in detail previously.[4] It provides a valid and highly reproducible technique and shows good agreement with invasive catheter measurements.[19] Moreover, in the study presented in this article, local aortic distensibility coefficients as measures of local aortic stiffness were calculated. In STEMI patients, the CMR-derived transit-time method and calculation of local aortic distensibility coefficients were shown to be valid and robust approaches to measure aortic stiffness.[15]

We detected a moderate correlation between PWV and age. Age is well accepted as the major determinant of PWV, whereas data regarding the relation of sex and PWV are controversial.[20] We showed a significantly higher PWV in women compared to men. However, in uni- and multivariable Cox regression analysis, sex was not significantly associated with the primary end point. This issue should be further investigated in larger studies in the future. In the study presented in this article, median PWV was 6.8 m/s, and mean age was 58±12 years. This is in line with data from literature (59±10 years; PWV 6.5±1.1 m/s) derived from similar patient cohorts using similar techniques.[19]

High aortic stiffness results in early pulse-wave reflection. Consequently, the arrival of the reflected pulse wave shifts from diastole to systole. Thus, the reflection wave augments systolic blood pressure but decreases diastolic blood pressure. These hemodynamic alterations result in increased LV afterload and myocardial wall stress on the one hand as well as impaired coronary perfusion on the other hand.[5,21] The transit-time–derived PWV, measured between the central ascending and abdominal aorta, reflects the "mean" PWV along the central aorta including the branching sites of the large arteries, where pulse wave reflection occurs. Data from a retrospective study by Hirsch et al showed an association between aortic stiffness and LV end-systolic volume in patients with chronic infarcts.[8] A rise in NT-proBNP concentration is a sensitive indicator of increasing myocardial wall stress and a strong predictor of outcome after acute

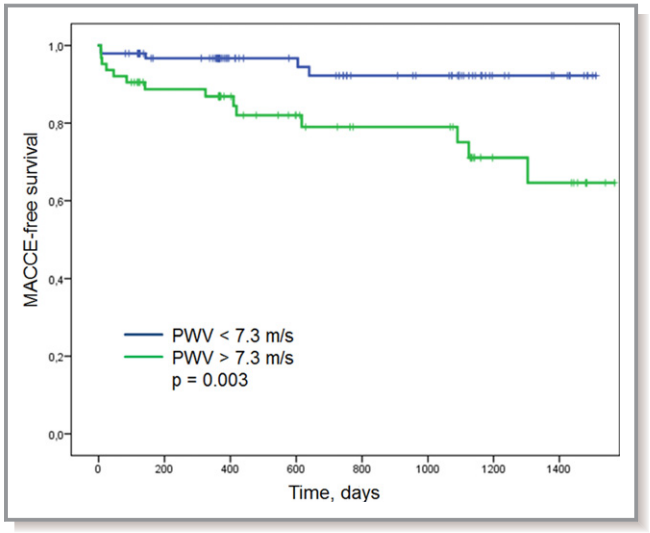

Figure 6. Kaplan-Meier curves for the occurrence of MACCE stratified by PWV. PWV was calculated by ROC analysis. MACCE indicates major adverse cardiac and cerebrovascular events; PWV, pulse wave velocity; ROC, receiver operating characteristics.

STEMI.[6,22] Our study group has recently shown an association between high aortic PWV and NT-proBNP levels in the subacute and chronic phase after STEMI.[2,3] In the present study a weak correlation of PWV and NT-proBNP concentrations was detected. Furthermore, PWV was found to independently predict hs-cTnT concentrations at 12 months after STEMI, indicating subclinical myocardial damage.[4] These findings strongly suggest deleterious effects of high aortic PWV on the LV myocardium.

Aortic Stiffness and Prognosis

High aortic stiffness is accepted as a predictor of morbidity and mortality in the general population and various patient cohorts.[23] To date, data on the prognostic role of aortic stiffness are almost completely lacking in patients after acute STEMI. The study of Akkus et al indicated a relation of PWV and outcome after STEMI[9]; however, interpretation of these data is hindered due to major limitations. At first, STEMI (n=45) and non-STEMI (n=49) patients were included in this study, and it remains unclear whether patients were included in the acute, subacute, or chronic stage after infarction. Second, patient characterization and procedures (ie, revascularization strategy, timepoint of PWV assessment, end-point definition, follow-up examinations) were poorly defined. Therefore, prognostic data on aortic PWV after acute STEMI, derived from a soundly designed prospective study, are lacking so far.

In the present study, during follow-up (median 1.2 years), 19 (12%) patients developed the primary end point MACCE, which is in line with data from literature.[12,24]

Table 2. Uni- and Multivariable Cox Regression Analysis for the Prediction of MACCE

	HR (95% CI)	*P* Value
Univariable analysis		
PWV >7.3 m/s	4.1 (1.5-11.5)	0.007*
DC aA, <2.5 10^{-3} mm Hg^{-1}	4.2 (1.6-11.6)	0.005*
DC dA, <3.0 10^{-3} mm Hg^{-1}	3.0 (1.1-8.3)	0.037*
DC abA, <4.1 10^{-3} mm Hg^{-1}	2.0 (0.7-5.4)	0.174
DC mean, <3.4 10^{-3} mm Hg^{-1}	3.2 (1.2-9.0)	0.025*
Age >60 y	3.9 (1.4-10.9)	0.009*
Female sex, n (%)	1.5 (0.5-4.6)	0.460
Mean BP >95 mm Hg	1.4 (0.5-3.4)	0.504
Current smoking, n (%)	0.7 (0.3-1.7)	0.441
NT-proBNP >1736 ng/L	5.1 (1.9-13.4)	0.001*
Multivessel disease, n (%)	3.2 (1.1-8.8)	0.027*
LVSV <73 mL	5.9 (2.0-17.9)	0.002*
LV muscle mass, g	2.3 (0.9-5.7)	0.071
IS >13% muscle mass	1.4 (0.5-3.8)	0.564
Multivariable analysis		
Model 1		
PWV >7.3 m/s	4.1 (1.5-11.5)	0.007*
Age >60 y	…	0.114
Model 2		
PWV >7.3 m/s	4.1 (1.5-11.5)	0.007*
Female sex, n (%)	…	0.823
Model 3		
PWV >7.3 m/s	4.0 (1.4-11.0)	0.008*
Mean BP >95 mm Hg	…	0.737
Model 4		
PWV >7.3 m/s	4.3 (1.4-13.3)	0.011*
NT-proBNP >1736 ng/L	4.6 (1.7-12.2)	0.003*
Model 5		
PWV >7.3 m/s	4.1 (1.5-11.3)	0.007*
Multivessel disease, n (%)	…	0.084
Model 6		
PWV >7.3 m/s	3.5 (1.2-9.6)	0.018*
LVSV <73 mL	5.3 (1.7-16.1)	0.003*

aA indicates ascending aorta; abA, abdominal aorta; BP, blood pressure; CI, confidence interval; dA, descending thoracic aorta; DC, distensibility coefficient; HR, hazard ratio; IS, infarct size; LVSV, left ventricular stroke volume; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PWV, pulse wave velocity.
* indicates statistical significance (P<0.05).

Patients who developed MACCE were older and showed a higher prevalence of coronary multivessel disease, highlighting the prognostic role of these conditions.[25] Moreover,

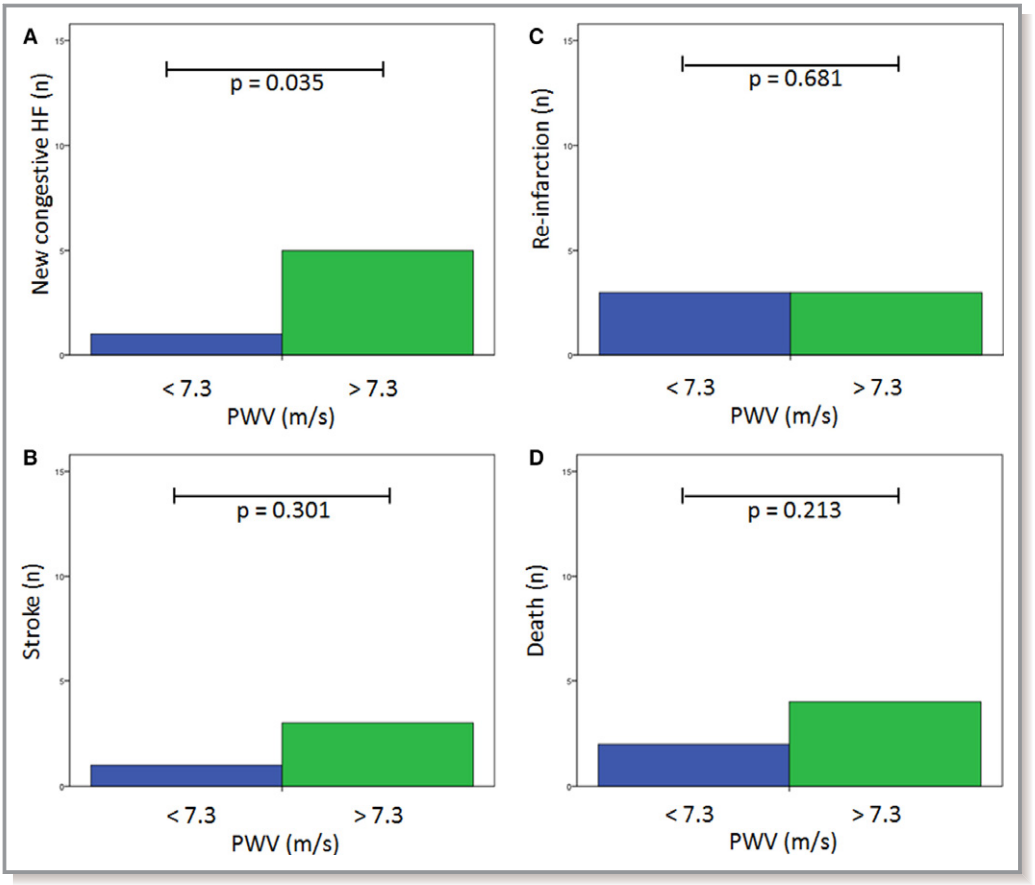

Figure 7. Number of new congestive heart failure (A), stroke (B), myocardial reinfarction (C), and death (D) incidents in patients with PWV above and below 7.3 m/s. HF indicates heart failure; PWV, pulse wave velocity.

patients with MACCE showed significantly higher NT-proBNP concentrations and lower LV stroke volume, confirming the prognostic role of natriuretic peptides and LV dysfunction after acute STEMI.[1,26] Although infarct size was not associated with MACCE, it was related to the occurrence of heart failure and trended to be related to mortality. In contrast, but in line with a recent analysis from Stone et al, infarct size was not associated with the risk of myocardial reinfarction.[27]

PWV was an independent predictor of the primary end point even after correction for age, sex, mean arterial blood pressure, NT-proBNP concentrations, presence of multivessel disease, and LV stroke volume. Moreover, the addition of aortic PWV to a risk model comprising major clinical prognostic determinants for MACCE significantly improved early risk stratification of STEMI patients. This finding is also of clinical relevance because in the future, assessment of aortic PWV might contribute to improved early risk stratification after acute STEMI, which is crucial for the assessment of prognosis and guidance of secondary prevention treatment.

Regarding secondary end points, new congestive heart failure occurred significantly more often in patients with PWV >7.3 m/s. Hence, the association between PWV and MACCE is mainly driven by the occurrence of congestive heart failure. This finding underlines the pathophysiological impact of high aortic stiffness on the LV myocardium. Early wave reflection due to high aortic stiffness increases LV afterload and wall stress and thereby triggers heart failure.

Limitations

A limitation of the present study is that it was restricted to stable patients with first STEMI. Unstable patients at admission and those who developed severe heart failure (Killip class >2) during the initial phase of the index event were not included. Therefore, the findings of this study are not generalizable to other STEMI cohorts, particularly not to those comprising patients with cardiogenic shock. Furthermore, data on LV function before the index event were lacking. However, because the study cohort was restricted to patients with no prior cardiac events, the inclusion of patients with preexisting cardiomyopathy was unlikely. Further limitations are the limited number of patients included as well as

the limited number of adverse events. Consequently, the findings of the present study should be confirmed with larger studies in the future.

Conclusions

For the first time in a well-defined cohort of STEMI patients, aortic PWV was proven to be an independent predictor of MACCE and new congestive heart failure at a median follow-up of 1.2 years. Furthermore, the addition of PWV to a risk model comprising traditional prognostic determinants for MACCE significantly improved early risk stratification.

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Disclosures

None.

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