Pulse pressure correlates with coronary artery calcification and risk for coronary heart disease: a study of elderly individuals in the rural region of Southwest China

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Aim This study aimed to define the relationship between pulse pressure (PP) and coronary artery calcification (CAC), a proven surrogate marker for coronary heart disease.

Patients and methods A total of 170 participants 50–70 years of age from 11 villages of Yunnan Province of China were enrolled randomly into this study. They were examined routinely for diastolic and systolic blood pressure, PP, and CAC.

Results The average PP in the CAC-positive group was significantly higher than that in the CAC-negative group. In the positive CAC group, there were significantly positive correlations between PP and CAC score, volume, mass, as well as density. The area under the receiver operating characteristic curve analysis showed that PP performed well in predicting CAC.

Conclusion In conclusion, among the rural people of southwest of China, PP correlates positively with the coronary calcium Agatston score, volume, mass, and density. PP predicted CAC as well as Framingham Risk Score. The measurement of PP widening may serve as an alternative and convenient method for assessing CAC risk in rural populations with poor accessibility and economic disadvantage over coronary computed tomography scanning. *Coron Artery Dis* 30:297–302 Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

Introduction

Coronary heart disease (CHD) has high morbidity and mortality in both developed and developing countries [1]. In China, there were 2.5 million myocardial infarctions in 2013 [2]. An early diagnosis is important for the prevention of acute cardiovascular events and improvement of quality of life. Screening for risk factors of coronary artery disease using the Framingham Risk Score (FRS) [3] or similar scores helps identify those benefiting from an early coronary risk intervention. However, in poor rural regions of developing countries such as China, the poor access to blood screening for lipid levels makes the risk score evaluation difficult [4].

Pulse pressure (PP) reflects the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP), which can be measured by village healthcare workers and does not require blood draws or clinical laboratories. PP has been considered an independent risk factor for CHD [5]. Accumulating evidence has shown that brachial PP may be associated independently with subclinical CHD [6]. In a survey of 30 different sites in China, PP was related positively to atherosclerosis [7]. PP is a simple and stable parameter in CHD risk prediction, particularly suitable for remote and poor areas in China.

Therefore, with arterial calcification scores and densities as the endpoint, in this study, we investigated whether blood pressure measurements, available to village doctors, could be used to risk stratify rural residents and drive preventive public health strategies. To our knowledge, few studies have been carried out on the relationship between CAC and PP in asymptomatic populations in China.

Patients and methods
Study enrollment
Participants ranging in age from 50 to 70 years were randomly selected from 11 remote villages located in

Yongping, Yongsheng, Yilong, and Weixi counties in the rural regions of Yunnan Province. We excluded patients with cardiovascular disease from the study population. The study was approved by the institutional review board of the first affiliated hospital of Dali University.

Evaluation of cardiovascular risk factors

All the participants received standardized questionnaires on the cardiovascular risk factors including basic information on age, sex, smoking status, cholesterol, or presence of diabetes. Their height and weight were measured with the participants wearing light clothing and no shoes. BMI was calculated as weight divided by height squared (kg/m^2). Resting blood pressure was measured three times with the participants in the seated position. Before the measurement, the participants were allowed to rest for at least 5 min without smoking or drinking any beverages. Using a calibrated standard cuff mercury sphygmomanometer, blood pressure was measured three times at an interval at of least 1 min and the average pressure was used in the analysis. PP was defined as the SBP minus DBP. Hypertension and diabetes mellitus were defined by international current standards. After obtaining informed consent, all participants were invited to the Affiliated Hospital of Dali University in Yunnan Province for further investigation. Fasting blood samples were obtained before computed tomography (CT) scans for the analysis of glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) (non-HDL-C was calculated using the equation: TC–HDL-C = non-HDL-C), high-sensitivity C-reactive protein, glycosylated hemoglobin, blood urea nitrogen, and creatinine.

Computed tomography scanning of coronary artery calcification

A prospective ECG-triggered sequential cardiac multiple detector CT scan was performed using a 16-detector row spiral CT scanner (Philips Brilliance 16-slice CT; Philips Healthcare Systems, Best, Netherlands) with 0.4-s rotation time, collimation 120 kV, and 200 mA. An ECG-gated prospective (axial mode) scan was performed on all patients. Data were acquired during diastole at 70% phase selection of the cardiac cycle and images were reconstructed in the axial plane at 2.5 mm slice thickness. All images were transferred to a Vitrea Vital Workstation (Vital Images, Minnetonka, USA) and analyzed by a cardiac radiologist (M.S.K.) who was blinded to clinical and demographic data. The amount of calcification was quantified using the Agatston score method as described before [8]. The coronary calcium score software on Vital was used to automatically identify calcification on the basis of at least three contiguous pixels exceeding the CT density of 130 Hounsfield units (HU). Then, the radiologist segmented the calcification in the left main, left anterior descending, left circumflex, and right coronary arteries. Calcifications in the side branches of left and right coronary arteries were also segmented and included

in the overall score (Fig. 1). The software could provide segmental and the total Agatston score, volume, and mass. We also obtained an age-matched and sex-matched percentile chart for the coronary calcium score in all patients. We applied mass/volume for calcium density from the report by Criqui et al. [9].

Statistical analysis

All the quantitative data were expressed as the mean ± SD. The relationships between PP and age, BMI, abdomen circumference, creatinine, cholesterol, hemoglobin A1c, and the CHD risk score from general FRS were examined by Spearman's correlation analyses. The unpaired Students' t-test and analysis of variance were carried out to assess statistical significance of the differences between groups. Correlations between PP and CAC Agatston score, volume, mass, and ln(density + 1) were calculated using Pearson's analysis. Receiver operating characteristic (ROC) curve analysis was used to assess the predicting power of age, PP, SBP, and the 10-year CHD risk score for detecting calcification. All statistical analyses were carried out using SPSS 17.0 software. A two-sided P value less than 0.05 was considered statistically significant.

Results

Elevation of pulse pressure increases 10-year coronary heart disease risk

A community study of risk factors and biomarkers for CHD was carried out to assess cardiovascular health of residents living in remote villages of the south of Yunan Province, China. The baseline and clinical characteristics of all the enrolled patients were collected and statistically analyzed as shown in Table 1. We observed that 24 patients had higher levels of SBP (151.3 ± 25.4 mmHg), but their DBP remained normal (82.7 ± 22.6 mmHg). Their average PP values were 68.6 ± 7.9 mmHg, much greater than that (43.0 ± 9.3 mmHg) in the rest of the patients who had a relatively low incidence of hypertension ($P < 0.01$). No significant differences in other risk factors (e.g. age, sex, smoking, BMI, and lipid profiles) were found between the PP-high (PP^{Hi}, 60 ≥ mmHg) and PP-low (PP^{Low}, <60 mmHg) groups (Table 1).

We further carried out the Pearson correlation analysis to determine whether the PP value elevation is associated with the risk for the development of atherosclerotic CHD. We observed that PP values were correlated positively with FRS 10-year CHD risk ($r = 0.498$, $P < 0.0001$) (Fig. 2).

Pulse pressure elevation is associated with coronary arterial calcification

To investigate the relationship between PP and CAC, the aggregation pattern of PP in different CAC status as well as CAC property in different BP groups were examined. We found that in patients with PP values
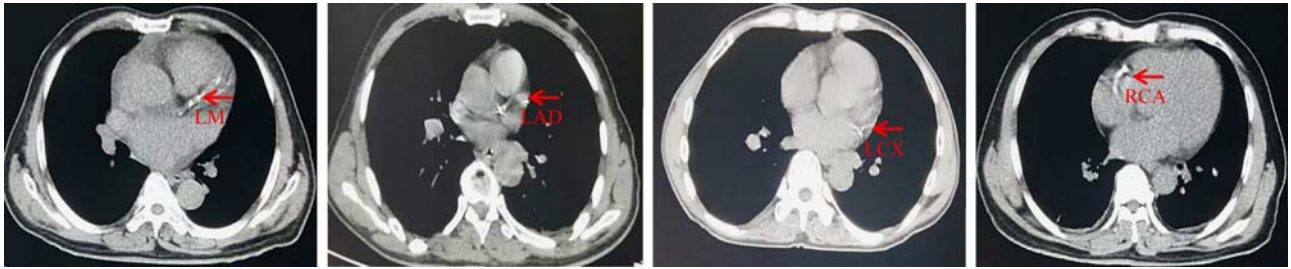
Calcifications in different parts of the coronary artery. LAD, left anterior descending; LCX, left circumflex; LM, left main; RCA, right coronary artery.

Table 1 Baseline clinical characteristics of the study population

Characteristics	PP ≥ 60 mmHg (*n* = 24) (mean ± SD)	PP < 60 mmHg (*n* = 146) (mean ± SD)	*P*
Sex (male/female) [*n* (%)]	13 (54.2)/11 (45.8)	69 (47.3)/77 (52.7)	NS
Age (years)	61.3 ± 5.6	59.1 ± 5.1	0.0876
BMI (kg/m^2)	21.4 ± 3.2	21.1 ± 2.8	0.7917
Abdomen circumference (cm)	78.3 ± 9.4	79.1 ± 8.6	0.4696
Total cholesterol (mg/dl)	207.3 ± 50.5	190.6 ± 45.0	0.1640
HDL cholesterol (mg/dl)	62.1 ± 15.8	64.8 ± 19.6	0.5547
Non-HDL cholesterol (mg/dl)	145.2 ± 51.5	125.8 ± 44.1	0.0599
Hypertension [*n* (%)]	11 (45.8)	34 (23.3)	< 0.001
Current smokers [*n* (%)]	10 (41.2)	55 (37.6)	0.89
SBP (mmHg)	151.3 ± 25.4	124.7 ± 16.8	< 0.001
DBP (mmHg)	82.7 ± 22.6	81.8 ± 17.1	0.5280
Pulse pressure (mmHg)	68.6 ± 7.9	43.0 ± 9.3	< 0.001

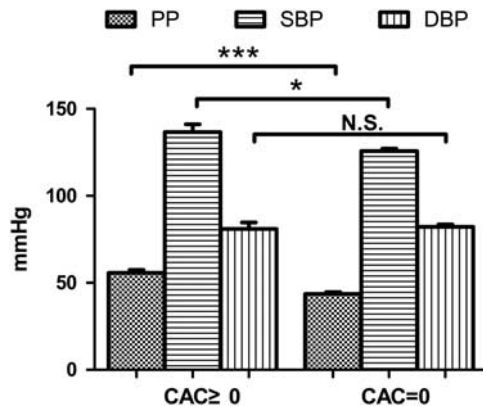DBP, diastolic blood pressure; HDL, high-density lipoprotein; PP, pulse pressure; SBP, systolic blood pressure.

Fig. 2
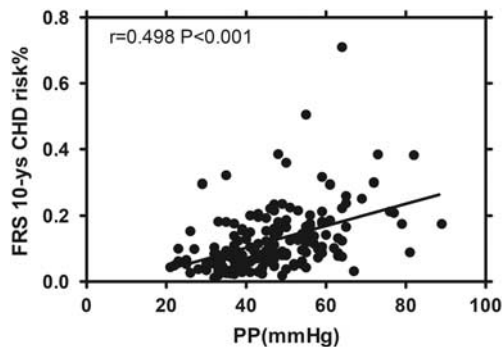
PP correlated with 10-year CHD risk. CHD, coronary heart disease; FRS, Framingham Risk Score; PP, pulse pressure.

Fig. 3

The aggregation pattern of blood pressure in different CAC status. *$P < 0.05$; ***$P < 0.0001$. CAC, coronary artery calcification; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

ranging from 22 to 88 mmHg, there were 42 patients who had positive CAC scores (24.71%). The CAC score ranged from 1 to 453. The patients with positive CAC were predominantly men older than 60 years of age, and current smokers with hyperlipidemia (data not shown). In particular, the average PP and the average SBP, but not the average DBP, were statistically significantly different between the CAC-positive group and the CAC-negative group (Fig. 3). In contrast, mean CAC score differences were observed between PP^{Hi} and PP^{Low} groups, as well

as between the SBP^{Hi} group and the SBP^{Low} group, but not between different DBP groups (Fig. 4). To further define the association of PP with CAC, the correlations between PP and individual calcium parameters were examined. The results of the correlation analysis showed that there were significant associations between the PP values and the CAC Agatston score, volume, mass, and ln

(density + 1) (Fig. 5). Thus, all the above data suggest that PP is associated positively with increased CAC in the population of remote villages in the south of Yunan Province.

Multifaceted comparison between age, systolic pressure, Framingham Risk Score coronary heart disease risk score, and pulse pressure coronary artery calcification prediction

Multifaceted analysis was carried out to assess the impact of PP changes against other risk factors, such as age, SBP, and FRS, for CAC prediction. The variations were plotted and the areas under the curve (AUCs) for each factor parementer were calculated (Fig. 6). The values of AUC for each factor were found to be the highest in PP (0.785), followed by CHD risk (0.765), age (0.699), and SBP (0.555) relative to positive CAC. Using ROC analysis, a cutoff point value for PP of at least 58.7 mmHg was determined with a sensitivity of 53.8%, a specificity of 87.5%, and positive and negative predictive values of 41.6 and 78.1%, respectively. The discriminatory ability of PP was equal to that of FRS. Hence, PP and, to a lesser extent, CHD risk might serve as better discriminators for CAC prediction than other factors, such as age or SBP.

Discussion

By 2015, CHD accounted for 44.6% of total mortality in China [11]. Atherosclerosis, the pathological basis of CHD, exists in a subclinical status characterized by the absence of clinical signs and symptoms for a prolonged period before symptomatic CHD. Almost 30% of out-of-hospital cardiac arrest occurs in patients previously undiagnosed with cardiac disease [12]. Therefore, the development of an early, accurate, and easy method suitable for screening atherosclerotic risk factors is appealing. CAC is a sensitive and specific biomarker for predicting the severity of coronary atherosclerosis. Detrano et al. [13] have recently shown that CAC serves as a reliable predictor of CHD and, in combination with traditional risk factors, it may yield better insight into the pathophysiological changes observed in patients with coronary atherosclerosis. However, the high cost and poor accessibility of coronary CT scanning preclude its clinical usage, particularly in patients who live in remote,

Fig. 4
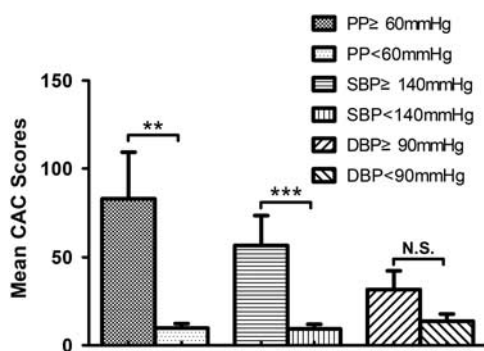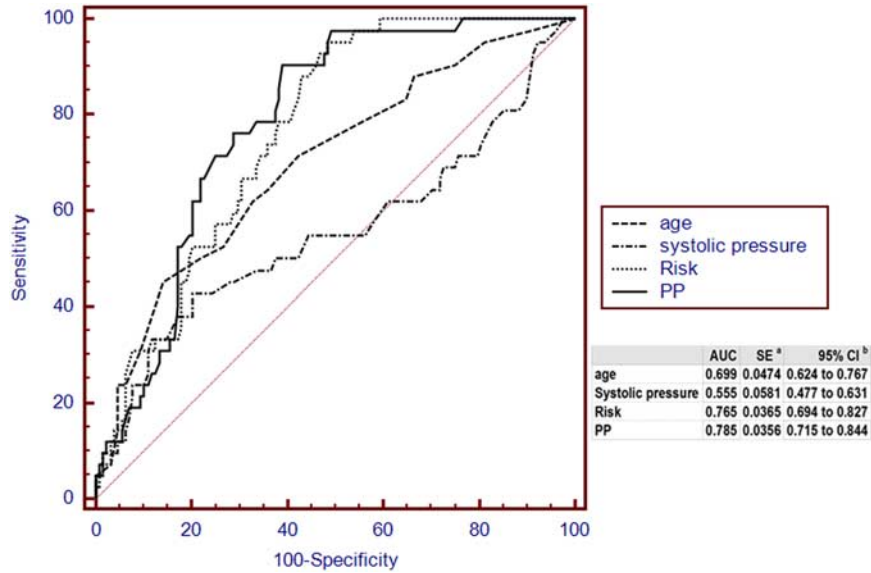

The mean CAC scores in different blood pressure groups. **$P < 0.001$; ***$P < 0.0001$. CAC, coronary artery calcification; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

Fig. 5
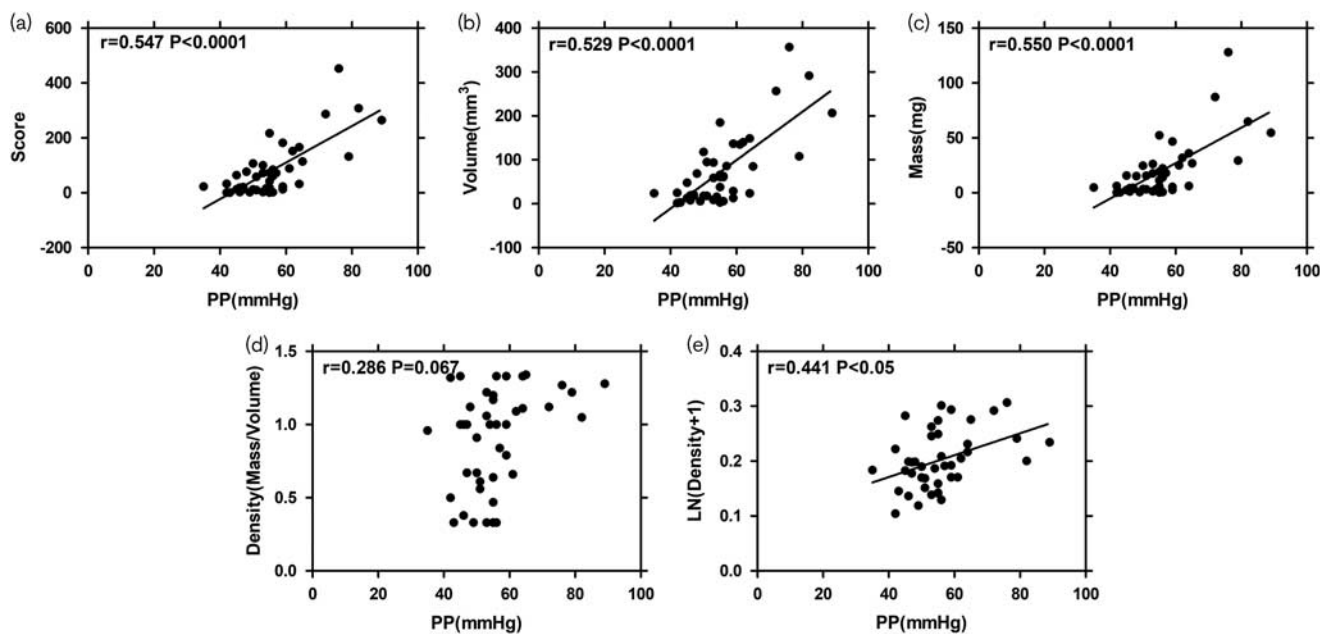
Correlation analysis between PP and coronary artery calcification Agatston score (a), volume (b), mass (c), density (d) and in (density +1) (e).

Fig. 6

Receiver operating characteristic curve and AUC showing the predicting power of age, systolic pressure, Framingham Risk Score 10-year coronary heart disease risk score, and PP in the prediction of coronary artery calcification. AUC, area under the curve; CI, confidence interval; PP, pulse pressure. [a]Methodology of DeLong *et al.* (1988) [10]. [b]Binomial exact 95% confidence intervals.

rural villages. To overcome this problem, we have attempted to find a valid way to predict CAC through the analysis of PP values in association with the changes of other risk factors.

Our data clearly point to the feasibility of using simple clinical measures such as PP in determining CAC and risk levels. As expected, approximately half of the participants had CAC positivity. The average PP values apparently increased with aging, consistent with the data reported by Franklin [14]. In addition to an increase in PP with aging, another major change in the artery with aging is calcium deposition, perhaps triggered by endothelial dysfunction, elastic fiber breakage, wall thickening, fibrosis, and less elastic stiffness [15]. This is in line with the results reported in our previous study [16]. Hypercholesterolemia is a known causative risk factor for atherosclerosis. This study supports the notion that the increase in the PP value may be, at least partly, related to the elevation of TC, non-HDL-C, and FRS (< 0.001). In fact, the increased PP values may be both a cause and a consequence of hyperlipidemia, as well as atherosclerosis. Widen PP and hyperlipidemia both lead to reduction in the elasticity of the arterial wall by inflammation [17].

The exact mechanism underlying the relationship between PP and CAC remains to be explored, even though the two factors are predictive of CHD morbidity. Our study showed that there was a statistical difference in PP between calcification-positive and calcification-negative groups. A recent European study [18] has shown

that PP value changes help identify patients with subclinical CAC while undertaking the procedure of dialysis. It is generally believed that in end-stage renal dysfunction, there is increased calcification in the arterial media, which may be associated with the all-cause and cardiovascular mortality of patients [19]. High PP should be alert to the indicator of coronary artery disease.

We also examined the relationship between PP and CAC through quantitative measurements, including the score, volume, mass from multiple detector CT results, and indirectly calculated density (mass/volume). The results show a positive correlation between PP and CACS, volume, mass, and ln(density + 1). Calcium density, measured as the CAC scores, provides useful values to predict future cardiovascular events beyond clinical risk factors. However, recently, Criqui *et al.* [9] have shown that the CAC scores may be associated independently and inversely with CHD risk at a given CAC volume, suggesting that the density should be considered when evaluating current CAC scoring systems. Pathophysiologically, more CAC density causes more relatively stable plaques, and data also showed that CAC progression and density run counter to each other when treated with statins [20,21]. Whether density change could affect the reliability of CHD risk by prediction CAC deserves further study.

We applied the analysis of ROC curves to define the predictive power of PP and CHD risk in the presence of CAC, although there was no significant difference between AUC of PP (0.785) and CHD risk score (0.765), but PP and risk score appeared to be superior to age

(0.699) and SBP (0.555). These results are consistent with the report by Bielak *et al.* [22], who concluded that compared with the SBP, PP is better in CAC prediction in populations older than 50 years of age. FRS requires a blood sample, which, in a rural village, may be challenging. It also requires some kind of laboratory or test kit. PP can be performed easily by a village doctor. Therefore, the data from our study may help triage patients who may benefit more from receiving the cardiac CT for coronary calcium score.

Considering that the study population consisted largely of rural residents in the southwest of China from four ethnic groups, these findings may not be generalizable to other patients and populations. Patients with negative calcium scores might have noncalcified plaque, and there may be a risk of plaque rupture.

Conclusion
This is the first study assessing the relationship between PP and CAC in rural Chinese individuals. The average PP in the CAC-positive group has a close association with the CAC scores compared with that in the CAC-negative group. There is a significantly positive correlation between PP and CAC Agatston score, volume, mass, as well as density. Finally, the AUC analysis confirmed that PP, a simple clinical parameter available from every rural resident and to every village doctor in rural China, is at least equivalent to FRS as a predictor of CAC.

Acknowledgements

Conflicts of interest
There are no conflicts of interest.

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