



openheart Impact of invasive aortic pulse pressure on coronary microvascular endothelial-independent dysfunction and on mortality in non-obstructive coronary artery disease

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ABSTRACT

Background Pulse pressure (PP), a raw index of arterial stiffness, is inversely related to coronary microvascular function, even among patients with non-obstructive coronary artery disease (CAD), as per non-invasive studies. We aimed to determine whether invasive aortic PP is associated with coronary microvascular endothelial dysfunction (CMED) and/or coronary microvascular endothelial independent dysfunction (CMEID) in patients with non-obstructed CAD.

Methods We retrospectively analysed a cohort of 1894 patients (mean age, 51.2 years; 1261 (66.6%) women) who presented with chest pain and non-obstructive CAD (angiographic stenosis <50%); coronary vasoreactivity was assessed in the mid-left anterior descending artery. The patients were classified based on whether aortic PP was high (≥ 50 mm Hg). CMEID was defined as abnormal coronary flow reserve (< 2.5) or hyperaemic myocardial resistance (> 2.0 mm Hg/cm/s), CMED was defined as abnormal acetylcholine-induced per cent change of coronary blood flow ($\leq 50\%$).

Results Patients with high aortic PP had a higher rate of CMEID than those with low aortic PP (40.9 vs 25.2%, $p < 0.001$). Conversely, aortic PP was not associated with CMED. On multivariate analysis, high aortic PP was associated with CMEID occurrence (OR 1.42, 95% CI 1.13 to 1.78; $p = 0.003$). On follow-up (median, 150 months), all-cause death was more frequent among patients with vs without high aortic PP (20.1% vs 7.3%, log-rank $p < 0.001$) and HR was 2.08 (95% CI 1.34 to 3.32, $p = 0.002$) on multivariate cox regression analysis. Furthermore, among patients with low aortic PP, CMEID was an independent risk factor for all-cause mortality (HR 2.04, 95% CI 1.01 to 4.16, $p = 0.048$).

Conclusion In patients with non-obstructive CAD, invasive aortic PP was significantly associated with CMEID, but not with CMED. High aortic PP was an independent predictor of all-cause mortality, but CMEID was an independent risk factor in patients with low aortic PP.

INTRODUCTION

The incidence of non-obstructive coronary artery disease (CAD) on coronary angiography is 20%–30% among patients who present with chest pain.¹ Coronary

Key questions

What is already known about this subject?

- Brachial pulse pressure (PP) was associated with coronary microvascular dysfunction in non-obstructive coronary artery disease (CAD) and PP and coronary microvascular dysfunction were important surrogate marker or cardiovascular outcomes in patients with CAD.
- Invasively measured aortic PP was more strongly positively correlated with arterial stiffness.

What does this study add?

- Invasively measured aortic PP was associated with coronary microvascular endothelial independent dysfunction (CMEID) in non-obstructive CAD.
- The aortic PP was an independent predictor of all-cause deaths, but CMEID increased the risk of all-cause death only in patients with low aortic PP.

How might this impact on clinical practice?

- Elevated aortic PP can be one of the key roles in CMEID, and choosing medical treatment based on measurements of these risk factors can improve clinical outcomes in non-obstructive CAD patients deserves further study.

microvascular dysfunction (CMD) plays an important role in the presentation of cardiac symptoms and increased future events in patients with non-obstructive CAD.² Elevated pulse pressure (PP) is usually regarded as a manifestation of reduced arterial elastic properties and increased arterial stiffness.³ The Strong Heart Study reported that PP was more strongly associated with vascular hypertrophy and atherosclerosis than systolic blood pressure (SBP).⁴ Increased PP also leads to fatigue and increased fracture in the elastic components of the vessel wall and is more likely to induce intimal damage, resulting in atherosclerosis.⁵ Increased PP with elevated

SBP is also associated with stress on cardiac work and increases myocardial oxygen demand, while low diastolic blood pressure (DBP) can be a limiting factor for coronary perfusion and ischaemia.⁶

Although previous studies have reported that PP was inversely related to CMD in patients with non-obstructive CAD, these studies used transthoracic echocardiography to measure coronary flow and velocity and measured non-invasive BP. Furthermore, the number of study participants was relatively small, and coronary endothelial function was not examined separately for coronary microvascular endothelial dysfunction (CMED) and coronary microvascular endothelium-independent dysfunction (CMEID).⁷⁻⁹

Therefore, this study aimed to evaluate the relationship between invasively measured arterial stiffness indices measured directly from invasive aortic PP and coronary vasoreactivity, including CMED and CMEID, in patients with non-obstructive CAD.

METHODS

Study population

A total of 1998 consecutive patients referred to the Mayo Clinic between January 1992 and November 2019 for cardiac catheterisation without evidence of significant obstructive CAD on initial angiography were enrolled. Patients were referred to the cardiology department by their physician for clinically indicated coronary angiography for evaluation of chest pain or abnormal stress test results. The decision to refer patients for the assessment of chest pain was based on the discretion of the attending physician. All patients had recurrent chest pain suspected to be of cardiac origin. A coronary vaso-reactive test was also performed on discretion of the attending physician following coronary angiography. Angiograms were reviewed prior to administration of any pharmacological agents. Non-obstructive CAD was defined as <50% luminal diameter obstruction.¹⁰ The exclusion criteria were as follows: (1) patients who had significant angiographic stenosis of any coronary artery requiring revascularisation; (2) pregnant patients; (3) patients with advanced chronic kidney disease (estimated glomerular filtration rate, eGFR <30 mL/min/1.73 m²); (4) patients with valvular heart disease; (5) patients without invasive aortic BP and (6) patients who underwent percutaneous coronary intervention (PCI) at the left anterior descending artery (LAD) due to acute myocardial infarction. Of all patients enrolled, 104 patients were excluded, so that a total of 1894 patients were consequently analysed. Clinical history, laboratory data and current medications were collected from a detailed chart review by investigators (AA and FS) who were blinded to the results of coronary vasomotor function testing. All-cause death data were ascertained by a combination of public and institutional databases, death certificates, mail surveys and telephone calls.

Invasive aortic BP and coronary reactivity test

Aortic BP was measured at the ascending thoracic aorta immediately prior to coronary angiography. The physician placed a catheter flushed with normal saline, and then performed a zero-balancing procedure. Aortic BP was then measured through the catheter automatically, and aortic PP was obtained by subtracting the aortic DBP from the aortic SBP. The Strong Heart Study reported that a high central PP (≥ 50 mm Hg) was an independent predictor of adverse cardiovascular events.¹¹ Accordingly, the current study defined high aortic PP as PP ≥ 50 mm Hg.

The procedure protocols for invasive coronary reactivity tests have been described in previous studies.¹² Nitrate and calcium channel blockers were discontinued prior to testing. The LAD was used as the target vessel for observation in this study. A 0.014-inch Doppler guide wire (Flowire, Volcano/Philips Corporation, Rancho Cordova, California, USA) was positioned in the middle portion of the left anterior descending artery. Acetylcholine (ACh)-induced coronary blood flow (CBF) changes and vasodilation were used to measure CMED. Therefore, CMED can be evaluated by the percentage change in CBF in response to ACh (% Δ CBF ACh). CMED was defined as a change in CBF of $\leq 50\%$ in response to ACh. CMEID was defined as abnormal coronary flow reserve (CFR) (< 2.5) or hyperaemic microvascular resistance (HMR) (> 2.0 mm Hg/cm/s) induced by adenosine.^{13 14}

HMR and baseline microvascular resistance (BMR) were used to assess microvascular resistance. HMR was defined as mean distal coronary artery pressure divided by average distal peak flow velocity (APV) at maximal hyperaemia, and BMR was defined as MAP divided by APV at baseline. CMD was defined as having either a CMED or CMEID.^{15 16} CMD was defined as having CMED, CMEID or both. Epicardial endothelial dysfunction was defined as a percentage decrease in coronary artery diameter (% Δ CAD ACh) $\geq 20\%$ in response to a maximum ACh dose. The percentage change in coronary artery diameter in response to nitroglycerine (% Δ CAD NTG) was measured between the baseline coronary artery diameter and the last coronary artery diameter after nitroglycerin administration.

Patient and public involvement

Participants contributed to the study but were not involved in determining the research question or outcome measures, nor were they involved in recruitment, design or implementation of the study.

Statistical analysis

Continuous variables are presented as mean \pm SD, while categorical variables are reported as frequencies and percentages. Normal distribution of measurements was confirmed using the Kolmogorov-Smirnov test. The Student's unpaired t-test for parametric continuous variables and the Wilcoxon signed-rank test for non-parametric continuous variables were used. Comparisons

between categorical variables were performed using the Pearson χ^2 test or Fisher's exact test, as appropriate.

Risk factors [old age (≥ 60 years old), female sex, high body mass index (BMI) (≥ 30 kg/m²), hypertension (HTN), diabetes mellitus (DM), dyslipidaemia, renal dysfunction (< 60 mL/min/1.73 m²) and current smoking], and high aortic PP were evaluated using univariate and multivariate logistic regression analyses for predicting the incidence of CMEID and CMED, respectively. We also analysed the association of aortic PP, measured as a continuous variable, with CMEID using the logistic regression model. Logistic regression analysis provided ORs and 95% CIs. We compared two or more ROC curves using the area under the curve (AUC) comparison analysis method, as described by DeLong *et al.* We also calculated integrated discrimination improvement (IDI) and net reclassification improvement (NRI) with a category-free option.

Multivariate Cox proportional hazard analysis was performed to identify independent correlates of all-cause death and to adjust for known potential confounders (high aortic PP, CMEID, old age, female sex, high BMI, HTN, DM, dyslipidaemia, renal dysfunction and current smoking status).

According to the profiles of aortic PP, cumulative all-cause death was constructed using Kaplan-Meier estimates and compared using the log-rank test. A $p < 0.05$ was considered statistically significant, and statistical analyses were performed using R V.4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

The study population included 1894 patients with non-obstructive CAD who underwent invasive physiology tests.

The clinical characteristics of the study groups are presented in [table 1](#). In general, the patients with high aortic PP (n=1803) showed higher risk profiles than those with low aortic PP (n=872) and were more likely to be women, have higher high-density lipoprotein and had a tendency for lower eGFR. Patients with high aortic PP had a higher atherosclerotic cardiovascular disease (ASCVD) risk score (2.3 vs 7.5%, $p < 0.001$) than patients with low aortic PP.

Determinants of CMEID

The high aortic PP group had lower CFR, higher HMR and higher base APV. Abnormal CFR (< 2.5) and abnormal HMR (> 2.0 mm Hg/cm/s) were also more common in the high aortic PP group. Patients with high aortic PP had a greater prevalence of CMEID than those with low aortic PP (40.9% vs 25.2%, OR 2.05, 95% CI 1.69 to 2.50, $p < 0.001$) (online supplemental table).

Multivariate analysis identified high aortic PP (OR 1.42, 95% CI 1.13 to 1.78, $p = 0.003$), old age (OR 1.79, 95% CI 1.40 to 2.33, $p < 0.001$), female sex (OR 1.29, 95% CI 1.03 to 1.61, $p = 0.027$), renal dysfunction (OR 1.41, 95%

CI 1.05 to 1.88, $p = 0.021$) and current smoking (OR 0.77, 95% CI 1.40 to 2.30, $p < 0.001$) as the major determinants of CMEID occurrence ([table 2](#)).

[Figure 1](#) shows the OR (95% CI) for risk of CMEID, by aortic PP, as a continuous variable, after adjustment of the covariates at baseline: old age, female sex, high BMI, HTN, DM, dyslipidaemia, renal dysfunction and current smoking status. An increase in aortic PP was significantly non-linear associated with risk in CMEID (per 1 mm Hg increase, OR: 1.02 (95% CI 1.01 to 1.02), $p < 0.001$).

We conducted an ROC curve analysis of the predictive models for CMEID with risk factors (defined old age renal dysfunction, sex), aortic PP and risk factors plus aortic PP. Based on the results of differences among the AUCs, conventional risk factors in addition to aortic PP were significantly more predictive of CMEID than conventional risk factors alone ([figure 2](#)). Additionally, to estimate the incremental value of aortic PP in predicting CMEID, we compared the probabilities of events and non-events of models using the relative IDI and category-free NRI ([table 3](#)). The IDI of adding aortic to the risk factors improved significantly (relative IDI=1.23, $p < 0.001$). The addition of aortic PP to the risk factors resulted in a significant improvement in the category-free NRI (total NRI 0.0499, $p < 0.011$).

Determinants of CMED

There was no difference in % Δ CBF Ach and % Δ CAD Ach between the aortic PP groups. The incidence of CMD was not different between the two groups (online supplemental table).

On univariate analysis, high aortic PP was not associated with the risk of CMED (51.1% vs 53.9%, OR 1.12, 95% CI 0.93 to 1.34, $p = 0.224$). On multivariate analysis, high aortic PP was not an independent predictor of CMED. Old age (OR 1.43, 95% CI 1.12 to 1.83, $p = 0.005$), high BMI (OR 1.40, 95% CI 1.16 to 1.71, $p = 0.001$) and current smoking status (OR 0.64, 95% CI 0.48 to 0.85, $p = 0.002$) were independent determinants of CMED occurrence ([table 4](#)).

All-cause deaths

The median follow-up duration was 150 months (IQR 81–210 months). Clinical endpoints constituting all-cause mortality occurred in 136 patients (7.2%).

Those with 'high aortic PP' had significantly higher cumulated rate of all-cause death than did those with low aortic PP (20.1% vs 7.3%; HR 2.51, 95% CI 1.69 to 3.71, $p < 0.001$, log-rank $p < 0.001$) ([figure 3A](#)). CMEID also increased the cumulative rate of death compared with those without CMEID (18.5% vs 12.5%; HR 1.56, 95% CI 1.11 to 2.19, $p = 0.010$, log-rank $p = 0.010$) ([figure 3B](#)).

Following multivariate analysis, several risk factors including 'high aortic PP' (HR 2.08, 95% CI 1.34 to 3.32, $p = 0.002$) were identified as the predictors of all-cause mortality in patients with non-obstructive CAD ([table 4](#)). Female sex (HR 0.64, 95% CI 0.32 to 0.66, $p < 0.001$) was a protective factor, and old age (HR 2.79, 95% CI

Table 1 Baseline characteristics according to aortic PP

	All (n=1894)	Low aortic PP (n=856)	High aortic PP (n=1038)	P value
Age, years	51.2±12.4	44.1±10.7	57.1±10.6	<0.001
Female, n (%)	1261 (66.6)	445 (52.0)	816 (78.6)	<0.001
SBP, mm Hg	130.4±22.8	113.2±11.7	144.6±19.8	<0.001
DBP, mm Hg	74.6±10.5	72.7±9.4	76.2±11.0	<0.001
Pulse pressure, mm Hg	55.8±18.4	40.5±6.6	68.4±15.2	<0.001
Hypertension, n (%)	801 (42.3)	254 (29.7)	547 (52.7)	<0.001
Diabetes mellitus, n (%)	204 (10.8)	68 (7.9)	136 (13.1)	<0.001
Dyslipidaemia, n (%)	1046 (55.2)	408 (47.7)	638 (61.5)	<0.001
Chronic kidney disease, n (%)	258 (13.6)	81 (8.7)	181 (18.0)	<0.001
Previous MI, n (%)	258 (14.0)	114 (13.7)	144 (14.3)	0.751
Previous vascular disease, n (%)	170 (9.0)	66 (7.7)	104 (10.0)	0.095
Current smoker, n (%)	228 (12.0)	138 (16.1)	90 (8.7)	<0.001
Body mass index, kg/m ²	29.0±6.3	29.1±6.3	28.9±6.2	0.469
Ejection fraction (%)	61.6±7.3	61.3±7.1	61.8±7.6	0.226
WBC, 10 ³ /mm ³	6.8±2.1	6.9±2.2	6.6±2.1	0.009
Haemoglobin, g/L	135.5±14.2	138.7±14.4	132.8±12.3	<0.001
Total cholesterol, mg/dL	186.2±43.1	182.7±41.8	189.0±43.9	0.002
Triglyceride, mg/dL	133.0±88.6	131.7±89.4	134.0±88.0	0.591
HDL, mg/dL	54.3±17.6	51.2±17.0	56.8±17.7	<0.001
LDL-C, mg/dL	105.5±37.2	105.5±36.4	105.5±37.9	0.998
BUN, mg/dL	14.8±4.9	14.3±4.7	15.2±5.0	0.001
Creatinine, mg/dL	1.0±0.3	1.0±0.3	1.0±0.3	0.044
eGFR (EPI), mL/min/1.73 m ²	78.6±17.7	84.1±16.8	74.2±17.1	<0.001
NT-pro-BNP, pg/mL	147.2±373.2	122.5±326.2	170.5±411.8	0.096
hs-CRP, mg/L	2.6±6.2	2.9±6.5	2.4±5.9	0.205
Aspirin, n (%)	918 (48.5)	382 (44.6)	536 (51.6)	0.003
ACE or ARB, n (%)	271 (14.3)	106 (12.4)	165 (15.9)	0.035
β-blocker, n (%)	579 (30.6)	229 (26.8)	350 (33.7)	0.001
Calcium channel blocker, n (%)	576 (30.4)	246 (28.7)	330 (31.8)	0.165
Nitrate, n (%)	750 (39.6)	323 (37.7)	427 (41.1)	0.144
ASCVD risk score	4.9±7.4	2.3±3.3	7.5±9.2	<0.001

Continuous variables were expressed in mean±SD as indicated.

ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EPI, epidemiology collaboration; HDL, high-density lipoprotein; hs-CRP, high sensitivity C reactive protein; LDL, low density lipoprotein; MI, myocardial infarction; NT-pro-BNP, N-terminal pro b-type natriuretic peptide; PP, pulse pressure; SBP, systolic blood pressure; WCC, white cell count.

1.85 to 4.19, $p<0.001$), DM (2.10, 95% CI 1.31 to 3.37, $p=0.002$), renal dysfunction (HR 1.87, 95% CI 1.25 to 2.79, $p=0.002$), and current smoking (HR 2.46, 95% CI 1.58 to 3.83, $p<0.001$) were independent predictors for all-cause mortality.

Subsequently, we evaluated the impact of CMEID on all-cause mortality according to the presence of 'high aortic PP'. Those with 'high aortic PP and CMEID' had significantly higher rate of all-cause deaths followed by 'high aortic PP without CMEID', 'low aortic PP with

CMEID' and 'low aortic PP without CMEID' (19.5% vs 20.1%, 17.3%, and 8.5%, HR 2.22, 2.17, 1.89, and reference 'Low aortic PP without CMEID') (figure 3C).

Among non-obstructive CAD patients with 'high aortic PP', CMEID was not associated with all-cause death (19.5% vs 20.9%, log-rank $p=0.562$). Among 'low aortic PP' patients, subjects with CMEID showed significant, independently associated risk of all-cause death (HR 2.04, 95% CI 1.01 to 4.16, $p=0.049$) on multivariate analysis.

Table 2 Determinants of coronary microvascular endothelial independent dysfunction

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
High aortic PP (≥ 50 mm Hg)	2.05	1.69 to 2.50	<0.001	1.42	1.13 to 1.78	0.003
Age ≥ 60 years old	2.50	2.01 to 3.10	<0.001	1.79	1.40 to 2.30	<0.001
Female sex	1.57	1.27 to 1.93	<0.001	1.29	1.03 to 1.61	0.027
Body mass index (≥ 30 kg/m ²)	0.83	0.69 to 1.02	0.072	0.82	0.67 to 1.31	0.273
Hypertension	1.35	1.11 to 1.63	0.002	1.07	0.86 to 1.33	0.547
Diabetes mellitus	1.33	0.99 to 1.79	0.062	1.27	0.92 to 1.74	0.147
Dyslipidaemia	1.25	1.03 to 1.15	0.025	1.06	0.86 to 1.31	0.573
Renal dysfunction (eGFR < 60 mL/min/1.73 m ²)	2.12	1.62 to 2.76	<0.001	1.41	1.05 to 1.88	0.021
Current smoking	0.62	0.45 to 0.85	0.003	0.77	1.40 to 2.30	<0.001

eGFR, estimated glomerular filtration rate; PP, pulse pressure.

DISCUSSION

This study demonstrates the association between directly assessed invasive aortic PP and coronary microvascular function and its prognostic implications. The main findings of this study were as follows: (1) High aortic PP was an independent determinant of CMEID, whereas CMED was not. The risk of CMEID increased non-linearly as aortic PP increased. Compared with the predictive models using the ROC curve analysis, IDI and NRI, the combination model that added aortic PP to risk factors was more predictive than the single predictive model of risk factors only for CMEID; (2) High aortic PP was an independent predictor of all-cause death; however, CMEID increased the risk of all-cause death only in patients with low aortic PP.

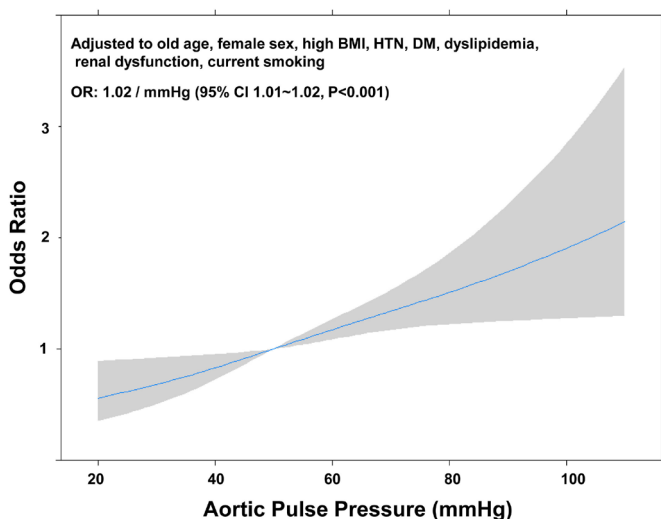


Figure 1 The estimated continuous OR of pulse pressures adjusted risk (OR; 95% CI) of pulse pressure for coronary microvascular endothelial independent dysfunction. Renal dysfunction, glomerular filtration rate < 60 mL/min/1.73 m²). BMI, body mass index; DM, diabetes mellitus; HTN, hypertension.

Arterial stiffness and coronary microvascular endothelial independent function

CMD is mainly determined by a lack of response to endothelium-dependent and/or endothelium-independent vasodilation processes.¹⁷ Endothelium-independent dysfunction mainly occurs due to impaired myocyte tone and vascular smooth muscle cells (VSMCs).¹⁸ Two types of mechanical forces affect vessels: (1) shear stress and (2) cyclic strain of the vascular wall, which, according to Laplace's law, are mainly determined by cyclic changes in BP.¹⁹ Shear stress predominantly affects endothelial function; however, pulsatile cyclic changes in BP influence all structures of the arterial wall. The changes in intramural tension in the arterial wall are well recognised as important factors in progression

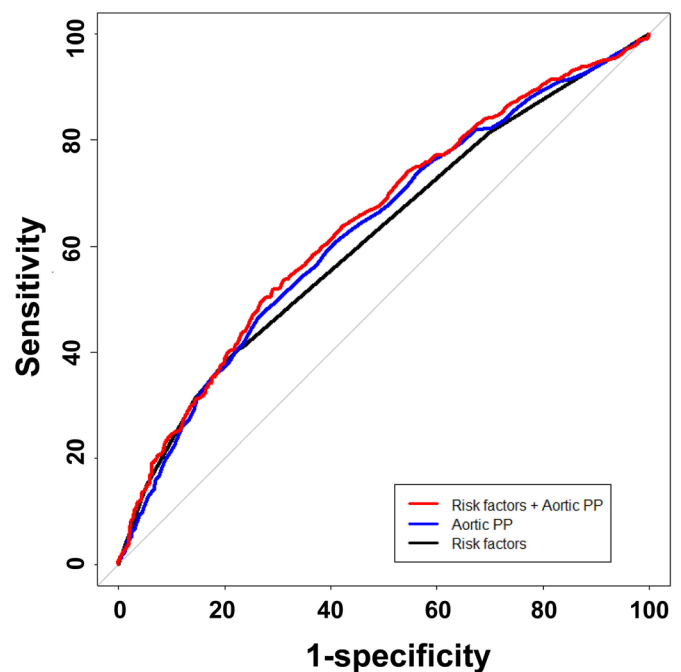


Figure 2 Receiver operating curve comparison comparison of receiver operating characteristic curves of risk factors and/or intra-aortic pulse pressure (PP).

Table 3 Comparisons of AUCs, IDI and NRI for risk factors and intra-aortic PP

Models	AUC		95% CI		P value for AUCs	IDI		Absolute IDI		95% CI		P value	Category-free NRI		
	AUC	95% CI	95% CI	95% CI		IDI	95% CI	Relative IDI (%)	Event (%)	Nonevent (%)	Total NRI		95% CI	P value	
Risk factors	0.615	0.590 to 0.641	reference	reference	0.243	-0.003	-0.047 to 0.007	0.547	0.933	-0.1	-1.1	-0.013	-0.0474 to 0.0219	0.470	
Aortic PP	0.630	0.604 to 0.657	0.243	0.0058 to 0.0158*	<0.001*	0.0108*	0.0058 to 0.0158*	<0.001*	1.227*	5.1*	-8.7*	0.0499*	0.0226 to 0.0773*	<0.001*	
Risk factors+Aortic PP	0.644	0.617 to 0.670	0.053†	0.008 to 0.019†	0.053†	0.0137†	0.008 to 0.019†	<0.001†	1.3072†	8.5†	-2.3†	0.063†	0.0334 to 0.0919†	<0.001†	

Risk factors: age \geq 60, renal dysfunction, female sex.

*Comparison with the ROC curves of risk factors (reference group).

†Comparison with the ROC curves of central PP.

AUC, area under the curve; IDI, integrated discrimination improvement; NRI, net reclassification improvement; PP, pulse pressure; ROC, receiver operating characteristics.

Table 4 Determinants of all-cause of death occurrence

Variables	HR	95% CI	P value
CMEID	1.25	0.88 to 1.78	0.211
High aortic PP (\geq 50 mm Hg)	2.08	1.34 to 3.32	0.002
Female sex	0.46	0.32 to 0.66	<0.001
Age \geq 60	2.79	1.85 to 4.19	<0.001
Body mass index (\geq 30 kg/m ²)	1.02	0.71 to 1.47	0.913
Hypertension	0.77	0.53 to 1.12	0.176
Diabetes mellitus	2.10	1.31 to 3.37	0.002
Dyslipidaemia	0.70	0.49 to 1.01	0.051
Renal dysfunction (eGFR $<$ 60 mL/min/1.73 m ²)	1.87	1.25 to 2.79	0.002
Current smoking	2.46	1.58 to 3.83	<0.001

CMEID coronary microvascular endothelial independent dysfunction; eGFR, estimated glomerular filtration rate; PP, pulse pressure.

of atherosclerosis.^{20 21} The central artery is located near the target organs, and is more influential to them.

The large artery is composed of VSMCs and involves prominent elastin and collagen. It is highly sensitive to changes in age and BP. In large arteries, dysfunction of VSMCs are a key determinant of wall stiffness, whereas small vessels are highly sensitive to vasoreactive substances, particularly those of endothelial origin.²² The current study measured aortic PP in the ascending thoracic aorta as arterial stiffness, which is more dependent on the function of VSMCs. Unfortunately, the toolkit for assessing the stiffness of smaller muscular vessels is much less developed. CMEID also correlated with VSMC function, hence it is one cause for aortic PP being an independent determinant in the current study.

Arterial stiffness can lead to reduced coronary perfusion. Increasing arterial stiffness increases the propagating pulse wave velocity and backward wave returning to the heart, which can cause a wide PP.³ Therefore, the wave reflection is increased in arterial stiffness, and the reflection time is faster and reduces diastolic coronary perfusion pressure.^{23 24} Kang *et al* reported that invasively measured aortic PP was strongly positively correlated with arterial stiffness as measured by pulse wave velocity in patients with CAD.²⁵

The basal myocardial flow can be enhanced in an aortic stiffness experimental model, primarily due to the augmentation of coronary flow during systole.²⁶ This study also showed that the high aortic PP group had a high base APV (26.6 vs 23.5 cm/s, $p<$ 0.001) compared with the low PP group.

Increased arterial stiffness leads to increased cardiac work and increased myocardial oxygen demand.⁶ Aortic stiffening increases afterload and left ventricle work load, resulting in left ventricular hypertrophy (LVH). Chung

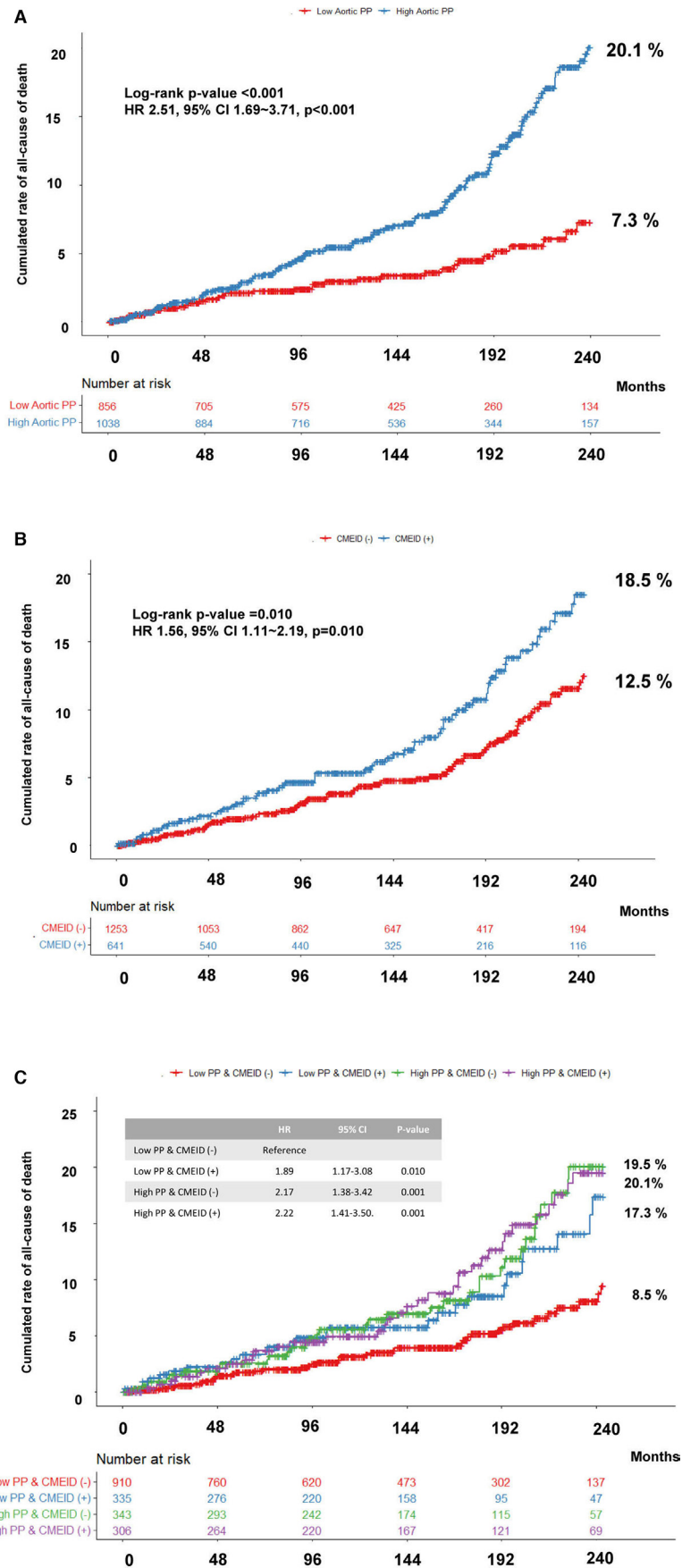


Figure 3 Kaplan-Meier curves; (A) groups as per intra-aortic PP for all-cause of death, (B) groups as per CMEID for all-cause death, (C) groups as per intra-aortic PP and CMEID for all-cause of death. CMEID, coronary microvascular endothelial independent dysfunction; PP, pulse pressure.

et al reported that pulse wave velocity was significantly associated with LVH, and large artery stiffening seemed to significantly contribute to LVH pathogenesis.²⁷ LVH may increase microvascular resistance and impair the CFR. CFR abnormalities have been observed in patients with LVH.²⁸ The current study did not collect the data as to whether participants had LVH; however, it revealed that HMR was increased in the higher aortic PP group. Muroya *et al* also reported that aortic stiffness (assessed using the cardio-ankle vascular index) was an independent determinant of the invasive HMR index ($\beta=0.25$, $p=0.007$).²⁹ The high aortic PP group had a high ASCVD risk score and was more likely to have comorbidities such as DM, HTN and dyslipidaemia. Although none of the patients had obstructive coronary disease, many patients may have minimal artery disease, and the high aortic PP group may more likely demonstrate minimal stenosis compared with patients with low aortic PP. HMR is defined as mean distal coronary artery pressure divided by average distal APV at maximal hyperaemia, and BMR is defined as MAP divided by APV at baseline.^{15 16} If patients have minimal stenosis, HMR can be increased by reduced distal flow and velocity; therefore, it is possible that HMR may be overestimated in patients with high PP. HMR has been debated in patients with coronary artery stenosis because it is overestimated in the presence of coronary artery stenosis compared with real microvascular resistance because collateral flow is not considered.³⁰ CFR is obtained based on the hyperaemic flow velocity and baseline resting flow velocity ratio using the Doppler wire technique.^{10 31} Baseline APV was higher in higher PP group, but flow velocity was not sufficient increased in hyperaemic state compared with lower aortic PP patients. Therefore, HMR and CFR can be overestimated and/or underestimated in high aortic PP.

Several studies have reported that increased aortic stiffness is independently associated with CMD in patients with non-obstructive CAD. Lembo *et al* reported that patients with angiographically non-obstructive CAD had a higher resting coronary flow velocity and lower CFR. This study examined transthoracic-derived CFR in a study population of 398 patients. However, the resting coronary flow velocity, and not the CFR, was significantly associated with PP and only on multiple linear regression analysis, at that.⁹ Other echo-based studies have also demonstrated that arterial stiffness is inversely related to CFR or hyperaemic coronary flow velocity in patients with non-obstructive CAD.⁷⁻⁹ Previous studies used transthoracic echocardiography to measure coronary flow and velocity, and recruited a relatively small number of participants. These studies did not measure invasive aortic BP.

This current study, on the other hand, measured coronary vasoreactivity using invasive Doppler wire, and the number of participants was >1800 patients. Invasive aortic PP was determined for all patients. Central PP more accurately reflects vascular load on the left ventricle and coronary vasculature, and, furthermore, central PP is more correlated with target organ damage and cardiovascular

outcomes than is brachial PP.¹¹ This study also suggested that old age, female sex, renal dysfunction and current smoking were independent determinants of CMEID.

Arterial stiffness and coronary endothelial function

Coronary endothelial dysfunction is the earliest stage of coronary atherosclerosis and is also a vascular dysfunction along with arterial stiffness, associated with the development of atherosclerotic disease, resulting in cardiovascular events.³²

Oxidative stress and chronic inflammation lead to endothelial dysfunction, leading to functional stiffness due to reduced endothelial nitric oxide production.³³ Peripheral endothelial function is usually assessed using flow-mediated dilatation or peripheral arterial tonometry. Beigel *et al* reported that arterial stiffness (PP) was inversely associated with brachial FMD.³⁴ However, there have been no studies on the relationship between peripheral arterial stiffness and coronary endothelial function.

The current study showed that high aortic PP did not correlate with CMED. Accordingly, aortic arterial stiffness may not be directly associated with coronary endothelial function. The current study revealed that old age, BMI and current smoking were independent determinants of CMED.

PP and CMEID for all-cause of death

Functional coronary microvascular dysfunction results in ischaemic symptoms, adverse cardiovascular events and increased cardiovascular mortality.² Several studies have reported that high PP (as arterial stiffness) increases adverse clinical outcomes and death. Roman *et al* suggested that a high central PP is independently associated with adverse cardiovascular outcomes.^{4 35} Consistent with other studies, the current study also showed that high aortic PP increased the risk of all-cause death in non-obstructive CAD patients. Among patients with low aortic PP, CMEID increased the risk of all-cause death in the multivariate analysis in patients with non-obstructive CAD.

Limitations

This was a single-centre, retrospective cohort study. Enrolled patients were referred for coronary angiography to a tertiary referral centre by an independent cardiologist and thus constituted a unique population, which may limit its generalisability. Second, we did not use intravascular imaging to evaluate the grade of atherosclerosis; therefore, we could not compare coronary atherosclerosis and CMD. Third, cardiovascular adverse outcomes are important during follow-up in non-obstructive CAD patients. However, data collection was performed retrospectively, and cardiovascular outcome data could not be attained, it was obtained all-cause mortality information. Fourth, HMR could be overestimated in patients with stenotic coronary disease even if there is minimal stenosis; however, we did not collect data on stenosis among our cohort. We also did not determine whether LVH was

present, which is one of the causes of the increase in HMR. Finally, we could not obtain data on follow-up BP status and maintenance medications. However, this study had the highest number of patients undergoing an invasive coronary vasoreactivity test performed by expert physicians, and aortic PP was measured invasively in this case at the ascending thoracic aorta. Furthermore, mortality data from all patients were collected in this study.

CONCLUSIONS

Our study attempted to identify the association between aortic PP, arterial stiffness and CMEID in patients with non-obstructive CAD. Whether choosing medical treatment based on measurements of these risk factors can improve clinical outcomes in non-obstructive CAD patients requires further study.

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Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study complied with the Declaration of Helsinki guidelines and was approved by the Mayo Clinic Institutional Review Board (05-004191). Participants gave informed consent to participate in the study before taking part.

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Data availability statement No additional data are available.

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