ORIGINAL RESEARCH

Aortic Stiffness and Infarct Healing in Survivors of Acute ST-Segment–Elevation Myocardial Infarction

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Background—In survivors of acute ST-segment–elevation myocardial infarction (STEMI), increased aortic stiffness is associated with worse clinical outcome; however, the underlying pathomechanisms are incompletely understood. We aimed to investigate associations between aortic stiffness and infarct healing using comprehensive cardiac magnetic resonance imaging in patients with acute STEMI.

Methods and Results—This was a prospective observational study including 103 consecutive STEMI patients treated with primary percutaneous coronary intervention. Pulse wave velocity (PWV), the reference standard for aortic stiffness assessment, was determined by a validated phase-contrast cardiac magnetic resonance imaging protocol within the first week after STEMI. Infarct healing, defined as relative infarct size reduction from baseline to 4 months post-STEMI, was determined using late gadolinium-enhanced cardiac magnetic resonance. Median infarct size significantly decreased from 17% of left ventricular mass (interquartile range 9% to 28%) at baseline to 12% (6% to 17%) at 4-month follow-up ($P<0.001$). Relative infarct size reduction was 36% (interquartile range 15% to 52%). Patients with a reduction >36% were younger ($P=0.01$) and had lower baseline NT-proBNP (N-terminal pro–B-type natriuretic peptide) concentrations ($P=0.047$) and aortic PWV values ($P=0.003$). In a continuous (odds ratio 0.64 [95% CI, 0.49–0.84]; $P=0.001$) as well as categorical (PWV <7 m/s; odds ratio 4.80 [95% CI, 1.89–12.20]; $P=0.001$) multivariable logistic regression model, the relation between aortic PWV and relative infarct size reduction remained significant after adjustment for baseline infarct size, age, NT-proBNP, and C-reactive protein.

Conclusions—Aortic PWV independently predicted infarct size reduction as assessed by cardiac magnetic resonance, revealing a novel pathophysiological link between aortic stiffness and adverse infarct healing during the early phase after STEMI treated with contemporary primary percutaneous coronary intervention. **(*J Am Heart Assoc*. 2020;9:e014740. DOI: 10.1161/JAHA.119.014740.)**

Key Words: aortic stiffness • magnetic resonance imaging • myocardial delayed enhancement • ST-segment–elevation myocardial infarction

Aortic pulse wave velocity (PWV), the reference standard for assessment of aortic stiffness, has emerged as an important marker of cardiovascular outcome in recent years.[1-4] Also, in patients suffering from ST-segment–elevation myocardial infarction (STEMI), aortic PWV was recently demonstrated to predict cardiovascular complications and all-cause mortality following infarction.[5] However, the mechanisms underlying the link between PWV and worse outcome following STEMI are not fully clarified so far.

From a pathophysiological point of view, elevated PWV leads to an early reflection of the aortic pulse wave, resulting in increased systolic aortic pressure and, subsequently, increased left ventricular wall stress.[6,7] In line with this concept, previous data could confirm a relation between aortic PWV and plasma concentrations of natriuretic peptides in the acute as well as chronic stage after STEMI.[8,9] On the other hand, premature aortic pulse wave reflection is associated with reduced diastolic aortic pressure that impairs coronary perfusion.[10] The combination of increased wall stress and impaired coronary perfusion due to enhanced PWV

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Clinical Perspective

What Is New?

- Aortic pulse wave velocity, the reference marker of aortic stiffness, significantly predicted the degree of infarct healing following ST-segment–elevation myocardial infarction.
- Moreover, the association between aortic pulse wave velocity and infarct healing remained significant after adjustment for clinical determinants of myocardial healing including age, baseline infarct size, and inflammatory state.

What Are the Clinical Implications?

- These novel insights suggest aortic stiffness as a key player in the pathophysiology of postinfarction healing processes as well as a potential therapeutic target to improve infarct healing after ST-segment–elevation myocardial infarction.

causes an imbalance in the oxygen supply–oxygen demand ratio that may induce myocardial ischemia and subclinical myocardial damage.[11] Such a pathophysiological constellation in the recovery period after STEMI might relevantly hamper processes of infarct healing; however, the potential impact of aortic PWV on myocardial infarct healing following STEMI has not yet been investigated.

Phase-contrast cardiac magnetic resonance (CMR) imaging enables accurate assessment of PWV,[12] and we have previously validated this technique in patients with STEMI.[13] Moreover, late gadolinium-enhanced CMR provides a unique in vivo view of myocardial tissues and represents the modality of choice to assess infarct-healing processes.[14] Pokorney et al have studied the dynamics of infarct healing after STEMI using CMR and reported highest reduction in infarct size within the first 4 months after STEMI.[15] However, little is still known about the natural history of infarct healing and the potential determinants of infarct-healing dynamics.

In the present study we therefore sought to prospectively investigate the relation of aortic PWV with infarct healing, as assessed by infarct size reduction from baseline to 4 months after infarction, in STEMI patients treated by primary percutaneous coronary intervention. We hypothesized that increased aortic stiffness in survivors of acute STEMI would be associated with adverse infarct healing as revealed by CMR imaging independent of other clinical parameters.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Biochemical Measurements

In this prospective observational study we included 103 consecutive STEMI patients admitted to the coronary care unit of Innsbruck University Hospital. Inclusion criteria were first STEMI defined in accordance to the European Society of Cardiology/American College of Cardiology committee criteria as the presence of clinical symptoms suggestive of ischemia and ST-segment elevation in at least 2 contiguous leads,[16,17] receiving treatment by primary percutaneous coronary intervention within 24 hours after symptom onset. Exclusion criteria were defined as follows: age <18 years, any history of a previous myocardial infarction or coronary intervention, estimated glomerular filtration rate <30 mL/min per 1.73 m^2, Killip class >II, and any contraindication to CMR examination (pacemaker, claustrophobia, orbital foreign body, cerebral aneurysm clip, known or suggested contrast agent allergy to gadolinium).

For biomarker analyses, serial measurements of high-sensitivity cardiac troponin T, NT-proBNP (N-terminal pro–B-type natriuretic peptide), and hs-CRP (high-sensitivity C-reactive protein) were performed according to our standard post-STEMI protocol.[18] An enzyme immunoassay (high-sensitivity cardiac troponin T; E170, Roche Diagostics, Vienna, Austria) was used for high-sensitivity cardiac troponin T analyses and NT-proBNP was measured by the E170 instrument (proBNP II assay; Roche Diagnostics).[19] Hs-CRP was measured by using the c702 module of cobas 8000 (Roche Diagnostics).

Before study inclusion all patients gave their written informed consent. The research protocol of the present investigation was approved by the local research ethics committee and complies with the Declaration of Helsinki.

Cardiac Magnetic Resonance Imaging

A 1.5-Tesla Magnetom AVANTO-scanner (Siemens, Erlangen, Germany) was used for all examinations. The imaging protocols used by our research group have been published in detail previously.[20,21]

Left ventricular (LV) volumes and infarct size were evaluated by comprehensive CMR scans 2 (interquartile range [IQR] 2-4) days as well as 4 (IQR 4-5) months after infarction. Volumetric analyses using standard software (ARGUS, Siemens, Erlangen, Germany) were conducted on short-axis (10-12 slices) cine images acquired by breath-hold, retrospective ECG-triggered trueFISP bright-blood sequences. For all volumetric measurements, papillary muscles were included in LV volume.[22] Infarct size was evaluated via late gadolinium enhancement (LGE) imaging, acquired 15 minutes after application of a 0.2 mmol/kg contrast agent bolus (Gadovist; Bayer, Leverkusen, Germany), using an ECG-triggered

phase-sensitive inversion recovery sequence. LGE was analyzed on a PACS workstation (IMPAX; Agfa HealthCare, Bonn, Germany) by defining "hyperenhancement" as +5 SD above the signal intensity of remote myocardial tissue.[23] After defining the endocardial and epicardial borders and nulling normal myocardium, the "hyperenhanced" area was quantified at consecutive short-axis slices, whereas microvascular obstruction was included in the infarct area. Infarct volume was calculated by multiplying the infarct area by the slice thickness. Finally, infarct mass in grams was derived by multiplying the infarct volume by the specific density of myocardial tissue (1.05 g/cm^3). Infarct size was presented in grams and as percentage of LV myocardial mass (LVMM). Infarct healing was defined as relative reduction of infarct size from baseline to 4 months of follow-up.[15]

At the baseline CMR scan, we additionally measured aortic PWV by a velocity-encoded phase-contrast sequence, which has been explained in detail in previous publications of our working group.[5,13,24] A retrospective ECG-gated acquisition with 128 phases per cardiac cycle was acquired. Spatial resolution was $1.3\times1.3\times8$ mm, and velocity encoding was set to 150 cm/s and adjusted in case of aliasing. Aortic PWV was determined by the transit-time method, whereas PWV was calculated as the ratio of distance between the ascending and abdominal aorta (Δx) and the propagation time of the pulse wave between these 2 levels (Δt)[13]:

$$PWV_{CMR} = \Delta x/\Delta t$$

Two slices were set perpendicular to the ascending and abdominal aorta to measure through-plane flow.[13] The distance between these 2 sites (Δx) was measured manually along the luminal midline of the aorta on an oblique sagittal slice.[13] To ascertain pulse wave propagation time, regression lines were automatically fitted to the linear phase of the systolic upslope of the flow curves at the 2 locations.[13] The gap between the intersection points of the 2 regression lines with the *x*-axis was defined as propagation time of the pulse wave (Δt).[13]

All CMR images were analyzed by experienced observers completely blinded to clinical data.

Statistical Analyses

All statistical analyses were calculated using SPSS Statistics 24.0 (IBM, Armonk, NY), MedCalc Version 15.8 (Ostend, Belgium), and R 3.3.0 (The R Foundation, Vienna, Austria). Continuous variables were expressed as median with IQR, and categorical variables as absolute numbers with corresponding percentages. Differences in continuous variables between 2 groups were evaluated by Mann-Whitney U test, and differences in categorical variables were evaluated by Chi-squared test. Pearson test was applied to assess correlations of continuous variables. Significance of infarct size reduction over time was determined by the Wilcoxon signed-rank test. Clinically relevant infarct size reduction was defined as relative decrease > median. Receiver operating characteristic analysis was applied to determine the area under the curve for the prediction of infarct size reduction. Optimal cutoff values of PWV and other significant determinants of infarct size reduction were determined via Youden Index.[25] Univariable and multivariable logistic regression analyses were calculated to disclose significant and independent predictors of infarct size reduction. For multivariable analysis, 2 different models were created: 1 model including variables in their continuous form ("raw data") and 1 model with dichotomized variables (dichotomization at optimal cutoff value by Youden Index) to allow for a better comparison of odds ratios.[18] Infarct healing ability was defined as follows: low (relative infarct size reduction <median), moderate (>median but <75th percentile), and high (>75th percentile). For all statistical calculations, a 2-tailed *P*-value of <0.05 was defined as significant.

Results

Baseline Characteristics

In total, 103 STEMI patients with a median age of 55 years (IQR, 49–66) were included. All baseline characteristics including clinical, angiographic, and CMR parameters are presented in detail in Table 1. The delay from symptom onset to CMR scan was 59 hours (IQR, 36–94). This CMR delay was not correlated to baseline infarct size (r=−0.13, P=0.90). Median aortic PWV was 6.7 m/s (IQR, 5.7–8.1). Aortic PWV was significantly correlated to age (r=0.71, P<0.001), peak NT-proBNP (r=0.23, P=0.02), and baseline ejection fraction (r=−0.23, P=0.02) but not with baseline stroke volume (r=−0.09, P=0.37). Furthermore, higher aortic PWV was detected in women (P=0.01), in patients with hypertension (P=0.005), and in patients with nicotine abuse (P=0.03).

Infarct Size Reduction

Median infarct size was 23 (IQR, 11–39) g at baseline and 15 (IQR, 8–23) g at 4 months. Accordingly, the absolute infarct size decrease was 6 (IQR, 2–13) g, the relative decrease 34% (IQR, 16% to 53%). Infarct size as percentage of LVMM significantly decreased from 17% (IQR, 9% to 28%) in median at baseline to 12% (IQR, 6% to 17%) at 4-month follow-up (P<0.001). The absolute infarct size reduction, therefore, was 5% of LVMM (IQR 1% to 11%), relative infarct size reduction was 36% (IQR 15% to 52%). Patients with absolute infarct size reduction of over 5% of LVMM had significantly higher baseline infarct size (28% [IQR 21% to 35%] versus 10% [IQR 6% to 17%] of LVMM, P<0.001), whereas the relation between

Table 1. Baseline Characteristics

	Total Population (n=103)	IS Reduction ≤36% (n=52)	IS Reduction >36% (n=51)	*P* Value
Age, y	55 [49–66]	60 [51–71]	53 [48–61]	0.01
Female, n (%)	14 (14)	9 (17)	5 (10)	0.27
Body mass index, kg/m^2	26.3 [24.7–28.7]	26.4 [24.5–28.7]	26.3 [24.7–28.7]	0.88
Hypertension, n (%)	62 (60)	34 (65)	28 (55)	0.28
Systolic blood pressure, mm Hg	124 [113–141]	129 [113–143]	123 [112–140]	0.48
Diastolic blood pressure, mm Hg	77 [70–89]	77 [70–90]	75 [64–86]	0.37
Current smoker, n (%)	59 (57)	28 (54)	31 (61)	0.40
Hyperlipidemia, n (%)	56 (54)	30 (58)	26 (51)	0.49
Diabetes mellitus, n (%)	9 (9)	7 (14)	2 (4)	0.16
Culprit lesion, n (%)				0.41
RCA	44 (43)	23 (44)	21 (41)	
LAD	44 (43)	21 (41)	23 (45)	
LCX	13 (12)	8 (15)	5 (10)	
RI	2 (2)	0 (0)	2 (4)	
Number of diseased vessels, n (%)				0.06
1	65 (63)	33 (63)	32 (63)	
2	30 (29)	18 (35)	12 (23)	
3	8 (8)	1 (2)	7 (14)	
Admission creatinine, mg/dL	0.99 [0.86–1.09]	0.97 [0.54–1.07]	1.02 [0.89–1.09]	0.29
Peak hs-cTnT, ng/L	5303 [2763–9146]	4436 [2340–8917]	6162 [3506–10 804]	0.13
Peak NT-proBNP, ng/L	802 [282–1514]	923 [578–1514]	537 [191–1276]	0.05
Peak hs-CRP mg/L	21 [10–45]	26 [10–53]	15 [9–44]	0.08
CMR parameters				
Symptom onset to CMR scan, h	59 [36–94]	71 [40–96]	55 [33–90]	0.20
Aortic PWV, m/s	6.7 [5.7–8.1]	7.3 [6.2–8.7]	6.4 [5.4–7.0]	0.003
LVSV baseline, mL	78 [66–89]	79 [61–93]	77 [66–87]	0.69
LVEF baseline, %	54 [46–60]	55 [46–64]	53 [47–58]	0.39
MVO, n (%)	59 (57)	29 (56)	30 (59)	0.28
IS baseline, % of LVMM	17 [9–28]	16 [9–24]	21 [9–31]	0.16
IS 4 mo, % of LVMM	12 [6–17]	13 [8–20]	10 [3–14]	0.006

Baseline patient characteristics in the overall cohort as well as in the 2 subgroups divided by the median of relative infarct size decrease (=36%, defining clinically relevant infarct size reduction). Data in brackets indicate interquartile range. CMR indicates cardiac magnetic resonance; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; IS, infarct size; LAD, left anterior descending artery; LCX, left circumflex artery; LVEF, left ventricular ejection fraction; LVMM, left ventricular myocardial mass; LVSV, left ventricular stroke volume; MVO, microvascular obstruction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PWV, pulse wave velocity; RCA, right coronary artery; RI, ramus intermedius.

relative infarct size reduction of >36% and higher baseline infarct size was not significant (21% [IQR 9% to 31%] versus 16 [IQR 9% to 24%] of LVMM, *P*=0.16).

Differences in baseline characteristics in relation to relative infarct size reduction (median of 36% as cutoff) are listed in Table 1. Patients with relative infarct size reduction >36% were significantly younger (*P*=0.01) and had significantly lower peak NT-proBNP concentrations (*P*=0.047) and aortic PWV values (*P*=0.003).

Aortic PWV and Prediction of Infarct Size Reduction

In univariable binary logistic regression analysis, continuous aortic PWV significantly predicted relative infarct size reduction >36% (odds ratio 0.69, 95% CI, 0.54–0.89, *P*=0.003; Table 2). Best cutoff value of aortic PWV (according to Youden Index) for the prediction of infarct size reduction of >36% was 7 m/s. Aortic PWV <7 m/s had an odds ratio of 4.96 (95% CI, 2.08–11.78, *P*<0.001) in predicting infarct size reduction >36%

(Table 2). In the continuous (P=0.001) as well as in the categorical binary regression model (P=0.001), the relation between aortic PWV and relative infarct size reduction remained significant after adjustment for baseline infarct size, age, and peak NT-proBNP as well as hs-CRP concentrations (Table 2). In multivariable linear regression analysis including all variables from Table 2, the association between relative infarct size reduction and PWV remained significant (regression coefficient B: −6.35 [95% CI, −10.92 to −1.79], P=0.007). The ability of infarct healing in relation to aortic PWV is further illustrated by Figure 1. Better infarct healing was associated with a significant and stepwise decrease in aortic PWV (P=0.001), low infarct size reduction (<36%) median PWV 7.3 m/s, moderate infarct size reduction (36–52%) median PWV 6.9 m/s, and high infarct size reduction (>52%) median PWV 5.9 m/s. The areas under the curve of aortic PWV for the prediction of infarct size reduction of >36% and >52% were 0.67 (95% CI, 0.56–0.77; P=0.003) and 0.73 (95% CI, 0.62–0.83, P=0.001), respectively. Two patient examples are provided by Figure 2.

When infarct size is expressed in grams (not adjusted for LVMM), patients with relative infarct size reduction >34% (=median) also showed significantly lower aortic PWV (6.6 [IQR, 5.4–7.0] versus 7.3 [IQR, 6.1–8.6] m/s, P=0.010). The area under the curve of aortic PWV for the prediction of infarct size reduction (in grams) of >34% was 0.65 (95% CI, 0.54–0.75).

Discussion

The present investigation represents the first study assessing the impact of aortic PWV on infarct healing in survivors of acute STEMI treated by contemporary primary percutaneous coronary intervention. The key findings of our analyses are as follows: (1) within the first 4 months after revascularized STEMI, significant infarct healing occurs, with a relative infarct size reduction of 36%; (2) age, NT-proBNP, and aortic PWV were significantly associated with infarct healing, whereas (3) aortic PWV emerged as an independent predictor of infarct size reduction post-STEMI. Together, these findings suggest a relevant detrimental impact of increased PWV on infarct healing processes during the early recovery phase in STEMI patients.

Infarct Healing Following STEMI

CMR imaging allows for an excellent evaluation of myocardial injury and has emerged as in vivo method of choice for infarct size quantification.[26] Both acute and chronic infarct size determined by CMR were shown to be strongly associated with clinical outcome of STEMI survivors.[27] Nonetheless, data on infarct healing dynamics following STEMI are limited. Until now, only studies with relatively small sample sizes have investigated the changes in infarct size post-STEMI. The largest study so far, including 66 STEMI patients, was published by Pokorney et al and demonstrated the highest infarct size reduction within the first 4 months after infarction.[15] They reported an absolute decrease in mean infarct size of 5% of LVMM (21% to 16%) within the 4 months.[15] This decrease is in agreement with the earlier published data by Ingkanisorn and colleagues analyzing 20 patients.[28] With a relevantly larger number of patients, the present study could validate those previous reports by detecting a median infarct size decrease of

Table 2. Logistic Regression Analysis for Prediction of IS Reduction >36%

	Univariable		Multivariable	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Model A				
Age	0.95 (0.91–0.98)	0.01	…	…
Aortic PWV	0.69 (0.54–0.89)	0.003	0.64 (0.49–0.84)	0.001
Baseline IS	1.03 (0.99–1.05)	0.09	…	…
Peak NT-proBNP	1.00 (1.00–1.00)	0.13	…	…
Peak hs-CRP	0.91 (0.82–1.01)	0.08	0.89 (0.80–0.99)	0.04
Model B				
Age <57 y	3.60 (1.58–8.23)	0.002	…	…
Aortic PWV <7.0 m/s	4.96 (2.08–11.78)	<0.001	4.80 (1.89–12.20)	0.001
Baseline IS >19%	1.95 (0.88–4.27)	0.09	…	…
Peak NT-proBNP <556 ng/L	3.10 (1.28–7.46)	0.01	…	…
Peak hs-CRP <21 mg/L	3.18 (1.42–7.12)	0.005	2.45 (1.00–6.05)	0.05

Model A includes continuous variables; in Model B the variables are dichotomized according to the best cutoffs derived by Youden Index. hs-CRP indicates high-sensitivity C-reactive peptide; IS, infarct size; NT-proBNP, N-terminal pro–B-type natriuretic peptide; OR, odds ratio; PWV, pulse wave velocity.

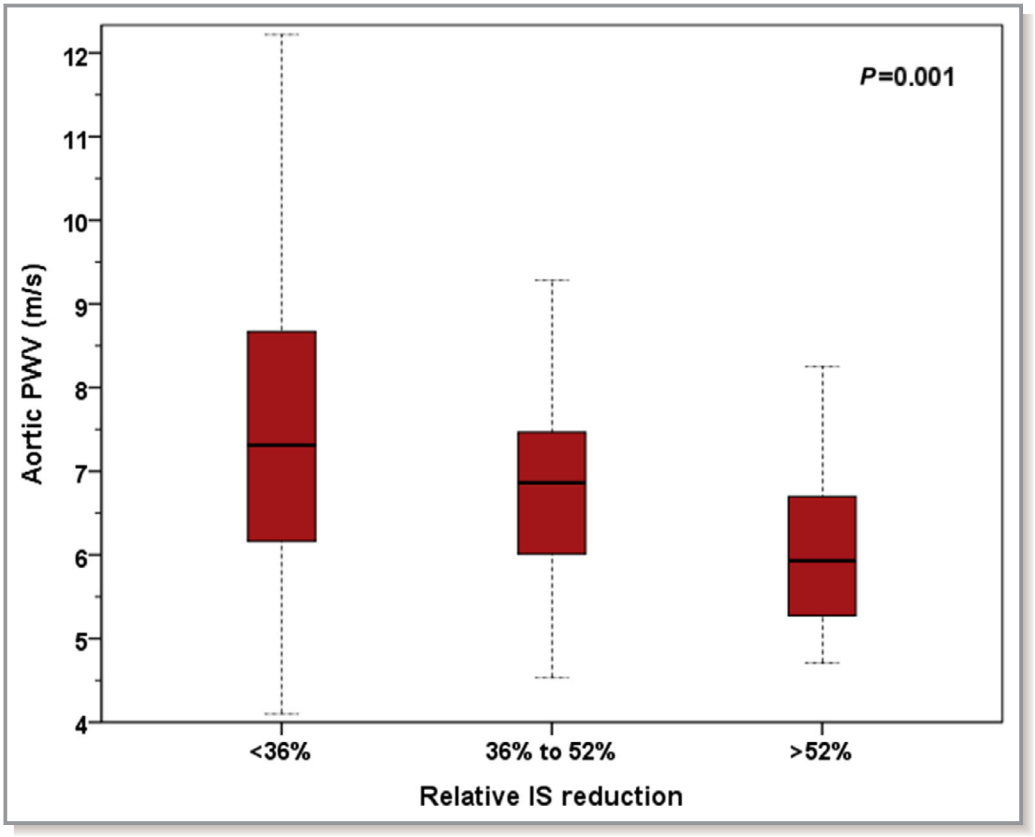

Figure 1. Boxplots displaying aortic PWV values in relation to relative IS reduction from baseline to 4 months after STEMI. The *x*-axis indicates the ability of infarct healing defined as low (relative infarct size reduction <median), moderate (>median but <75th percentile), and high (>75th percentile). IS indicates infarct size; PWV, pulse wave velocity; STEMI, ST-segment–elevation myocardial infarction.

5% of LVMM until 4 months of the follow-up. However, it has to be pointed out that the absolute changes in infarct size are heavily dependent on the initial extent of myocardial damage. Indeed, both the study by Pokorney et al and our investigation clearly highlight the strong influence of baseline infarct size on absolute infarct size reduction.[15] Accordingly, the determination of relative infarct size reduction, which has been proven to be independent of baseline infarct size, has been suggested.[15] Underscoring this approach, in our study the significant impact of initial infarct size also dissolved when infarct size was analyzed as a percentage reduction instead of an absolute decrease. Concretely, the relative infarct size reduction in our patient cohort had a median of 36%, which is comparable with the previous reports.[28] Taken together, due to the minor influence of initial myocardial damage on relative infarct size reduction, this measure may allow for a more standardizable evaluation of infarct healing post-STEMI rather than absolute infarct size reduction.[15]

Aortic PWV and Infarct Healing Post-STEMI

The individual capacity for infarct healing and the potential influence of clinical factors on infarct size dynamics as determined by CMR following STEMI are largely unknown. With the present study, we provide first-time data regarding the impact of clinical parameters on CMR-determined infarct size reduction.

First, we could find a significant association between infarct size reduction and age. Worse infarct healing potential in older patients was hypothesized earlier, particularly in light of the age-related differences in wound repair processes including extracellular matrix deposition, angiogenesis, and endothelial function.[29] However, our analysis provides a new perspective on this subject matter of infarct healing and the role of aging. In line with several previous studies,[30] we demonstrated a close correlation of age with aortic PWV. This well-established relationship is based on the age-dependent loss of elasticity of the aorta and its major branches, which generates higher velocities of the pulse wave.[31] That increase in PWV due to more pronounced aortic stiffness has important hemodynamic consequences because both the antegrade systolic pressure wave and, consequently, the retrograde reflection wave occur earlier.[6] The premature arrival of the reflection wave during systole leads to an augmentation of cardiac afterload and, thus, to increased cardiac wall stress.[6] Indeed, previous investigations as well as the present data

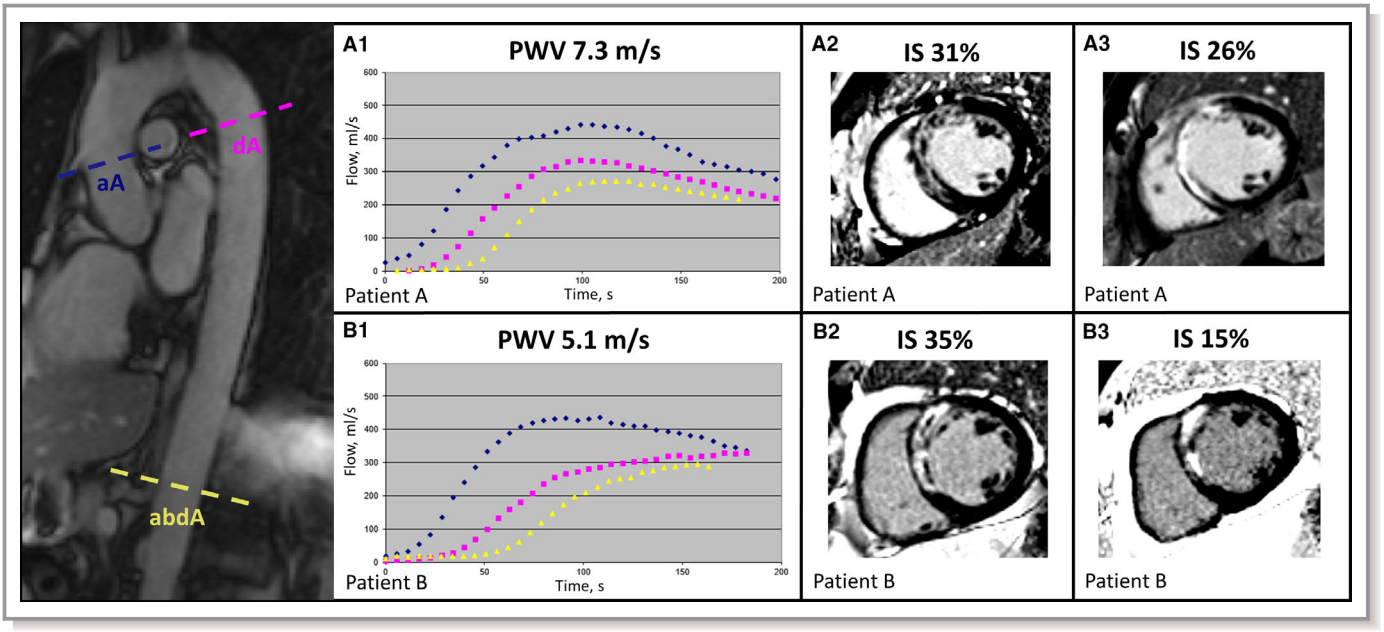

Figure 2. Case examples. Representative example of 2 male patients with anterior wall STEMI (Patient A first row, Patient B second row) and comparable baseline IS (Patient A 31% [A2], Patient B 35% [B2]) but markedly diverging PWV (Patient A 7.3 m/s, Patient B 5.1 m/s) as well as IS reduction (follow-up IS: Patient A 26%, Patient B 15%). aA indicates ascending aorta; abdA, abdominal aorta; dA, descending aorta; IS, infarct size; PWV, pulse wave velocity; STEMI, ST-segment–elevation myocardial infarction. Note: only 2 locations (ascending and abdominal aorta) were used for PWV calculation.

clearly demonstrated a relationship between aortic PWV and natriuretic peptides.[8] Above and beyond this raise in cardiac afterload, a premature pulse wave reflection is associated with decreased diastolic blood pressure, which diminishes coronary perfusion.[10] In addition, increased aortic stiffness may compromise the microcirculation, causing higher resistance to mean flow.[32] From a pathophysiological point of view, the combination of wall stress increase, coronary perfusion decrease, and microvascular dysfunction may provoke myocardial ischemia, which would be particularly unfavorable in the postinfarction healing phase. Previous investigations indeed verified an association between aortic PWV and high-sensitivity cardiac troponin T concentration in the chronic stage post-STEMI,[11] indicating that elevated aortic PWV could induce subclinical myocardial damage. Confirming these previous data by a more comprehensive approach using LGE CMR imaging, we could reveal an independent association between aortic PWV and infarct size reduction, highlighting that aortic PWV may adversely affect infarct healing following STEMI. Importantly, in multivariable analysis the significant relation of infarct size reduction with age dissolved with adjustment for aortic PWV, suggesting that aortic PWV represents the underlying pathophysiological link between age and infarct healing.

There is a large body of evidence that more pronounced myocardial injury leads to higher NT-proBNP levels in the acute setting of STEMI,[33] which was also found in the present overall cohort. However, interestingly, the patient group exhibiting better infarct healing had, despite more pronounced initial myocardial damage, significantly lower peak NT-proBNP levels. That discrepancy between acute infarct size and NT-proBNP on the one hand confirmed that acute myocardial injury is not the only determinant of cardiac wall stress but on the other hand disclosed that wall stress determines infarct healing independently of acute infarct size. This discrepancy, however, can be explained by taking aortic PWV into account because PWV was significantly related to NT-proBNP but not to acute infarct size, revealing PWV to be an infarct size–independent correlate of wall stress in the acute setting of STEMI. Furthermore, multivariable analysis disclosed aortic PWV but not NT-proBNP as an independent predictor of infarct size reduction, which emphasizes that aortic PWV acts as a pathophysiological link between wall stress and infarct healing. In sum, the present findings indicate that low aortic PWV may compensate for the unfavorable wall stress increase associated with large infarct size in the acute phase of infarction; however, the effects of aortic PWV on infarct healing post-STEMI go above and beyond this NT-proBNP–reflected mechanism.

Clinical Implications

The present data could confirm previous findings by highlighting the adverse clinical effects of high aortic PWV

in survivors of acute STEMI.[5] Hence, PWV is suggested as a novel promising biomarker for optimized early risk stratification of STEMI patients in clinical routine. Above and beyond risk assessment, our results indicate aortic PWV as a potential therapeutic target to improve infarct healing processes following STEMI. Although to date there is no approved specific therapy to reduce aortic stiffness, different experimental and clinical investigations have reported on effective reductions of aortic PWV by different pharmacological agents.[34-36] The novel link between aortic PWV and infarct healing revealed by the present analysis may pave the way for future trials testing new therapeutic approaches to reduce aortic PWV and thus improve infarct healing and subsequent clinical outcome post-STEMI. However, the observational design of the present analysis as well as of previous studies could not prove causality between aortic PWV and adverse clinical effects, which remains to be further answered by dedicated randomized clinical trials.

Limitations

The present study has some limitations. Aortic PWV was assessed within the first week after STEMI to investigate its value for the prediction of future infarct size dynamics in the postacute stage. Although aortic PWV in general is a relatively stable parameter with only slight, nonsignificant variations within 1 year,[37-39] a limitation is that we did not measure PWV at a 4-month follow-up. Due to the inclusion and exclusion criteria of the current study, findings are not generalizable to unstable patients presenting with cardiogenic shock, who are, however, a minority of patients presenting with STEMI.[40] Primarily as a result of myocardial edema, LGE CMR in general overestimates infarct size in the acute setting following STEMI.[41] Accordingly, infarct size reduction as determined by LGE CMR reflects myocardial healing processes but should not be equated with the actual degree of necrotic tissue healing. Based on prognostic data in the acute[42] and chronic phases[43] after STEMI as well as on recommendations of the Society for Cardiovascular Magnetic Resonance expert consensus document,[44] we assessed LGE by the threshold approach based on signal intensity in comparison to remote myocardium. However, the different intensities between acute and chronic LGE signals may have influenced this approach. Finally, based on the observational design of the present study, causal conclusions cannot be drawn from our data.

Conclusions

In survivors of acute STEMI treated with primary percutaneous coronary intervention, aortic PWV emerged as an independent predictor of infarct size reduction, revealing a new pathophysiological link between aortic stiffness and adverse infarct healing in these patients. These findings suggest aortic stiffness as a promising early risk stratification tool in clinical practice and also as a potential therapeutic target to improve healing processes following STEMI.

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Disclosures

None.

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