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ORIGINAL ARTICLE

U-shaped association of central pulse pressure with long-term prognosis after ST-segment elevation myocardial infarction

Gjin Ndrepepa[1] · Salvatore Cassese[1] · Sebastian Kufner[1] · Erion Xhepa[1] · Massimiliano Fusaro[1] · Karl-Ludwig Laugwitz[2,3] · Heribert Schunkert[1,3] · Adnan Kastrati[1,3]

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Abstract

The relationship between central pulse pressure (CPP) measured at the time of primary percutaneous coronary intervention (PPCI) and long-term prognosis after ST-segment elevation myocardial infarction (STEMI) has not been investigated. CPP measurements were performed in 1348 patients with STEMI (327 women; mean age 62.5 ± 12.1 years) undergoing PPCI. Aortic systolic and diastolic blood pressure was measured before intervention. The primary outcome was 8-year all-cause mortality. The median [25–75th percentile] CPP value was 55.0 [43.0–70.0] mmHg. CPP correlated negatively with heart rate ($P < 0.001$), body mass index ($P = 0.007$), Killip class ($P < 0.001$) and initial area at risk ($P < 0.001$) and positively with age ($P < 0.001$), female sex ($P < 0.001$), diabetes ($P = 0.012$), arterial hypertension ($P < 0.001$) and glomerular filtration rate ($P = 0.004$). There were 181 deaths over the follow-up. In patients with CPP within the 1st, 2nd and 3rd tertiles, the Kaplan–Meier estimates of mortality were 17.3%, 10.8% and 24.2%, respectively; univariable hazard ratio [HR] = 1.52, 95% confidence interval [CI] 0.99 to 2.32; $P = 0.055$ for tertile 1 vs. tertile 2 and HR = 2.09 [1.36–3.21]; $P < 0.001$ for tertile 3 vs. tertile 2. For CPP values lower than 35 mmHg and higher than 71 mmHg, the association between CPP and all-cause mortality was significant (HR = 1.276 [1.004–1.621] for the 35 mmHg value and HR = 1.289 [1.003–1.657] for the 71 mmHg value) compared with the CPP reference value (54 mmHg). After adjustment, the association between CPP and all-cause mortality was attenuated (P = 0.304). In patients with STEMI undergoing PPCI there is a U-shaped association between CPP and mortality up to 8 years after PPCI.

Keywords Mortality · Pulse pressure · ST-segment elevation myocardial infarction

Introduction

Pulse pressure (PP) is a metric of pulsatile components of blood pressure that is associated with increased risk of cardiovascular disease, myocardial infarction, stroke and cardiovascular mortality [1]. Several studies have investigated the association between PP and cardiovascular outcomes in various conditions and populations including general population [1, 2], hypertensive [3–5] and elderly [6, 7] subjects, patients undergoing coronary revascularization [8], patients with left ventricular systolic dysfunction after myocardial infarction [9, 10], patients with congestive heart failure [11–13] and ambulatory patients at increased cardiovascular risk [14]. A recent community-based prospective study in United Kingdom showed that higher PP values were associated with increased risk of myocardial infarction, coronary artery disease, heart failure and cardiovascular mortality up to 2.8 years of follow-up [15]. Limited and somewhat inconsistent evidence exists with respect to the association between PP and adverse cardiovascular events in patients with acute coronary syndromes (ACS) [16–19] and ST-Segment elevation myocardial infarction (STEMI) [20]. In ACS studies, lower [16–18] or higher [19] PP values were found to be associated with increased risk of mortality or other adverse outcomes. This creates confusion as to which part of the PP values bears prognostic information in ACS

✉ Gjin Ndrepepa
ndrepepa@dhm.mhn.de

1 Department of Adult Cardiology, Deutsches Herzzentrum München, Technische Universität, Lazarettstrasse 36, 80636 Munich, Germany

2 I. Medizinische Klinik, Klinikum Rechts Der Isar, Technische Universität, Munich, Germany

3 DZHK (German Centre for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany

patients. Although central PP (CPP) is a better prognosticator than peripheral (brachial) PP[21], all ACS (or STEMI) studies have investigated the association between peripheral PP usually measured on admission and inhospital or short-term outcomes. Although it has been suggested that short term and long term prognostic value of PP may differ [18], no study so far has investigated whether there is an association between PP and long-term prognosis after STEMI. We undertook this study with 2 main objectives: first, to assess whether there is an association between CPP measured at the time of primary percutaneous coronary intervention (PPCI) and long-term risk of mortality, and; second to identify clinical correlates of CPP in patients with STEMI.

Methods

Patients

The study included 1348 patients with STEMI who underwent PPCI in 2 university hospitals (Deutsches Herzzentrum München and 1. Medizinische Klinik, Klinikum rechts der ISAR) in Munich, Germany from 2002 to 2007. The diagnosis of STEMI was based on typical chest pain lasting > 20 min, electrocardiographic (ST-segment elevation of ≥ 0.1 mV in ≥ 2 limb leads or ≥ 0.2 mV in ≥ 2 contiguous precordial leads or complete left bundle branch block of new onset) and biomarker elevation (creatine kinase myocardial band or conventional cardiac troponin T) criteria. The diagnosis was confirmed by angiography. Details of the source sample were provided in a previous study from our group [22]. Of 1861 patients presenting with STEMI during the study period, 1348 patients fulfilled criteria for this study. Patients who presented beyond 24 h from the symptom onset and those who underwent conservative medical therapy, fibrinolysis or coronary artery bypass surgery as primary reperfusion therapy and those with mechanical failures to open the occluded arteries, aortic stenosis (left ventricular aortic pressure gradient > 10 mmHg) or missing aortic systolic or diastolic blood pressure measurements at the time of PPCI procedure were excluded. The study conforms to the Declaration of Helsinki.

Procedures and measurements

Cardiovascular risk factors—arterial hypertension, hypercholesterolemia, type 2 diabetes and smoking—were defined according to the standard criteria. PPCI was performed as per standard practice. Coronary stents were implanted in 1185 patients (87.9%). All patients received intravenous aspirin (325–500 mg), a loading dose of clopidogrel (600 mg orally) and unfractionated heparin before PPCI procedure. Postprocedural antithrombotic therapy included aspirin (200 mg/day indefinitely) and a thienopyridine (predominantly clopidogrel 75 mg/day for ≥ 6 months). Other cardiovascular medications were prescribed at the discretion of the treating physician.

CPP was calculated as the difference between the aortic systolic blood pressure and diastolic blood pressure, both measured after placement of a fluid-filled pig-tail catheter in the aorta before intervention and ventricular angiography. The global left ventricular ejection fraction was measured on the left ventricular angiograms obtained in the right anterior oblique view using the area-length method [23]. Epicardial blood flow was graded according to the Thrombolysis in Myocardial Infarction definition [24]. Collateral class was defined according to the Rentrop classification [25]. Congestive heart failure in the acute stage of STEMI was assessed according to the Killip criteria [26]. Serum creatinine, creatine kinase myocardial band and C-reactive protein were measured using commercially available assays. The status of renal function was assessed by calculating the estimated glomerular filtration rate according to the Cockcroft-Gault formula [27]. Patient's height and weight were measured during the hospital course and used to calculate the body mass index. The extent of myocardial ischemia in acute phase and the infarct size were measured using the 99mTc-sestamibi single photon emission computed tomography (SPECT) imaging performed before PPCI and 7 to 14 days after PPCI, as previously described[28].

Outcomes and follow-up

The main study outcome was all-cause mortality. Cardiac mortality was also assessed according to the Academic Research Consortium criteria [29]. The follow-up information was obtained by a telephone call at 1 month, a visit at 6 months, a telephone call at one year, and annual telephone calls thereafter. Patients who had cardiac complaints underwent a complete clinical, electrocardiographic and laboratory evaluation. Information on deaths was obtained from hospital records, death certificates and phone contact with relatives of the patient or referring physician, insurance companies or registration of address office. The follow-up information was obtained by personnel blinded to the clinical characteristics of the patients.

Statistical analysis

Patients are categorized in groups according to the CPP tertiles. The distribution pattern of continuous data was assessed using the Kolmogorov–Smirnov test and data with skewed distribution are presented as median (with 25th and 75th percentiles) and compared with the Kruskal–Wallis rank sum test. Discrete data are presented as counts and proportions (percentages) and compared with the chi-square

test. Multiple linear regression model was used to assess correlates of CPP. The Least Absolute Shrinkage and Selection Operator (LASSO) regression method was used to select the variables entered into the model. The following variables were entered: heart rate, baseline TIMI flow grade, age, sex, body mass index, diabetes mellitus, history of arterial hypertension, smoking, hypercholesterolemia, previous myocardial infarction, previous coronary artery bypass surgery, estimated glomerular filtration rate, anterior wall infarction, Killip class, time-to-admission interval and initial perfusion defect. Survival analysis was performed using the Kaplan–Meier method. We used univariable Cox proportional hazards regression model to calculate hazard ratios (HRs) and quantify the risk for all-cause (or cardiac) mortality. We used restricted cubic spline regression with 4 knots at CPP 27.00, 48.65, 62.35 and 98.05 mmHg to assess a potentially non-linear association between CPP and all-cause (or cardiac) mortality. The multivariable Cox proportional hazard model was used to test the association between CPP and mortality while adjusting for eventual confounders. Variables entered into the model (selected using the LASSO regression method) were: CPP (entered as a continuous variable with restricted cubic splines), infarct size, postprocedural TIMI flow grade, age, sex, diabetes, smoking, hypercholesterolemia, previous myocardial infarction, previous coronary artery bypass surgery, C-reactive protein, estimated glomerular filtration rate, anterior wall infarction, Killip class, time-to-admission interval, collateral class, multivessel disease and therapy at discharge (aspirin, clopidogrel, angiotensin-converting enzyme inhibitors, beta-blockers and statins). Missing baseline data are imputed by predictive mean matching (R-package "mice", version 2.46). The statistical analysis was performed using the R 3.4.0 Statistical Package (The R foundation for Statistical Computing, Vienna, Austria). A two-sided $P < 0.05$ was considered as significant.

Results

Baseline data

The tertile values of CPP were used to divide patients into three groups: a group with CPP within the 1st tertile (CPP ≤ 50.0 mmHg; $n = 594$ patients), a group with CPP within the 2nd tertile (CPP > 50.0 mmHg to 66.0 mmHg; $n = 321$) and a group with CPP within the 3rd tertile (CPP > 66.0 mmHg to 147 mmHg; $n = 433$ patients). Baseline characteristics in groups according to CPP tertile values are shown in Table 1. Several characteristics including age, proportion of women, diabetes, arterial hypertension, current smoker, peak creatine kinase myocardial band, glomerular filtration rate, systolic blood pressure, heart rate, Killip class, cardiogenic shock, time to admission, left ventricular ejection fraction, initial area at risk (assessed by SPECT imaging before PPCI) and statins at discharge differed significantly in groups according to CPP tertiles. Angiographic characteristics are shown in Table 2. The highest proportion of patients with multivessel disease was observed in patients of upper CPP tertile. There appears to be a significant difference in collateral class according to CPP tertiles, as well. In patients with CPP within the 1st, 2nd and 3rd tertiles, the scintigraphic infarct size in the 7 to 14 days SPECT imaging was 12.0% [3.1–25.0%], 10.9% [2.0–25.0%] and 8.0% [2.0–20.0%] of the left ventricle, respectively ($P < 0.001$).

Correlates of CPP

Correlates of CPP were assessed using the multiple linear regression model (see "Methods" for variables that were entered into the model). The model identified heart rate (coefficient: − 0.12036; $P < 0.001$), age (coefficient: 0.54290; $P < 0.001$), female sex (coefficient: 5.46168; $P < 0.001$), body mass index (coefficient: − 0.38771; $P = 0.007$), diabetes (coefficient: 3.23344: $P = 0.012$), arterial hypertension (coefficient: 6.85415; $P < 0.001$), glomerular filtration rate (coefficient: 0.06477; $P = 0.004$), Killip class (coefficient: − 4.24840; $P < 0.001$) and initial area at risk (coefficient: − 0.11844; $P < 0.001$) as independent correlates of CPP. The minus sign before the coefficient denotes an inverse association between respective variables (heart rate, body mass index, Killip class and initial area at risk) and CPP.

All-cause and cardiac mortality

Patients were followed up to 8 years after primary PCI (median [25–75th percentiles]: 6.1 [3.9–8.1] years). The primary outcome (all-cause deaths) occurred in 181 patients: 78 deaths, 29 deaths and 74 deaths occurred in patients with CPP values in the 1st, 2nd and 3rd tertiles, respectively (Kaplan–Meier estimates of mortality were 17.3%, 10.8% and 24.2%, respectively; univariable hazard ratio [HR] = 1.52, 95% confidence interval [CI] 0.99–2.32; $P = 0.055$ for tertile 1 vs. tertile 2; HR = 2.09 [1.36–3.21]; $P < 0.001$ for tertile 3 vs. tertile 2; and HR = 1.17 [1.00–1.37]; $P = 0.050$ for tertile 3 vs. tertile 1; Fig. 1). Cardiac deaths occurred in 128 patients: 57 deaths, 22 deaths and 49 deaths occurred in patients with CPP values in the 1st, 2nd and 3rd tertiles, respectively (Kaplan–Meier estimates of cardiac mortality were 12.8%, 8.3% and 16.4%, respectively; univariable HR = 1.47 [0.89–2.38]; $P = 0.130$ for tertile 1 vs. tertile 2; HR = 1.81 [1.10–3.00]; $P = 0.020$ for tertile 3 vs. tertile 2; and HR = 1.11 [0.92–1.35]; $P = 0.270$ for tertile 3 vs. tertile 1; Fig. 2).

Table 1 Baseline data

Variable	Central pulse pressure tertiles			*p* value
	1 (*n* = 594)	2 (*n* = 321)	3 (*n* = 433)	
Age (years)	57.3 [48.8–65.8]	62.5 [54.4–71.4]	70.1 [60.5–77.6]	<0.001
Female sex	98 (16.5)	69 (21.5)	160 (37.0)	<0.001
Body mass index (kg/m^2)	26.3 [24.3–28.5]	26.3 [24.5–29.1]	26.2 [23.7–28.6]	0.269
Type 2 diabetes	91 (15.3)	61 (19.0)	117 (27.0)	<0.001
Arterial hypertension	355 (59.8)	242 (75.4)	351 (81.1)	<0.001
Hypercholesterolemia (≥220 mg/dl)	314 (52.9)	173 (53.9)	220 (50.8)	0.678
Current smoker	310 (52.2)	120 (37.4)	139 (32.1)	<0.001
Previous myocardial infarction	70 (11.8)	32 (10.0)	61 (14.1)	0.219
Previous coronary artery bypass surgery	16 (2.7)	9 (2.8)	20 (4.6)	0.197
Peak creatine kinase MB (U/L)	143.5 [70.0–287.8]	139.5 [61.3–280.3]	113.0 [61.3–229.5]	0.025
C-reactive protein (mg/L)	4.5 [0.0–10.3]	4.1 [0.0–9.9]	4.0 [0.0–11.3]	0.540
Glomerular filtration rate (ml/min)	90.6 [69.8–111.2]	85.6 [67.8–109.0]	72.7 [52.7–94.4]	<0.001
Infarct location				0.053
Anterior	275 (46.3)	149 (46.4)	166 (38.3)	
Inferior	242 (40.7)	128 (39.9)	186 (43.0)	
Lateral	77 (13.0)	44 (13.7)	81 (18.7)	
Systolic blood pressure (mmHg)	110.0 [100.0–120.0]	130.0 [121.0–140.0]	154.0 [140.0–165.0]	<0.001
Diastolic blood pressure (mmHg)	70.0 [60.3–80.0]	70.0 [65.0–80.0]	70.0 [65.0–80.0]	0.448
Pulse pressure (mmHg)	40.0 [35.0–50.0]	60.0 [55.0–60.0]	80.0 [70.0–90.0]	<0.001
Heart rate (beats/min)	79 [67–90]	72 [65–81]	75 [65–85]	<0.001
Killip class				<0.001
I	390 (65.6)	241 (75.1)	329 (76.0)	
II	120 (20.2)	66 (20.6)	78 (18.0)	
III	29 (4.9)	8 (2.5)	16 (3.7)	
IV	55 (9.3)	6 (1.8)	10 (2.3)	
With cardiogenic shock	55 (9.3)	6 (1.8)	10 (2.3)	<0.001
Time-to-admission interval (hours)	4.0 [1.8–9.0]	4.5 [2.0–9.3]	5.0 [2.3–10.3]	0.014
Door-to-balloon time (hours)	1.2 [0.9–1.8]	1.2 [0.9–1.7]	1.2 [0.9–1.7]	0.751
Left ventricular ejection fraction (%)	48.0 [40.0–55.0]	48.5 [42.0–57.8]	50.0 [44.0–57.0]	0.003
Initial area at risk (% of the left ventricle)[a]	25.0 [14.0–43.2]	25.0 [13.2–43.7]	19.0 [10.0–34.0]	<0.001
Therapy at discharge				
Aspirin	586 (98.6)	318 (99.1)	430 (99.3)	0.681
Thienopyridines	590 (99.3)	320 (99.7)	433 (100.0)	0.554
Statins	556 (93.6)	312 (97.2)	402 (92.8)	0.023
Beta-blocking agents	578 (97.3)	317 (98.8)	421 (97.2)	0.314
Angiotensin-converting enzyme inhibitors	546 (91.9)	304 (94.7)	407 (94.0)	0.209

Data are median [25th; 75th percentiles] or number of patients (%)

[a]Measured with the 99mTc-sestamibi single photon emission computed tomography (SPECT) imaging performed before primary percutaneous coronary intervention procedure

For a more detailed assessment of the relationship between CPP and mortality a quintile-based analysis was performed (Fig. 3). This analysis showed a non-linear relationship between CPP and all-cause and cardiac mortality with higher mortality in lower and upper quintiles compared with 3rd quintile (CPP > 51 to 61 mmHg). To further analyze the relationship between CPP and mortality the restricted cubic spline regression was used. The analysis showed a U-shaped association between CPP and the risk of mortality. In all-cause mortality analysis, for CPP values lower than 35 mmHg and higher than 71 mmHg, the hazard ratios for association with all-cause mortality were significant (HR = 1.276 [1.004–1.621] for the 35 mmHg value and HR = 1.289 [1.003–1.657] for the 71 mmHg value) compared with the CPP reference value (54 mmHg; Fig. 4). In cardiac mortality analysis, for CPP

Table 2 Angiographic data

Variable	Central pulse pressure tertiles			*P* value
	1 (*n* = 594)	2 (*n* = 321)	3 (*n* = 433)	
Extent of coronary artery disease				<0.001
1	228 (38.4)	126 (39.3)	115 (26.6)	
2	192 (32.3)	89 (27.7)	132 (30.5)	
3	174 (29.3)	106 (33.0)	186 (42.9)	
Multivessel disease	366 (61.6)	195 (60.7)	318 (73.4)	<0.001
Infarct-related artery				0.060
Left main coronary artery	3 (0.5)	0 (0)	1 (0.2)	
Left anterior descending coronary artery	283 (47.7)	149 (46.4)	173 (40.0)	
Left circumflex coronary artery	87 (14.6)	51 (15.9)	88 (20.3)	
Right coronary artery	213 (35.9)	118 (36.8)	159 (36.7)	
Bypass graft	8 (1.3)	3 (0.9)	12 (2.8)	
Baseline TIMI flow grade				0.159
0	298 (50.3)	141 (43.9)	197 (45.5)	
1	70 (11.8)	41 (12.8)	44 (10.2)	
2	133 (22.4)	82 (25.5)	97 (22.4)	
3	92 (15.5)	57 (17.8)	95 (21.9)	
Collateral class				0.029
0	416 (70.0)	244 (76.0)	328 (75.7)	
1	109 (18.4)	48 (15.0)	61 (14.1)	
2	57 (9.6)	19 (5.9)	25 (5.8)	
3	12 (2.0)	10 (3.1)	19 (4.4)	
Post-interventional TIMI flow grade				0.726
0	7 (1.2)	5 (1.6)	7 (1.6)	
1	15 (2.5)	13 (4.0)	9 (2.0)	
2	54 (9.1)	30 (9.3)	44 (10.2)	
3	518 (87.2)	273 (85.1)	373 (86.2)	
Type of intervention				0.430
Stenting	521 (87.7)	277 (86.3)	387 (89.4)	
Balloon angioplasty	73 (12.3)	44 (13.7)	46 (10.6)	

Data are number of patients (%)

TIMI thrombolysis in Myocardial Infarction

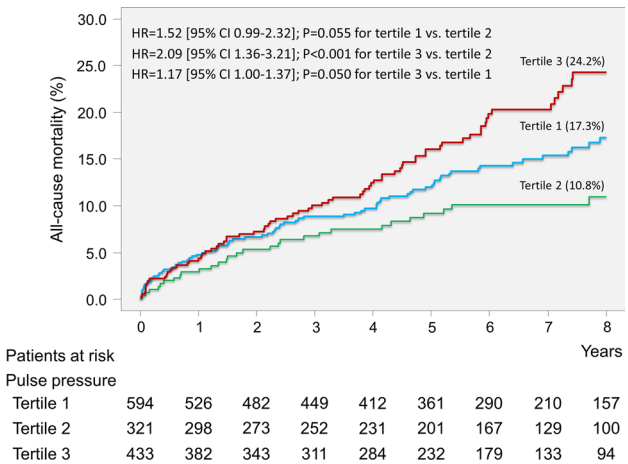


Fig. 1 Kaplan–Meier curves of all-cause mortality. *CI* confidence interval, *HR* hazard ratio. The time zero begins at approximately 10 days after primary percutaneous coronary intervention

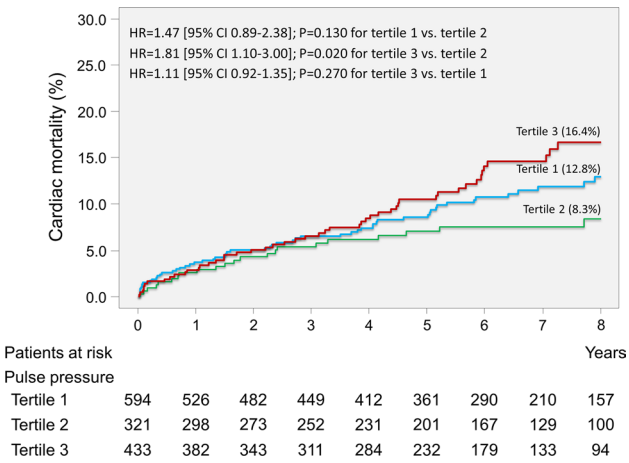
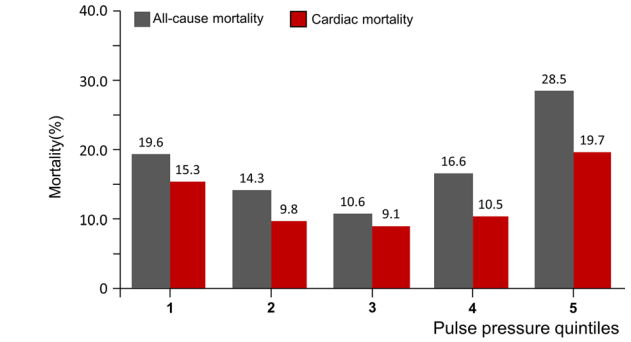


Fig. 2 Kaplan–Meier curves of cardiac mortality. *CI* confidence interval, *HR* hazard ratio. The time zero begins at approximately 10 days after primary percutaneous coronary intervention



Pulse pressure (mmHg)	<41.0	>41.0-51.0	>51.0-61.0	>61.0-76.0	>76.0
All-cause deaths	45	33	21	35	47
Cardiac deaths	35	22	18	22	31
Number of patients	320	274	247	262	245

Fig. 3 Eight-year all-cause and cardiac mortality according to quintiles of central pulse pressure. Numbers on the top of the bars are Kaplan–Meier estimates of all-cause and cardiac mortality

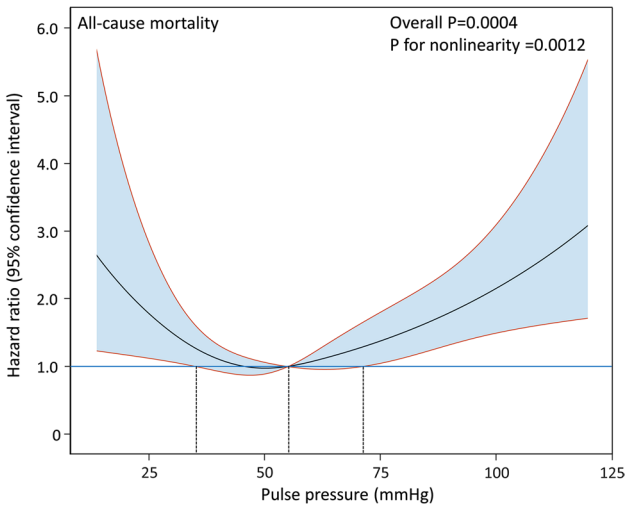


Fig. 4 U-shaped association between central pulse pressure and all-cause mortality. Central pulse pressure values lower than 35 mmHg and higher than 71 mmHg were associated with increased risk of all-cause mortality compared with the reference value of 54 mmHg. The 35 mmHg, 54 mmHg and 71 mmHg values are marked with dashed lines

values lower than 39 mmHg and higher than 80 mmHg, the hazard ratios for association with all-cause mortality were significant (HR = 1.244 [1.005–1.539] for the 39 mmHg value and HR = 1.409 [1.005–1.975] for the 80 mmHg value) compared with the CPP reference value (55 mmHg; Fig. 5).

The multivariable Cox proportional hazards model was used to assess the association between CPP and all-cause and cardiac mortality while adjusting for other variables (see "Methods" for variables that were entered into the models). The model showed that the association between CPP and the risk of all-cause (overall $P = 0.304$) or cardiac (overall

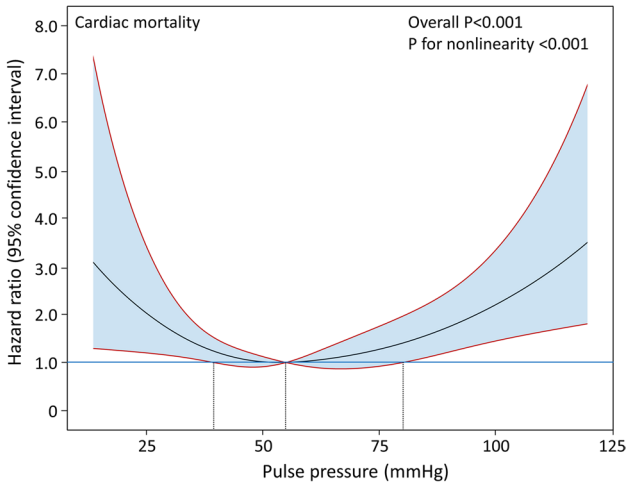


Fig. 5 U-shaped association between central pulse pressure and cardiac mortality. Central pulse pressure values lower than 39 mmHg and higher than 80 mmHg were associated with increased risk of cardiac mortality compared with the reference value of 55 mmHg. The 39 mmHg, 55 mmHg and 80 mmHg values are marked with dashed lines

$P = 0.060$) mortality was attenuated after adjustment for demographic and clinical variables.

Discussion

The main findings of current study can be summarized as follows: (1) in patients with STEMI undergoing PPCI, there is a U-shaped relationship between CPP and 8-year all-cause or cardiac mortality with higher mortality rates in patients with lower and higher CPP values compared with the mid CPP values. (2) The distribution of cardiovascular risk across the CPP values spectrum seems to differ markedly: indexes of disease severity (larger myocardial ischemia and infarct size and advanced Killip class) were more prevalent in patients with lower CPP values whereas advanced age, diabetes and arterial hypertension were more prevalent in patients with higher CPP values. (3) After adjustment for cardiovascular risk factors and markers of disease severity, the association between CPP and long-term prognosis was attenuated.

Several previous studies have investigated the association between peripheral PP and inhospital or short-term outcome in patients with ACS or STEMI with the preponderance of evidence favoring an association between lower PP and worse short-term prognosis. In patients with ACS, El-Menyar et al. [16] showed an association between low brachial PP and inhospital risk of mortality and stroke in the whole group of patients. Moreover, there was an association between lower PP and recurrent ischemia in non-STEMI patients and heart failure in STEMI patients. However, in

this study coronary angiography was perfomed in < 20% of the patients. A recent study by Tan et al. [18] that pooled data from 2 registries of patients with ACS showed an independent association between lower brachial PP values and inhospital mortality but no improvement in the discriminatory performance of the multivariable model with PP compared with the model with systolic blood pressure. The study showed that higher PP values were associated with older age and more prevalent cardiovascular risk factors whereas lower PP values were associated with worse clinical characteristics. In 1413 patients with STEMI, Shiraishi et al. [20] showed that PP values < 40 mmHg were associated with highest inhospital mortality (11.8%) whereas PP values between 49 and and 57 mmHg were associated with lowest inhospital mortality (2.8%). After adjustment, the association between PP <40 mmHg and mortality was attenuated. Notably, patients with PP values ≥ 71 mmHg tended to have higher inhospital mortality (6.0%). However, tests for nonlinearity were not performed and the study focused on the PP values associated with low inhospital mortality. Contrary to these studies, a recent study of patients with ACS showed an association between higher PP values and the risk for allcause mortality or recurrent myocardial infarction in the first year after the index event [19].

To our knowledge, this is the first study that has assessed the association between CPP and long-term (8-year) mortality in patients with STEMI. Although, a J-shaped association between PP and the risk of cardiovascular death or stroke in ambulatory patients has been reported, [14] this is the first demonstration of a U-shaped association between CPP and the risk of long-term mortality in patients with STEMI. Mechanisms for this pattern of association remain unknown. However the distribution of cardiovascular risk across the CPP values spectrum may provide important clues in this regard. As shown in this study, patients with lower CPP values had more extensive myocardial damage (larger initial area at risk and infarct size) and more advanced congestive heart failure in acute phase of STEMI. Thus it is highly likely that lower CPP values reflect lower stroke volumes and lower cardiac output in the setting of an extensive myocardial damage which may explain poorer outcome both at short term and long term in these patients [14]. This may help to understand the increased risk of mortality in patients with lower PP values. The current study and other studies [14, 18, 20] showed that older age and cardiovascular risk factors tend to cluster in patients with higher PP values. The association of older age and cardiovascular risk factors particularly arterial hypertension and diabetes with elevated PP sounds reasonable considering the deletereous effcts of these factors on the compliance of aorta and large arteries. According to the Windkessel model of arterial blood pressure, arterial wall compliance and stroke volume are main determinants of PP. The increased risk of mortality associated with higher PP values may by explained by cardiovascular risk factors clustered in patients with higher PP values and deletereous effects of a widened PP per se. In acute phase of STEMI, a widened PP may exacerbate myocardial ischemia by increasing afterload and consequently mural tension and oxygen consumtion and reducing coronary reperfusion [30]. A widened PP exerts cyclic stress on vascular structures facilitating atherosclerotic remodeling, migration of proinflammatory cells and increased oxidative stress [31] and endothelial dysfunction [32]. A widened PP may reflect age-related elastin loss in aortic wall which leads to reduced aortic complicance (increased stifness) and reduced elastic recoil which under normal conditions contribute to maintenance of diastolic blood pressure and tissue perfusion [33]. Low diastolic blood pressure—a contributor of widened PP—is assciated with increased risk of mortality in patients with coronary artery disease [34].

The current study has strengths and limitations. Strengths of the study include the assessemnt of CPP which is better related to future cardiovascular events than is brachial PP [21], the use of a well-characterized group of patients with STEMI in terms of myocardial ischemia/necrosis assessment (scintigraphy-based measurement of myocardial ischemia and infarct size), uniformity of received reperfusion therapy (PPCI in all patients) and long-term follow-up. The study has also limitations. First, a U-shaped relationship between PP and mortality may require an acute acute myocardial damage and cardiovascular risk factors which increase the risk of mortality in lower and upper parts of PP values spectrum, respectively. Consequently this pattern of association may be characteristic for patients with STEMI and long term prognosis and may not be extrapolated to patients with other morbid condtions. Second, since patients had to be alive at the time of myocardial scintigraphy (7–14 days after admission), patients dying before this time point were not included in this analysis, Third, some patients were lost to follow-up. However, the Kaplan–Meier method used for survival analysis may compensate at least partially for incomplete follow-up data. We do not believe that these limitations impact on the main findings of the study.

In conclusion, in patients with STEMI undergoing PPCI, the relationship between CPP and all-cause and cardiac mortality up to 8 years of follow-up is U-shaped with increased risk of mortality in the lower and higher parts of CPP values spectrum. The U-shaped association between CPP and mortality may be explained by specific distribution of cardiovascular risk over CPP values spectrum with indexes of disease severity (larger myocardial ischemia and infarct size) being more prevalent in patients with lower CPP values and advanced age and diabetes and arterial hypertension being more prevalent in patients with higher CPP values.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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