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Relation of plasma adiponectin levels and aortic stiffness after acute ST-segment elevation myocardial infarction

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Abstract

Background: Pulse wave velocity is a measure of aortic stiffness and an independent predictor of cardiovascular morbidity and mortality. Adiponectin is involved in atherosclerosis and inflammation. In the present study we aimed to explore the association between plasma adiponectin concentrations and pulse wave velocity in the acute phase after ST-segment elevation myocardial infarction (STEMI).

Methods: Forty-six consecutive STEMI patients (mean age 57±11 years) treated with primary percutaneous coronary intervention (PCI) were enrolled in this cross-sectional study. Plasma adiponectin was measured 2 days after index event by enzyme-linked immunosorbent assay. Aortic pulse wave velocity (PWV) was calculated by the transit-time method with the use of a velocity-encoded, phase-contrast cardiac magnetic resonance protocol.

Results: Median plasma adiponectin concentration was 2385 ng/ml (interquartile range 1735–5403). Males had lower plasma adiponectin values than females and current smokers had lower values than non-smokers (all $p<0.02$). Adiponectin was significantly associated with PWV ($r=0.505$, $p<0.001$), age ($r=0.437$, $p=0.002$), and total cholesterol ($r=0.468$, $p=0.001$). Multiple linear regression analysis revealed adiponectin as a predictor of PWV independently of age, sex, smoking status, total cholesterol, and N-terminal pro-B-type natriuretic peptide ($p=0.027$).

Conclusions: Plasma adiponectin concentrations are strongly associated with aortic stiffness in patients after acute STEMI treated with primary PCI. Our data support a possible role for adiponectin as an independent risk marker for increased aortic stiffness in STEMI patients.

Keywords

Adiponectin, aortic stiffness, cardiac magnetic resonance, pulse wave velocity, ST-segment elevation myocardial infarction

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Introduction

Adiponectin, a member of the adipokine family, is primarily synthesized in adipocytes and abundantly secreted into the blood. Adiponectin possesses antiatherosclerotic effects, mediated via pleiotropic modulations of multiple vascular cell types.[1,2] Adiponectin is therefore thought to play a protective role in cardiovascular disease. In fact, in healthy subjects, low levels of adiponectin were associated with an increased risk for cardiovascular disease independent of other known risk factors.[3,4] In healthy subjects, those with low plasma adiponectin levels showed also an increased aortic stiffness.[5] Strong evidence suggests that elevated aortic stiffness is an independent marker of cardiovascular morbidity and mortality.[6–8]

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Paradoxically, in patients with manifest cardiovascular disease, increased concentrations of adiponectin were associated with adverse outcome.[9,10] Also in ST-elevation myocardial infarction (STEMI) patients, high levels of circulating adiponectin were associated with all-cause mortality and cardiovascular mortality.[11] A possible explanation for these conflicting results between healthy and diseased populations is that, in patients with existing cardiovascular disease, elevated levels of adiponectin might reflect a compensatory protective but insufficient mechanism.[12] In line with this hypothesis, a positive correlation between adiponectin and arterial stiffness was found in patients with stable coronary artery disease.[13] Data regarding a possible association between adiponectin and arterial stiffness in patients with unstable coronary artery disease are missing.

Measurement of pulse wave velocity (PWV) is the current gold-standard technique to assess stiffness of large arteries in vivo.[14] Velocity-encoded, phase-contrast cardiac magnetic resonance imaging (PC-CMR) represents a non-invasive, accurate and reproducible method for the determination of PWV.[15,16] Compared with other non-invasive approaches (e.g. ultrasound techniques), PC-CMR is not affected by geometrical assumptions on the course and length of the aorta and the need for an accurate acoustic window.[8,17]

Because of the inverse correlation of adiponection with aortic stiffness in recent cohort studies[5,18] and the conflicting results in patients with established CAD,[13] we sought to investigate the relationship between plasma levels of adiponectin and PWV after STEMI for the first time.

Methods

Study population

Consecutive patients with first STEMI according to the redefined ESC/ACC committee criteria[19] and successful reperfusion by primary PCI were included in this single-centre, prospective, cross-sectional study. Patient recruitment was performed between April 2011 and March 2012. Patients with renal dysfunction (an estimated glomerular filtration rate <30 ml/min/1.73m^2), contraindications for CMR (e.g. pacemaker, claustrophobia, orbital foreign body, cerebral aneurysm clip), history of coronary artery disease as well as unstable patients (Killip class >2) were not included. Patient characteristics were assessed by a detailed medical history and physical examination during hospitalization. All participants provided written informed consent before inclusion in the trial. The study was approved by the local ethics committee.

Blood sample and adiponectin ELISA

Venous blood for the measurement of plasma adiponectin was collected in EDTA tubes and immediately centrifuged for 10 min at 2000 *g*. Isolated plasma was stored at −80°C until analysis. Total plasma adiponectin was measured by a commercially available enzyme-linked immunosorbent assay (R&D Systems Europe, Abingdon, UK). The lower limit of detection of the assay is 0.246 ng/ml. Intra- and interassay coefficients of variation are <7%. The high-molecular-weight (HMW) isoform of adiponectin was also measured by a commercially available enzyme-linked immunosorbent assay (R&D Systems Europe). The minimum detectable dose is 0.195 ng/ml. Intra- and interassay coefficients of variation are <9%.

Routine laboratory analysis (including creatine kinase (CK) activity, cardiac troponin T (cTnT), high-sensitivity C-reactive protein (hs-CRP), and N-terminal pro-B-type natriuretic peptide (NT-proBNP)) were performed as described previously.[20]

Aortic pulse wave velocity analysis

For the determination of PWV, PC-CMR was applied. All scans were performed on a 1.5 Tesla Magnetom AVANTO-scanner (Siemens, Erlangen, Germany) within the first week after the index event. Two slices (128 phases per cardiac cycle) of retrospectively triggered, free-breathing, gradient echo sequences with a temporal and spatial resolution of ~20 ms and 1.3×1.3×8 mm, respectively were acquired. Slices were planned perpendicular to the ascending and descending aorta to measure trough plane flow.[21] Initial velocity encoding was set to 150 cm/s and corrected as appropriate if aliasing artefacts occurred. PWV was calculated by the transit-time method.[22] The path length (distance between two recording sites) divided by the run time of the pulse wave gives the PWV. The pulse wave is considered to 'arrive' at a certain level when the systolic upstroke in volume-flow begins.

Statistical analysis

SPSS Statistics 19.0.0 (IBM, Armonk, NY, USA) was used for statistical calculations. Kolmogorov–Smirnov test was applied to test for normal distribution. Normally distributed continuous variables are presented as mean±standard deviation and nonnormally distributed continuous variables as median with corresponding interquartile range (IQR). Pearson or Spearman rank correlations were calculated as indicated. Adiponcetin was log transformed for correlation analysis. To study whether there is an independent association between PWV and plasma adiponectin concentrations, multiple linear regression analysis was performed. For this analysis, all nonnormally distributed variables were log-transformed. In the first model, only variables with $p<0.05$ in univariate analyses were entered. In the second model, variables with $p<0.1$ were entered. To calculate the predictive value of adiponectin for increased PWV in this population, receiver operating characteristic analyses was performed.

Table 1. Baseline characteristics of the study cohort.

Characteristic	Study population (*n*=46)
Age (years)	57±11
Female	6 (13)
Body mass index (kg/m^2)	27±3
Hypertension	36 (78)
Blood pressure (mmHg)	131±26/77±12
Family history for AMI	12 (26)
Smoking status	19 (41)
Hyperlipidaemia	32 (70)
Total cholesterol (mg/dl)	182±44
Diabetes mellitus	5 (11)
CKD	3 (6)
Creatinine	0.91±0.17
eGFR (ml/min/1.73m^2)	91±19
Anterior STEMI	20 (43)
Number of diseased vessels	
1	24 (52)
2	18 (39)
3	4 (9)
Left ventricular ejection fraction (%)	54±11
CK max (U/l)	2206 (1156–4058)
cTnT max (ng/l)	6161 (3739–9237)
NT-proBNP max(ng/l)	1155 (616–2214)
hs-CRP max (mg/dl)	2.4 (1.1–5.0)
Adiponectin (ng/ml)	2385 (1735–5403)

Values are given as mean±standard deviation, *n* (%), or median (interquartile range).
AMI, acute myocardial infarction; CK, creatine kinase; CKD, chronic kidney disease; cTnT, cardiac troponin T; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; STEMI, ST-segment elevation myocardial infarction.

For all data, a two-tailed *p*-value of $p<0.05$ was considered to indicate statistical significance.

Results

Characteristics of the study cohort are listed in Table 1. All patients (*n*=46; mean age 57±11 years; six females) were successfully treated with primary PCI (median onset-of-pain-to-balloon time 248 min, IQR 131–525 min). Dual antiplatelet therapy with aspirin and a P2Y12 receptor blocker (clopidogrel, prasugrel, or ticagrelor) was initiated in all patients before primary PCI. At 24 h after primary PCI treatment with a β-blocker, a calcium-channel blocker, an angiotensin-converting-enzyme inhibitor (ACE-I)/angiotensin receptor blocker, and a statin was initiated in 41 (89.1%), 2 (4.3%), 41 (89.1%), and 46 (100%) patients, respectively. Participants underwent PC-CMR within a median of 3 days (IQR 2–4 days) after symptom onset. Blood samples for measurement of plasma adiponectin levels were drawn 2 days (IQR 1–3 days) after the index event. Median plasma adiponectin concentration was 2385 ng/ml (IQR 1735–5403 ng/ml). Female patients displayed significantly higher plasma adiponectin concentrations compared with male patients: 7578 ng/ml (IQR 3458–8537 ng/ml) vs. 2308 ng/ml (IQR 1731–4327ng/ml; $p=0.011$). Furthermore, current smokers had lower levels of plasma adiponectin than non-smokers: 1976 ng/ml (IQR 1653–2322 ng/ml) vs. 3923 ng/ml (IQR 2159–6419 ng/ml; $p=0.009$). There was no difference in adiponectin levels between patients with or without β-blocker ($p=0.948$), calcium-channel blocker ($p=0.669$), and ACE-I/angiotensin receptor blocker ($p=0.409$) treatment at 24 h after primary PCI. In addition, there was no significant difference in plasma adiponectin levels between patients with and without diabetes ($p=0.214$).

Correlations between plasma adiponectin or PWV and baseline parameters are summarized in Table 2. Importantly, adiponectin concentrations were significantly correlated to PWV ($r=0.505$, $p<0.001$) (Figure 1A), age ($r=0.437$, $p=0.002$), and total cholesterol on admission ($r=0.468$, $p=0.001$).

We found a strong relationship between PWV and patient's age ($r=0.611$, $p<0.001$; Figure 1B). There was no significant difference in PWV between male and female patients, patients with/without diabetes, patients with/without hypertension, patients with/without hyperlipidaemia, and patients with/without a positive family history of cardiovascular disease (all $p>0.05$).

To test whether circulating adiponectin concentrations were independently associated with PWV a multiple linear regression analysis was performed. In the first model, PWV was taken as the dependent variable, and age, sex, smoking status, total cholesterol, and log adiponectin concentration as independent variables. This model revealed that plasma adiponectin levels (β=0.521, $p=0.004$) as well as age (β=0.447, $p=0.004$) were significantly correlated with PWV ($R=0.711$, $p<0.001$; Table 3). In the second model, independent variables were age, sex, smoking status, total cholesterol, log adiponectin, and log NT-proBNP. Also in this model ($R=0.730$, $p<0.001$), age (β=0.547, $p=0.001$) and log adiponectin (β=0.408, $p=0.027$) remained significant predictors of PWV.

We further conducted the same correlation studies for the HMW isoform of adiponectin. HMW adiponectin levels were strongly associated with total adiponectin concentrations ($r=0.949$, $p<0.001$). HMW adiponectin was significantly correlated with age ($r=0.505$, $p<0.001$), PWV ($r=0.464$, $p=0.001$), and total cholesterol ($r=0.362$, $p=0.016$), but not with body mass index, systolic blood pressure, diastolic blood pressure, triglycerides, creatinine, estimated glomerular filtration rate, maximum CK, maximum cTnT, maximum hs-CRP, or maximum NT-proBNP (all $p>0.05$). In multivariate analysis, HMW adiponectin remained significantly associated with PWV after

Table 2. Univariate correlations between plasma adiponectin/PWV and baseline parameters.

	Log adiponectin		PWV	
	r	*p*	*r*	*p*
PWV (m/s)	0.505	<0.001	–	–
Age (years)	0.437	0.002	0.611	<0.001
BMI (kg/m^2)	−0.183	0.223	−0.135	0.370
Systolic blood pressure (mmHg)	0.185	0.217	0.160	0.287
Diastolic blood pressure (mmHg)	0.100	0.509	0.038	0.803
Heart rate (beats/min)	−0.061	0.687	−0.040	0.794
Total cholesterol (mg/dl)	0.468	0.001	−0.031	0.842
Triglycerides (mg/dl)	−0.240	0.120	−0.203	0.191
Creatinine (mg/dl)	−0.174	0.248	−0.016	0.914
eGFR (ml/min/1.73m^2)	−0.054	0.719	−0.109	0.470
CK max (U/l)	0.077	0.610	−0.102	0.501
cTnT max (ng/l)	0.113	0.454	−0.010	0.948
NTpro-BNP max (ng/l)	0.257	0.092	0.290	0.056
hs-CRP max (mg/dl)	−0.207	0.168	−0.099	0.513
Left ventricular ejection fraction (%)	−0.079	0.600	−0.237	0.113
Log adiponectin (ng/ml)	–	–	0.505	<0.001

BMI, body mass index; CK, creatine kinase; cTnT, cardiac troponin T; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PWV, pulse wave velocity.

adjustment for age, sex, smoking status, and total cholesterol (β=0.413, p=0.027).

According to PWV (median 7.0 m/s, IQR 5.8–8.3 m/s) patients were divided in two groups. The area under the curve (AUC) of total plasma adiponectin (0.84, 95% CI 0.72–0.95) with the optimal cut-off level of 2282 ng/ml revealed 87% sensitivity and 74% specificity in the prediction of patients with a increased PWV (>7.0 m/s). A further distinction was made between patients with a PWV ≥10.0 m/s (n=4) and those with a PWV <10.0 m/s (n=42). The AUC of plasma adiponectin for prediction of PWV >10.0 m/s was 0.82 (95% CI 0.61–0.10). The optimal cut-off value of plasma adiponectin was 6358 ng/ml (sensitivity 75%, specificity 90%).

Discussion

The current study is the first in investigating the relationship between circulating levels of adiponectin and aortic stiffness in patients after acute STEMI. Aortic stiffness was determined by PWV with the use of PC-CMR. Our main finding is that high plasma adiponectin concentrations are associated with increased aortic stiffness in patients after acute STEMI, independently of age, sex, smoking status, total cholesterol, and NT-proBNP.

Increased aortic stiffness entails haemodynamic changes which promote left ventricular hypertrophy[23] and might lead to subsequent left ventricular remodelling.[24] Both are associated with increased risk for adverse clinical events.[25] In addition, elevated aortic stiffness was suggested as a potential promoter of coronary atherosclerosis and thus ischaemic heart disease.[26,27] In the present study, we measured plasma adiponectin in the acute phase after STEMI and observed a positive correlation between adiponectin levels and aortic stiffness. Adiponectin remained an independent predictor of PWV even after adjustment for relevant covariates (age, sex, smoking status, total cholesterol, and NT-proBNP). Although our study size is relatively small, our results indicate that determination of plasma adiponectin in the acute phase after STEMI might help identify patients with increased aortic stiffness (>7.0 m/s and >10.0 m/s). Patients with increased adiponectin levels might particularly benefit from interventions that reduce the progression of arterial stiffening.

Data on the role of adiponectin in cardiovascular disease are conflicting. On the one hand, adiponectin is thought to possess cardioprotective, anti-inflammatory, and antiatherosclerotic effects.[1] In healthy subjects, low concentrations of adiponectin are considered an independent risk factor for cardiovascular disease.[3,4,28,29] On the other hand, a diametrically opposite association between adiponectin and cardiovascular mortality has been described in patients with existing cardiovascular disease.[9–11,30] It is conceivable that adiponectin has possibly a dual role to play in cardiovascular disease.[12,31] Rathmann and Herder suggested that counter-regulatory vasculoprotective and anti-inflammatory mechanisms lead to an increase in adiponectin levels in these patients.[12] This hypothesis might explain the difference between our results and previous reports showing an inverse association between plasma adiponectin concentrations and arterial stiffness in healthy men[5] and patients with

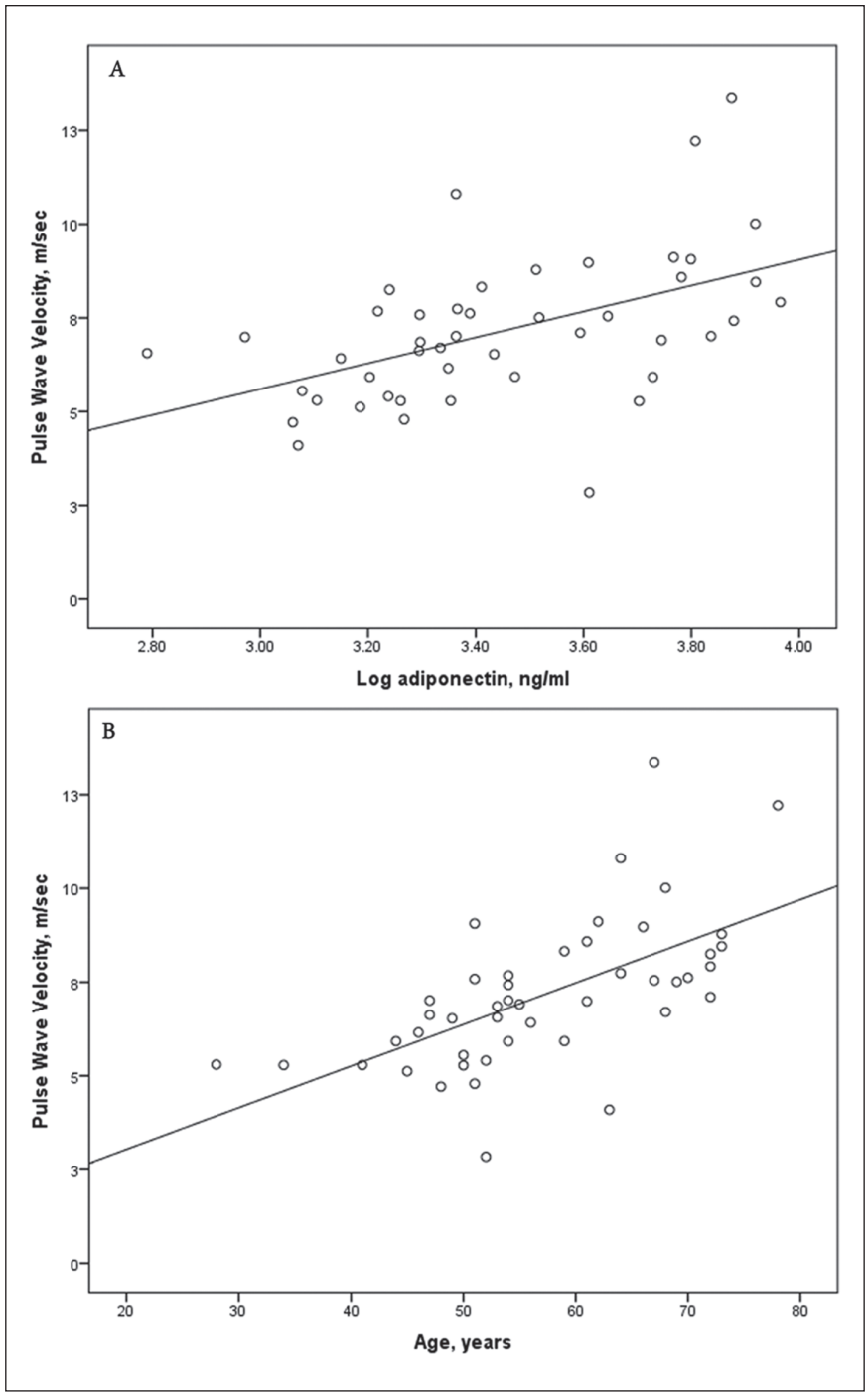

Figure 1. (A) Linear correlation between plasma adiponectin and aortic pulse wave velocity (r=0.505, p<0.001) in patients after acute STEMI (n=46). (B) Linear correlation between age and aortic pulse wave velocity (r=0.611, p<0.001) in the same population.

hypertension.[32] In fact, Ikonomidis et al.[13] reported a positive association between pulse wave velocity and adiponectin in 71 patients with angiographically proven coronary artery disease, which is in line with our results. Another possible explanation for the conflicting results is that elevated levels of adiponectin might mirror an impaired adiponectin signalling in patients with cardiovascular disease. Khan et al.[18] found that, in patients with advanced heart failure, increased levels of adiponectin were accompanied by downregulation of adiponectin receptors in the myocardium. Adiponectin resistance might therefore also explain the direct association between adiponectin and PWV in patients after STEMI. Nevertheless, to identify the pathomechanism behind our

Table 3. Multiple linear regression analysis with PWV as dependent variable.

	Model 1		Model 2	
	β	*p*	β	*p*
Age (years)	0.447	0.004	0.547	0.001
Sex (0=female, 1=male)	0.212	0.100	0.195	0.134
Current smoking (0=no, 1=yes)	0.212	0.233	0.229	0.114
Total cholesterol (mg/dl)	−0.147	0.322	−0.063	0.671
Log adiponectin (ng/ml)	0.521	<0.004	0.408	0.027
Log NT-proBNP (ng/l)	–	–	0.034	0.795

Model 1: R=0.711, p<0.001; model 2: R=0.730, p<0.001.

observation is far beyond the scope of the present study. We, however, believe that the hypothesis which is generated from our data might be worth further investigations.

A limitation of our study is that we measured adiponectin at different time points (median 2 days after STEMI) and relatively late after STEMI. Moreover, the natural evolution of adiponectin concentrations after acute STEMI is unknown so far. Nevertheless, our data suggest that adiponectin levels assessed during the first days after STEMI seem useful as an independent risk marker for increased aortic stiffness in these patients. Further trials with serial and more exact time points for the measurement of adiponectin are warranted to define the most appropriate time point for assessing adiponectin levels. Contrary, the different time points of PWV measurement in this study might be less important, since the PWV is considered to change only slowly over years.[8]

In this study cohort, adiponectin levels were significantly influenced by age and sex, which is in line with other trials reporting higher levels of plasma adiponectin in the elderly and women.[11,31,33] Current smokers displayed lower levels of adiponectin compared with nonsmokers. Such an association has been described in some[11] but not all studies.[32] However, one limitation of this work is that the study cohort is relatively small and consists of multiple small subgroups (e.g. five patients with diabetes, six female patients) which might have an influence on circulating adiponectin levels. Nonetheless, there was still a significant correlation between adiponectin and PWV in the nondiabetic subgroup of male patients (n=35, r=0.557, p=0.001) or in the nonsmoking subgroup of male patients (n=21, r=0.645, p=0.02).

In the present study, only patients presenting with Killip class 1 or 2 were included. Adiponectin was not related to the left ventricular ejection fraction or NT-proBNP concentrations. The same observation was made in previous studies with coronary artery disease patients and STEMI patients.[11,34] If the results of this study hold true for patients with severely impaired left ventricular function has to be clarified in future studies

β-blockers, ACE-I, and statins were reported to influence the plasma adiponectin concentration.[34,35] In our study, all patients received statins. In nearly all patients, β-blocker and ACE-I treatment was initiated. Therefore, the potential impact of medical therapy on plasma adiponectin concentrations might be comparable between all patients.

In patients without known coronary heart disease, serum adiponectin was significantly associated with markers of systemic inflammation, such as CRP[3] and high-sensitivity CRP.[36] This relation, however, did not exist in patients with coronary heart disease or patients after acute STEMI.[11,37] The lack of correlation between adiponectin and circulating hs-CRP in our study is in agreement with this previous finding and does not support the hypothesis that total adiponectin is related to the inflammatory response during STEMI.

The present study also determined the HMW adiponectin concentrations. We found no substantial difference between total adiponectin and HMW adiponectin, indicating that both isoforms are equally suited as risk markers for increased aortic stiffness in these patients.

In conclusion, plasma adiponectin concentrations are associated with increased aortic stiffness, as assessed by PC-CMR, in patients after acute STEMI. This association remained significant even after correction for age, sex, smoking status, total cholesterol, and NT-proBNP. Our data indicate a possible role for adiponectin as an independent risk marker for increased aortic stiffness in STEMI patients, but further studies are necessary to confirm the validity of this suggestion.

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Conflict of interest

The authors declare that there is no conflict of interest.

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