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Relationships between blood pressure measurements and target organ damage: Data from the Korea women's chest pain registry

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This study was performed to investigate the association between four BP measurements (systolic blood pressure [SBP], diastolic blood pressure [DBP], mean arterial pressure [MAP], and pulse pressure [PP]) and four TOD parameters (left ventricular mass index [LVMI], E/e', estimated glomerular filtration rate [eGFR], and obstructive coronary artery disease [CAD]). Data were obtained from a nation-wide registry, composed of 652 patients (471 women, 58.4 ± 10.5 years) with suspected CAD who underwent elective invasive coronary angiography (CAG). A total of 217 patients (33.2%) had obstructive CAD (≥50%). In multivariable analyses, E/e' was associated with SBP, MAP and PP, and CAD was associated with SBP and PP ($P < 0.05$ for each). All four BP measurements were not associated with LVMI and eGFR ($P > 0.05$ for each). In patients undergoing elective invasive CAG, SBP, and PP had stronger relationships with E/e' and CAD than DBP and MAP.

1 | INTRODUCTION

High blood pressure (BP) is the leading cause of cardiovascular mortality and morbidity.[1,2] Sustained high blood pressure causes structural and functional changes in major organs, such as the heart, kidneys, brain, and eyes, which is generally called "target organ damage (TOD)."[3] As subclinical TOD is an important predictor as an intermediate endpoint for cardiovascular events,[4-9] early detection and proper management of TOD, as well as BP control, are key determinants of cardiovascular prognosis.[10] Fortunately, high BP-associated subtle damage to several organs can be detected by modern medical technologies before an overt clinical event occurs.[10]

There are four main BP measurements: systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and pulse pressure (PP). As the association between elevated SBP and worse cardiovascular outcome has been well-documented, SBP is commonly used as the major criteria for diagnosis, staging, and treatment of hypertension.[9,11,12] DBP is related to coronary perfusion, and its predictive value on coronary heart disease has been reported especially in younger subjects.[13,14] MAP is an average blood pressure in an individual, and it is considered a classic indicator of perfusion to vital organs.[15,16] PP is the difference between SBP and DBP, and it increases with age. It is well-known that PP reflects arterial stiffness, and PP is considered a strong independent predictor of cardiovascular complications and mortality.[17,18]

Kong and Kim contributed equally to this work.

Information on the association between each BP measurement and TOD is clinically important. If we know which BP measurement is more correlated with certain types of TOD, we can use it to treat hypertension in practice. However, data from systemic evaluation of the influence of each BP measurement on various TOD has been limited. Therefore, this study was performed to investigate the association between BP components and several types of TOD. Our hypothesis is that each BP measurement has a different influence on TOD. More specifically, SBP and PP rather than DBP and MAP are more strongly associated with TOD.

2 | METHODS

2.1 | Patient population

Our study data were obtained from a prospective nation-wide registry, the KoRean wOmen'S chest pain rEgistry (KoROSE). The registry was constructed for multicenter study aims to investigate characteristics and outcomes of Korean women with or without coronary artery disease (CAD).[19] Women with stable chest pain undergoing invasive coronary angiography (CAG) for the evaluation of CAD were enrolled in the registry. Men were also enrolled in the ongoing registry for gender comparison with the same enroll criteria of women.[19,20] Due to the small number of enrolled men, gender comparison was not performed in the present study. Patients with the end-stage renal disease, chronic obstructive pulmonary disease, primary pulmonary hypertension, malignancy, and autoimmune disease were excluded. Between February 2011 and Jun 2015, a total of 933 patients were registered into the registry database from well-qualified 29 cardiac centers in Korea. Among the patients, 652 (men = 181, women = 471) with available data on brachial BP and results of TOD measurement, including renal function, transthoracic echocardiography (TTE), and invasive CAG, were included in this study. All the patients provided their written informed consent to this study. This study protocol was approved by the Institutional Review Board (IRB) of each center. The IRB number of Seoul National University Boramae Medical Center (Seoul, Korea) was 06-2011-222.

2.2 | Clinical data collection

Body mass index (BMI) was calculated by weight (kg)/height (m²). Hypertension was defined based on the following criteria: (a) a history of hypertension diagnosis, or (b) the use of anti-hypertensive medications, or (c) SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg in repeated measurements. Diabetes mellitus was defined based on following criteria: (a) a history of diagnosis of diabetes mellitus, or (b) the use of anti-glycemic medications, or (c) serum fasting glucose level ≥126 mg/dL at least two times. Dyslipidemia was defined based on following criteria: (a) a history of diagnosis of dyslipidemia, or (b) the use of anti-dyslipidemic medications, or (c) serum low-density lipoprotein (LDL)-cholesterol level ≥130 mg/dL. Current smoker was defined as a person who smoked regularly for the past 12 months. Blood samples were collected after overnight fasting to obtain baseline data for laboratory tests, including hemoglobin, total cholesterol, LDL-cholesterol, and creatinine for estimated glomerular filtration rate (eGFR). Then, eGFR was calculated by the Modification of Diet in Renal Disease equation: $186 \times SCr^{-1.154} \times age^{-0.203}$ (×0.742, if women).[21] Data on current medications, including renin-angiotensin system (RAS) blockers, beta-blocker, calcium channel blocker, and diuretics at registry enrollment, were also recorded in detail.

2.3 | BP measurement

BP was measured on the right upper arms, after at least 5 minutes of rest in the sitting position on the day of invasive CAG. SBP and DBP were read by using phase I and V (disappearance) Korotkoff sounds, respectively. MAP was calculated as 1/3 (SBP) + 2/3 (DBP). PP was calculated as the difference between SBP and DBP.

2.4 | TTE

Data of left ventricular ejection fraction (LVEF), left ventricular mass index (LVMI), and the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e′) at septal annulus (E/e′) were obtained using TTE based on the recommendations of current guidelines.[22,23]

2.5 | Invasive CAG

Obstructive CAD was defined as a ≥50% stenosis of one or more major epicardial coronary arteries in CAG by visual estimation. The extent of CAD was defined as 1-, 2- or 3-vessel disease. After diagnostic CAG, percutaneous coronary intervention (PCI), or optimal medical treatment was done appropriately for each patient in accordance with diagnosis.

2.6 | TOD

TOD parameters investigated in our study were selected based on data availability and current guidelines.[10] Several TOD parameters of the heart and the kidney were focused in this study: LVMI for LV hypertrophy, E/e′ for LV diastolic dysfunction, eGFR for renal dysfunction and the presence of obstructive CAD in CAG.

2.7 | Statistical analysis

Statistical analyses were performed using the SPSS software (version 20.0; IBM, Armonk, NY). Data are presented as the mean ± standard deviation for continuous variables and percentage for categorical variables. The linear relationship between two continuous variables was analyzed by Pearson's correlation. Multiple linear regression analyses were performed to evaluate independent relationships of each BP measurement with LVMI, E/e′, and eGFR. Mean values of BP measurements between groups

with or without obstructive CAD were compared with Student *t* test. The mean values of BP measurements according to CAD extent were compared using analysis of variance (ANOVA). Multiple binary logistic regression analysis was performed to determine independent relationships between each BP measurements and CAD. Age, gender, BMI, heart rate, diabetes mellitus, hypercholesterolemia, smoking, eGFR, and concomitant cardiovascular medications were adjusted in each multivariable model. Each BP measurement was input to multiple binary logistic regression analysis using tertile stratification. A *P* value of less than 0.05 was defined as statistically significant.

3 | RESULTS

3.1 | Clinical characteristics of study patients

The clinical characteristics of 652 patients are shown in Table 1. Their mean age was 58.4 ± 10.5 years, and 471 patients (72.2%) were female. Proportions of patients with hypertension, diabetes mellitus, dyslipidemia, and current smoking were 46.5%, 15.5%, 19.8%, and 11.8%, respectively. Mean values of SBP, DBP, MAP, and PP were 127 ± 17 mm Hg, 79.1 ± 11.0 mm Hg, 95.0 ± 11.8 mm Hg, and 47.9 ± 14.0 mm Hg, respectively. The distributions of values of each BP measurement are demonstrated in Figure S1. There was no significant abnormality in the blood test results, including hemoglobin, total cholesterol, LDL-cholesterol, and eGFR. The major parameters of TTE also showed no significant abnormality. A total of 217 patients (32.2%) had obstructive CAD in CAG. The proportions of patients with 1-, 2-, and 3-vessel disease were 19.6%, 7.5%, and 6.1%, respectively. The proportions of patients with current medications, including RAS blockers, beta-blockers, calcium channel blockers, and diuretics were 25.0%, 16.7%, 32.1%, and 6.1%, respectively.

3.2 | Associations of BP measurements with LVMI, *E/e'*, and eGFR

The results of simple correlation analyses showing the associations between each BP component and TOD are summarized in Table 2. LVMI was positively correlated with DBP (*r* = 0.102, *P* = 0.026) and MAP (*r* = 0.098, *P* = 0.031), but not with SBP and PP (*P* > 0.05). Septal *E/e'* was positively correlated with SBP (*r* = 0.227, *P* < 0.001), MAP (*r* = 0.135, *P* = 0.001), and PP (*r* = 0.257, *P* < 0.001), but not with DBP (*P* > 0.05). eGFR was negatively correlated with SBP (*r* = −0.088, *P* = 0.040), but not with DBP, MAP, and PP (*P* > 0.05). The results of multiple linear regression analyses showing independent associations between each BP measurement and TOD are summarized in Table 3. Significant correlations of *E/e'* with SBP (β = 0.183, *P* < 0.001), MAP (β = 0.110, *P* = 0.023), and PP (β = 0.202, *P* < 0.001) remained even after controlling for potential confounders including age, gender, BMI, heart rate, diabetes mellitus, dyslipidemia, smoking, and medications. LVMI and eGFR were not associated with any of the BP measurements in these multivariable analyses (*P* > 0.05 for each).

TABLE 1 Clinical characteristics of study patients

Characteristic	Value (n = 652)
Age, y	58.4 ± 10.5
Women, n (%)	471 (72.2)
Body mass index, kg/m^2	25.2 ± 3.3
Traditional risk factors, n (%)	
Hypertension	303 (46.5)
Diabetes mellitus	101 (15.5)
Dyslipidemia D	129 (19.8)
Current smoker	77 (11.8)
Blood pressure measurements, mm Hg	
Systolic blood pressure	127 ± 17
Diastolic blood pressure	79.1 ± 11.0
Mean arterial pressure	95.0 ± 11.8
Pulse pressure	47.9 ± 14.0
Major laboratory findings	
Hemoglobin, g/dL	13.3 ± 1.5
Total cholesterol, mg/dL	179 ± 41
LDL-cholesterol, mg/dL	107 ± 35
Estimated GFR, mL/min/1.73 m^2	82.8 ± 22.1
Echocardiographic findings	
Left ventricular ejection fraction, %	61.7 ± 6.4
Left ventricular mass index, g/m^2	92.3 ± 25.0
Septal *E/e'* ratio	10.2 ± 3.4
Coronary angiographic findings, n (%)	
Insignificant	435 (66.7)
One-vessel disease	128 (19.6)
Two-vessels disease	49 (7.5)
Three-vessels disease	40 (6.1)
Current medications history, n (%)	
RAS blocker	163 (25.0)
Beta-blocker	109 (16.7)
Calcium channel blocker	209 (32.1)
Diuretics	40 (6.1)

GFR, glomerular filtration rate; LDL, low-density lipoprotein; RAS, renin-angiotensin system.

3.3 | Association between BP measurements and CAD

SBP (133 ± 18 vs 123 ± 16 mm Hg, *P* < 0.001), MAP (94.5 ± 12.2 vs 93.8 ± 11.2 mm Hg, *P* < 0.001), and PP (54.5 ± 15.5 vs 44.6 ± 11.9 mm Hg, *P* < 0.001) were significantly higher in patients with obstructive CAD than those without (Figure 1). SBP, MAP, and PP showed a gradual increase according to the increase of CAD extent (*P* < 0.05 for each) (Figure 2). Multiple binary logistic regression analyses showed that SBP (third vs first tertile; odds ratio [OR], 2.43; 95% confidence interval [CI], 1.28-4.61; *P* = 0.020) and PP (third vs first tertile; OR, 2.52; 95% CI, 1.29-4.93; *P* = 0.018) were

TABLE 2 Simple correlation analyses showing the associations between each blood pressure measurement and TOD (n = 652)

TOD parameter		SBP	DBP	MAP	PP
LVMI	r	0.072	0.102	0.098	0.010
	P	0.118	0.026	0.031	0.827
E/e'	r	0.227	0.035	0.135	0.257
	P	<0.001	0.401	0.001	<0.001
eGFR	r	−0.088	−0.041	−0.069	−0.076
	P	0.040	0.333	0.103	0.076

DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; TOD, target organ damage.

TABLE 3 Multiple linear regression analyses showing the associations between each blood pressure measurement and TOD (n = 652)

TOD parameter		SBP	DBP	MAP	PP
LVMI	β	0.057	0.114	0.100	−0.026
	P	0.343	0.052	0.092	0.665
E/e'	β	0.183	0.037	0.110	0.202
	P	<0.001	0.440	0.023	<0.001
eGFR	β	0.010	0.029	0.023	0.023
	P	0.845	0.568	0.651	0.651

DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; TOD, target organ damage.
Each blood pressure measure as independent variable was entered into separate model. Age, gender, body mass index, heart rate, diabetes mellitus, dyslipidemia, smoking, and medications were adjusted in each model.
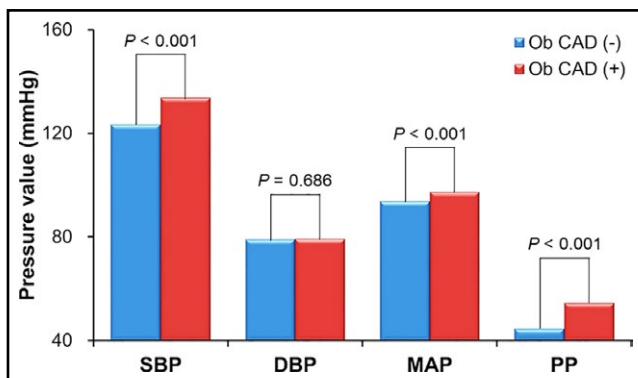
FIGURE 1 Blood pressure values according to the presence of obstructive coronary artery disease (n = 652). DBP, diastolic blood pressure; MAP, mean arterial pressure; Ob CAD, obstructive coronary artery disease; PP, pulse pressure; SBP, systolic blood pressure [Colour figure can be viewed at wileyonlinelibrary.com]

independent risk factors for obstructive CAD even after adjusting for potential confounding factors, including age, BMI, diabetes mellitus, dyslipidemia and smoking, renal function and current medications (Table 4). MAP and DBP were not associated with CAD in the
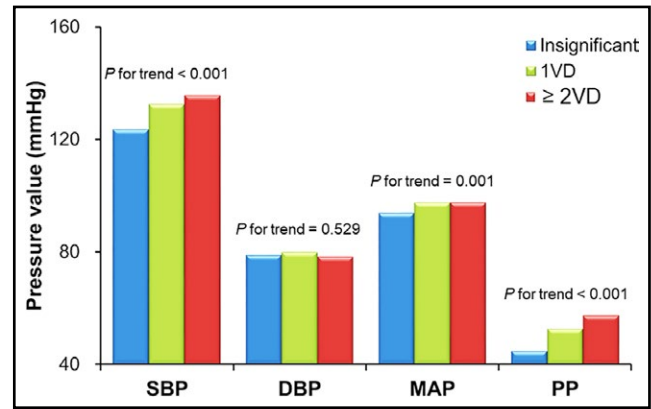
FIGURE 2 Blood pressure values according to the severity of coronary artery disease (n = 652). DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; VD, vessel disease [Colour figure can be viewed at wileyonlinelibrary.com]

same multivariable analyses (P > 0.05 for each). Scatter plots showing the linear associations between E/e' and each BP measurement are demonstrated in Figure 3.

4 | DISCUSSION

Among patients undergoing elective CAG, we investigated the association between four BP measurements and several TOD parameters. Among three TOD parameters including LVMI, E/e', and eGFR, E/e' was correlated with SBP, MAP, and PP even after controlling for potential confounders including age, gender, BMI, heart rate, diabetes mellitus, dyslipidemia, smoking, and cardiovascular medications. On the other hand, there were lack of significant associations of BP measurements with LVMI and eGFR. We also found that SBP and PP had a stronger relationship with CAD than DBP and MAP.

Our study has several strengths compared to prior other studies. First, prior studies have usually determined the association between some BP measurements and only one of the markers for TOD.[12,24,25] However, our study evaluated the association between all of the BP measurements and several markers for TOD. Secondly, since CAD was confirmed by invasive CAG, we could more accurately define CAD than prior studies. Thirdly, given that most of the previous studies have been performed in Western countries, our data from a nationwide Korean registry may deserve attention.

The DBP has classically been thought of as an important target of anti-hypertensive treatment and prognostic value of cardiovascular disease until 1980s. In 1977, the first guideline of Joint National Committee recommended DBP as the basis of diagnosis and treatment for hypertension.[26] In this context, the treatment of hypertension was based on DBP in some studies.[27,28] However, in the 1990s, the Framingham cohort showed that the cardiovascular event risk was more strongly associated with SBP than with DBP.[29] Moreover, numerous studies have proved that SBP is associated with cardiovascular outcomes and TOD.[9,12,19,30,31]

TABLE 4 Multiple binary logistic regression analyses showing the associations between each blood pressure measurement and coronary artery disease (n = 652)

Blood pressure measurement	OR (95% CI)	P value
SBP (3rd vs 1st tertile)	2.43 (1.28-4.61)	0.020
DBP (3rd vs 1st tertile)	0.91 (0.48-1.73)	0.779
MAP (3rd vs 1st tertile)	1.36 (0.71-2.61)	0.357
PP (3rd vs 1st tertile)	2.52 (1.29-4.93)	0.018

CI, confidence interval; DBP, diastolic blood pressure; MAP, mean arterial pressure; OR, odds ratio; PP, pulse pressure; SBP, systolic blood pressure.

Dependent variable is obstructive coronary artery disease (≥50% stenosis). Each independent variable was entered into separate model. Age, sex, body mass index, heart rate, diabetes mellitus, dyslipidemia, smoking, renal function, and concomitant medications were adjusted in each model.

In a cross-sectional analysis of 1315 Chinese subjects who were either normotensive or had untreated hypertension, SBP was the most powerful determinant of LV mass among other BP measurements including DBP.[30] Likewise, Lekakis et al[31] investigated 48 untreated hypertension and showed that LV hypertrophy was associated with SBP but not with DBP in univariable analysis. In line with these findings, our study showed that SBP had a stronger association with TOD including CAD and LV diastolic dysfunction than with DBP. Otherwise, studies investigating the relationship between MAP and TOD have been limited. A few studies have attempted to demonstrate the association between MAP and LV mass; however, their results were negative.[30,31] Supporting this finding, MAP showed weaker association with only E/e' among several TOD in our study.

Recently, the importance of PP has been recognized as an independent risk factor for cardiovascular morbidity and mortality.[17,18] The association between PP and TOD has also been demonstrated. In a 10-year follow-up study, Jokiniitty et al[32] evaluated 97 men and showed that PP was the most significant BP parameter related to
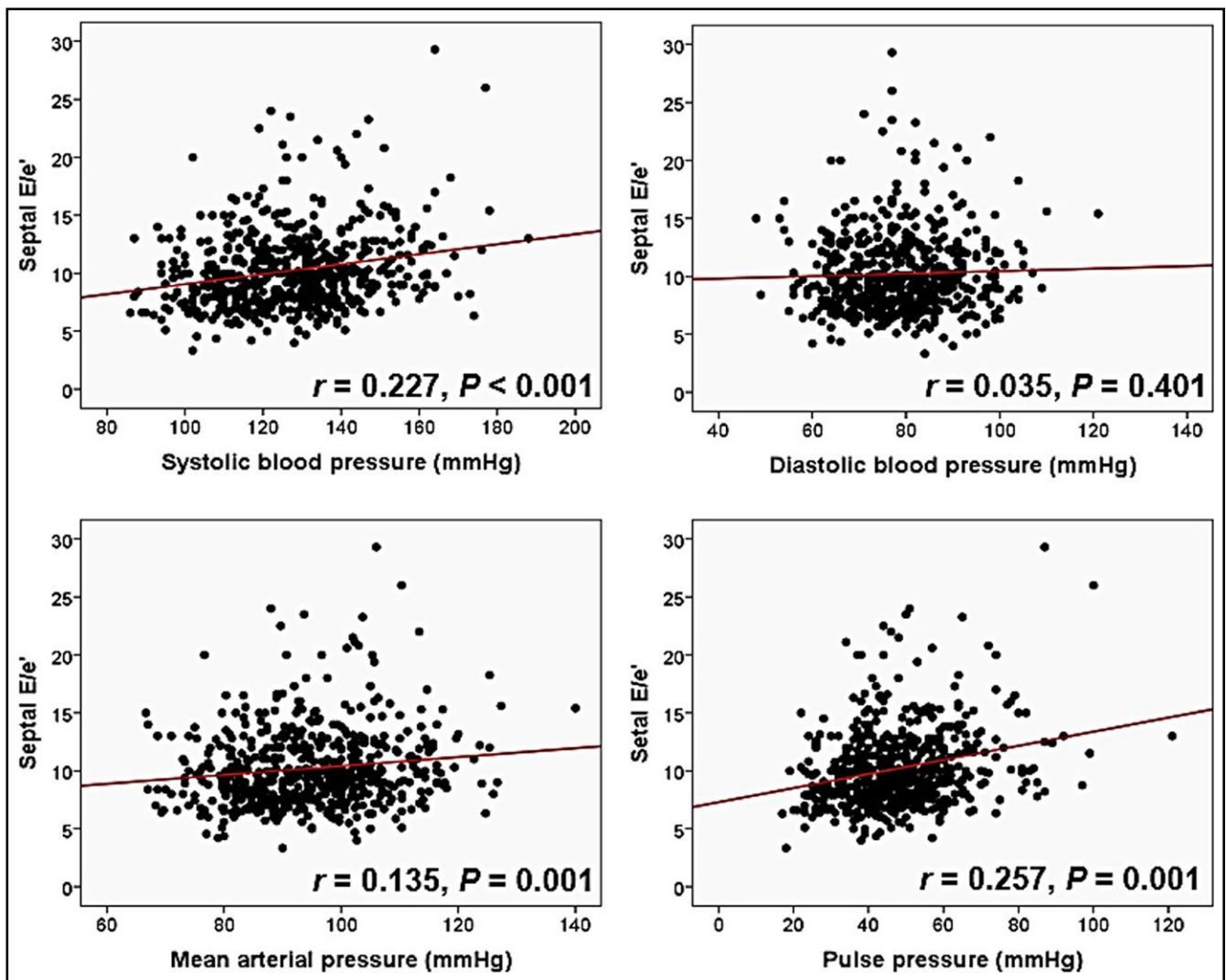

FIGURE 3 Scatter plots showing linear correlations between septal E/e' and blood pressure measurements (n = 652). DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; VD, vessel disease [Colour figure can be viewed at wileyonlinelibrary.com]

future LVMI and its change. Abhayaratna et al[33] showed that PP had a significant correlation with LV diastolic dysfunction in their 233 subjects, although the correlation power was weaker than pulse wave velocity. Cirillo et al[34] performed a large cross-sectional analysis (n = 1567) and demonstrated that PP was significantly related to the prevalence of microalbuminuria in nondiabetic middle-aged adults. Similarly, our study showed that PP had more strong associations with E/e' as LV diastolic dysfunction and CAD than the other BP measurements, including SBP, DBP, and MAP.

Our results showed that SBP was not associated with LVMI. These unexpected results may be due to the fact that mean SBP in our subjects was lower (127 ± 17 mm Hg) than that of previous studies (≥140 mm Hg).[9,31] In addition, about half of the patients were untreated with vasoactive drugs in our study, which might have an impact on the association between SBP and LVMI. Elevated SBP is well-known risk factors for renal dysfunction.[35] Our study also showed significant and negative correlation between SBP and eGFR in univariable analysis. However, the significance disappeared when controlling for several clinical covariates. This suggests that several cardiovascular risk factors such as age and diabetes mellitus play a significant role as confounding factors, and emphasizes the importance of controlling the effects of these potential confounders.

There are some theoretical backgrounds that SBP and PP are better indicators of TOD. Generally, an increase in SBP increases end-systolic stress, leading to an increase in LV mass.[36] An increase in PP causes vascular endothelial damage and mechanical fatigue, leading to atherosclerosis.[37] Increased PP is also associated with increased afterload and reduced coronary perfusion.[37] Arterial stiffness is a key mechanism for ventricular remodeling, diastolic dysfunction, and CAD.[33] Especially, it has well-known that SBP and PP have better implication power than DBP and MAP for diastolic dysfunction and CAD, both consequences of increased arterial stiffness.[38,39] Increased arterial stiffness promotes an increase in SBP and a decrease in DBP, leading to an increase in PP, but not MAP, as an offsetting effect. These processes can at least partially explain that SBP and PP have a more pronounced impact on TODs and cardiovascular events than MAP and DBP.

4.1 | Study limitations

There are several limitations in our study. First, our cross-sectional study could not clarify the causal relationship between BP measurements and TOD. Second, BP was measured from brachial pressure, not central hemodynamics in our study. Several studies have shown that central BP has a stronger association with TOD than with brachial BP.[31,40] However, measurement of central hemodynamics requires a specialized instrument, some technical skills or invasive catheterization. Therefore, the use of brachial pressure is more practical in clinical practice. Third, we used BP values obtained in a single measurement. Twenty-four-hour ambulatory BP values may be more valuable.[41,42] Fourth, gender comparison was not reliable in our study due to differences in numbers between genders and small number of enrolled men. Further studies with a large sample size are required for this issue. Finally, our study population is restricted to middle-aged and elderly

patients with high-risk features requiring invasive CAG. Therefore, generalization of our results to other population needs caution.

5 | CONCLUSIONS

In patients undergoing elective invasive CAG, four BP measurements including SBP, DBP, MAP, and PP were differentially associated with several TOD parameters including LVMI, E/e', eGFR, and CAD. More specifically, SBP and PP had stronger relationships with E/e' and CAD than DBP and MAP. Targeting SBP and PP rather than DBP and MAP may be more efficient in preventing LV diastolic dysfunction and CAD in this group of patients.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.