

**Relative Contributions of Pulse Pressure and Arterial Stiffness
to Cardiovascular Disease: The Framingham Heart Study**

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Abstract

Pulse pressure has been frequently used as a surrogate marker of arterial compliance. However, the prevalence and prognostic significance of mismatch between pulse pressure and arterial stiffness remains unclear. We measured carotid-femoral pulse wave velocity (CFPWV) and central pulse pressure (CPP) in 2119 Framingham Offspring Cohort participants (mean age 60 years, 57% women). The participants were divided into 4 groups according to CPP and CFPWV status (categorized as high/low based on \geq age- and sex-specific median values) and followed up for cardiovascular disease (CVD) events. At baseline, 832 of 2119 (39%) of participants had discordant CPP and CFPWV status; 417 with low CPP and high CFPWV and 415 with high CPP and low CFPWV. The multivariable-adjusted risk for CVD events ($n=246$, median follow-up 12.6 years) in individuals with a CPP-CFPWV mismatch (hazard ratio [HR] for low CPP with high CFPWV: 1.21, 95% confidence interval [95% CI] 0.83-1.76; HR for high CPP with low CFPWV: 0.76, 95% CI 0.49-1.19) was comparable to the CVD risk observed in the low CPP with low CFPWV (referent group). In contrast, participants with a high CPP with high CFPWV (HR 1.52, 95% CI 1.10-2.11) experienced significantly increased CVD risk. The interaction term between CPP and CFPWV status on CVD risk was borderline significant in the multivariable model ($P=0.08$). Our results demonstrate that pulse pressure-arterial stiffness mismatch is common in the community. CFPWV may modify the association of CPP with CVD risk, with greatest risk being observed in those with elevated CPP and CFPWV.

Keywords: Cardiovascular Disease, Epidemiology, High Blood Pressure, Hypertension, Risk Factors, Vascular Disease

Introduction

Increased pulse pressure and arterial stiffness are both associated with elevated risk of cardiovascular disease (CVD).^{1,2} Pulse pressure and arterial stiffness are strongly correlated, as age-associated vascular calcification and elastin breakdown leads to arterial stiffening, which in turn results in larger forward wave amplitude, earlier reflected wave arrival and a greater pulse pressure.^{3,4} Although not a direct measure of arterial stiffness, pulse pressure has been often used as a surrogate marker of arterial compliance.⁵ However, major gaps still exist in our understanding of the interplay between pulse pressure and aortic stiffness. Albeit pulse pressure is sometimes used as a surrogate marker of arterial stiffness, the prevalence and prognostic significance of a mismatch between pulse pressure and arterial stiffness in the community have not been well studied. Such information could be of interest to elucidate the validity of pulse pressure as a surrogate measure of arterial stiffness. In addition, these data could help clinicians understand the relative and conjoint importance of pulse pressure and arterial stiffness in the assessment and pathogenesis of CVD risk.

To clarify the prevalence and predictive value of pulse pressure-arterial stiffness mismatch, we assessed measures of central hemodynamics and large artery stiffness in 2119 community-dwelling individuals and assessed the relations of pulse pressure-arterial stiffness mismatch to prevalence of left ventricular hypertrophy (LVH; a marker of cardiovascular target organ damage) cross-sectionally and to the incidence of CVD prospectively.

Methods

Anonymized data have been made publicly available at the database of Genotypes and Phenotypes and can be accessed at <https://www.ncbi.nlm.nih.gov/gap/>.

Participants

We included individuals who attended the seventh examination of the Framingham Offspring cohort ($n=3539$; 1998–2001) in the present investigation. The characteristics and study protocol for the Framingham Heart Study Offspring cohort have been published.⁶ Tonometry measurements were obtained in 2660 participants as described previously.^{3,7} We excluded participants who had incomplete tonometry data ($n=367$) or prevalent CVD ($n=174$) from the present analysis.

Measurements for echocardiographic and electrocardiographic (ECG) LVH were performed during the participants' previous sixth examination cycle (1995–1998). A subpopulation of 1579 participants with ECG and echocardiography data available from the sixth examination cycle was used for analyses of LVH. Boston University Medical Center's Institutional Review Board approved all study protocols, and participants provided written informed consent.

Clinical Evaluation and Definitions

All participants provided a medical history and underwent laboratory assessment of CVD risk factors and a physical examination.⁶ We assessed the participants for the prevalence of hypertension, diabetes mellitus (fasting glucose level of ≥ 126 mg/dL or the use of antidiabetic medications), and self-reported smoking. We measured blood pressure using a standardized

protocol (mean of 2 auscultatory values obtained by a physician using a mercury column sphygmomanometer on the left arm of seated participants), body mass index, serum total cholesterol levels, and high-density lipoprotein cholesterol concentrations. We derived heart rate from a standard 12-lead ECG.

Carotid-Femoral Pulse Wave Velocity (CFPWV) and Central Pulse Pressure (CPP)

We evaluated arterial stiffness with carotid-femoral CFPWV.¹⁷ We acquired arterial tonometry measures from the right side of the body after more than 5 minutes of rest in the supine position as previously described.^{3,7} Arterial tonometry with a simultaneously acquired electrocardiogram was obtained for the femoral and carotid arteries. We estimated the carotid-femoral transit distance by measuring the body surface distance from the suprasternal notch to the carotid and femoral sites and taking the difference to account for parallel transmission along the brachiocephalic and carotid arteries and around the aortic arch. We divided this corrected distance by the carotid-femoral transit time delay to calculate CFPWV.

We used the oscillometric systolic and diastolic cuff blood pressures obtained at the time of the tonometry acquisition to calibrate the peak and trough of the signal-averaged brachial pressure waveform. We used the diastolic and integrated mean brachial pressures to calibrate carotid pressure tracings.⁸ Central pulse pressure (CPP) was defined as the difference between the peak and trough of the calibrated carotid pressure waveform.

Left Ventricular Hypertrophy

We defined LVH as a composite of presence of electrocardiographic or echocardiographic LVH. We defined LVH by ECG according to the Cornell voltage criteria (sum of R-wave in aVL plus S-wave in V3 >20 mV in women and >28 mV in men).⁹ We performed two-dimensional echocardiography with Doppler color flow imaging using a Sonos 1000 Hewlett-Packard ultrasound device at the sixth examination cycle (approximately three years preceding the CFPWV measurements). Digitized images were stored and measured using an off-line analysis system by certified sonographers or cardiologists. We measured left ventricular mass according to the American Society of Echocardiography guidelines.¹⁰ We defined echocardiographic LVH as values of left ventricular mass index >115 g/m² in men and >95 g/m² in women.¹⁰

Cardiovascular Disease Outcomes

We used the incidence of a major CVD disease event as the primary outcome. This was a composite outcome that consisted of CVD death, fatal or nonfatal myocardial infarction, heart failure, unstable angina (prolonged ischemic episode with documented reversible ST-segment changes), and stroke. Medical records were obtained for all hospitalizations and physician visits related to CVD events during follow-up and were reviewed by an adjudication panel consisting of 3 investigators. Clinical criteria for adjudication of these CVD events have remained mostly unchanged over the duration of The Framingham Heart Study and been described previously.¹¹

Statistical Methods

We divided the participants into 4 groups according to their CPP status (CPP under vs. at or above 5-year age- and sex-specific median) and presence of high vascular stiffness (CFPWV under vs. at or above 5-year age- and sex-specific median) at the seventh examination cycle. We used age- and sex-specific cutpoints to partition participants into categories (of CPP and CFPWV) as these two factors are key correlates of CPP and CFPWV. Participants with low CPP and low CFPWV were used as the referent group in all analyses.

First, we used Pearson's correlation to assess correlation between CFPWV and CPP. To reduce the impact of heteroscedasticity (the SD increases with mean value across various groupings, such as age), we inverted CFPWV and multiplied by -1000 to restore directionality, resulting in a variable with a normal distribution and uniform SD. We log-transformed CPP to achieve normal distribution. Second, we assessed baseline characteristics according to the four groups cross-classified by CPP and CFPWV status. Third, we studied the associations between the four groups defined above and the presence of LVH cross-sectionally using multivariable-adjusted logistic regression models (adjusting for covariates noted below). Fourth, we evaluated the association between the four participant groups and incidence of CVD events with Kaplan-Meier plots (compared with a log-rank test), and multivariable-adjusted Cox proportional hazards regression models. The statistical interaction between the exposure categories (high/low CFPWV and high/low CPP) were tested by entering these variables as interaction terms into the multivariable models. We also tested for the statistical interaction between the four-category exposure variable and age (<65 versus ≥65 years) by entering these variables as interaction terms into the multivariable models while removing continuous age from the covariates. Improvement in discrimination was assessed using the

C-statistic for conventional cardiovascular risk factors, and change in C-statistic from addition of the four-category exposure variable. In addition, we performed a secondary analysis in the subsample of participants who had data for LVH available (N=1579) by including LVH among the covariates. We also performed another secondary analysis while including antihypertensive medication in the covariates and using overall medians as the cutoffs as the original age- and sex-specific groupings increased the sensitivity of the groups to antihypertensive medication.. The assumption of proportionality of hazards was met when we evaluated Schoenfeld residuals. All multivariable models were adjusted for age, sex, body mass index, smoking status, diabetes mellitus, heart rate, serum total cholesterol, and HDL cholesterol. A two-sided value of $P < 0.05$ was considered statistically significant for main effects and a $p < 0.10$ was deemed significant for tests of interactions.¹² All analyses were performed with Stata software version 13.1 (StataCorp, College Station, Texas, USA).

Results

We studied up to 2119 community-dwelling participants (mean age 60.4 years, 56.6% women). Baseline characteristics in groups according to their CPP and CFPWV status are shown in **Table 1**. We found discordant CPP and CFPWV status in 832 of 2119 participants (39%): 417 with low CPP and high CFPWV and 415 with high CPP and low CFPWV. Apart from hemodynamic variables, differences between groups were mostly unremarkable except for the two groups with low CFPWV had lower heart rate and lower prevalence of diabetes than the two groups with high CFPWV. The age- and sex-adjusted correlation between CPP and CFPWV was $r=0.44$ (**Figure 1**).

Presence of LVH in Groups by CPP and CFPWV Status

In a subgroup of 1579 participants who had LVH data available (mean age 60.0 ± 9.4 , 59.8% women), the prevalence of LVH in groups by CPP and CFPWV status are reported in **Table 2**. In the unadjusted and multivariable-adjusted models, only the group with high CPP and high CFPWV was significantly related to the odds of prevalent LVH compared to the referent group with low CFPWV and low CPP. No statistical interaction was observed for the effects of CPP and CFPWV status on the prevalence of LVH ($P=0.91$ in the multivariable model).

Risk of CVD Events in Groups by CPP and CFPWV Status

During a median follow-up of 12.6 years, 246 CVD events occurred. The Kaplan-Meier curves in **Figure 2** illustrate the cumulative incidence of CVD events in groups according to the CPP and CFPWV status (log-rank $P<0.001$). In unadjusted Cox regression models, the hazard

ratios for CVD events were significantly higher in the groups with 1) high CPP and high CFPWV and 2) low CPP and high CFPWV relative to the referent group with low CPP and low CFPWV. In the multivariable-adjusted model, only the group with high CPP and high CFPWV had a higher risk of incident CVD compared to the referent group. The interaction term between CFPWV and CPP status on CVD risk was borderline significant in the multivariable model ($P=0.08$). The interaction term between the four-category exposure variable and age on CVD risk was non-significant ($P=0.82$). Addition of the four-category CPP/CFPWV variable to the model without this variable did not increase the c-statistic (**Table 3**). In a subsample of 1579 individuals, including LVH among the covariates resulted in the association of high CPP and high CFPWV with CVD outcomes becoming non-significant (**Table S1**; HR, 1.41 [95% CI, 0.95-2.10]; $P=0.09$). When antihypertensive medication was included among the covariates, the results remained essentially same (**Table S2**).

Discussion

The results of our study imply that pulse pressure-arterial stiffness mismatch is common, affecting 39% of individuals in the community when age- and sex-specific partition values are used to define high and low CPP and CFPWV. We observed that the combination of higher CPP and arterial stiffness was associated with a considerably elevated risk of LVH cross-sectionally, and incidence of CVD prospectively. Higher arterial stiffness seems to be a more important driver of CVD risk as individuals with low CPP and high CFPWV tended to have an increased risk of prevalent LVH and incident CVD compared with individuals with high CPP and low CFPWV. We also observed an interaction between CFPWV and CPP status and CVD risk, demonstrating effect modification by arterial stiffness on the the relations of pulse pressure to CVD risk.

Our results indicate that considerable disagreement between pulse pressure and arterial stiffness status exists in community-dwelling middle-aged adults. In our study, nearly two-fifths of the participants had discordant pulse pressure and arterial stiffness status based on the partition values used to define these categories. Consistent with the foregoing observation, the correlation between CPP and CFPWV was only moderate ($r=0.43$). In prior smaller studies, correlation coefficients for peripheral pulse pressure and CFPWV have varied between -0.16 and 0.36.^{3,13-15} When directly measured or tonometry-derived estimates of CPP have been used instead of peripheral pulse pressure, the correlation coefficients have been somewhat higher, ranging between 0.52 and 0.64^{16,17} Furthermore, it has been previously demonstrated that a large part of the variation in CPP is not explained by

measures of arterial stiffness.¹⁸⁻²⁰ The results from our and other prior studies suggest, therefore, that the pulse pressure and CFPWV are frequently discordant, and the correlation may be particularly weak when peripheral PP is used or in select populations, such as in young, healthy individuals¹⁴ and in patients with lower limb ischemia.¹⁷ Caution should be exercised, therefore, before using pulse pressure as a surrogate marker for arterial stiffness.

Previous studies that have assessed the prognostic significance of a CPP-CFPWV mismatch are extremely limited. In our search of the published literature, we noted only one prior study that had examined the relations of CPP/CFPWV ratio and critical limb ischemia in a sample of 136 South African patients and 194 age- and sex-matched controls.¹⁷ In that study the CPP/CFPWV ratio was increased in participants with critical limb ischemia and provided a similar level of accuracy and a greater specificity as compared with carotid intimal-medial thickness.¹⁷ However, the study evaluated a highly selected sample of patients with severe peripheral atherosclerosis, and the results may not be generalizable to other populations. The results of the present investigation suggest that the effects of CFPWV and CPP on the odds of LVH are additive. Although the differences were statistically non-significant in multivariable-adjusted models, participants with a CFPWV/ CPP mismatch had a higher odds of LVH that was intermediate between those observed for individuals with low CPP and low CFPWV, and high CPP and high CFPWV. In contrast, individuals with low CFPWV did not have an increased risk of incident CVD, irrespective of CPP status. Furthermore, CFPWV status influenced the relations of CPP and CVD risk (*P* for interaction was 0.08). The exact physiological underpinnings of this finding require further research. Although including LVH as a covariate resulted in the association of high CPP and high CFPWV with CVD outcomes

becoming non-significant, this finding must be interpreted with caution. Even though this analysis was performed in a smaller subsample of 1579 participants which resulted in a considerable loss in statistical power, the association of high CPP and high CFPWV with CVD remained borderline significant with a HR of 1.41. Additional studies of larger samples are therefore needed to elucidate the relative importance of PWV and LVH. In any case, physicians need to acknowledge that presence of both elevated CPP and CFPWV elevates the risk of incident CVD.

Several factors may explain the observed mismatch in CPP and CFPWV status. The two major components of CPP are the first systolic shoulder in the arterial pulse waveform and the augmentation pressure.^{3,21} Furthermore, the first shoulder of the arterial pulse waveform is mainly dependent on peak systolic flow rate and arterial stiffness whereas augmentation pressure is determined by timing and amplitude of wave reflection. A prior study on 496 twins has indeed demonstrated that CFPWV is not a major determinant of arterial wave reflection and that the main determinant of the augmentation pressure is the ratio of distal to proximal arterial diameters.²¹ These findings are also consistent with those from other studies that have shown that the dissociation between measures of wave reflection and CFPWV increases during interventions that influence vasomotor tone.^{22,23} Results from our study and prior studies highlight that pulse pressure and arterial stiffness (CFPWV) are not the same, and that physiological differences between the two hemodynamic variables exists.

Studying the separate roles of CPP and arterial stiffness as predictors of CVD outcomes has distinct challenges as CFPWV may be both a marker of hypertensive organ damage and also

a precursor of hypertension. Furthermore, both arterial stiffness and hypertension may be part of a vicious cycle in the age-related increase in blood pressure.²⁴ Addition of the four-category CPP/CFPWV-variable to the model without this variable did not increase the c-statistic. However, the primary objective of our investigation was to explore the conjoint impact of CPP and PWV on CVD risk, rather than CVD risk prediction per se. Furthermore, increments in c-statistic with addition of biomarkers associated with CVD risk can often be challenging to achieve.²⁵ The strengths of our investigation include the moderate-sized community-based sample with long-term follow-up and assessment of both LVH prevalence and CVD incidence as outcomes. Our results must be interpreted with caution, however. First, our study could have benefited from a larger sample and greater number of CVD events to provide even more reliable estimates on the risks associated with a pulse pressure-arterial stiffness mismatch. Second, CFPWV is only a measure of large-artery stiffness, and does not adequately reflect stiffness or function of smaller conduit arteries. Third, our sample consisted mainly of older white individuals of European ancestry. Our results may not be generalizable to other races/ethnicities or age groups. Fourth, we opted to not adjust our models for antihypertensive treatment as it tracked closely with CPP/CFPWV group membership, resulting in collinearity among predictor variables. Fifth, measurements for echocardiographic LVH were performed one examination cycle (approximately three years) preceding the CFPWV measurements.

Perspectives

Mismatch between pulse pressure and arterial stiffness is common in the community and caution should therefore be taken if contemplating on using pulse pressure as a surrogate marker of arterial stiffness. CPP may modify the effects of CFPWV on cardiovascular risk, with greatest vascular risk being experienced when both CPP and CFPWV are elevated.

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Disclosures

Gary F. Mitchell is owner of Cardiovascular Engineering, Inc., a company that designs and manufactures devices that measure vascular stiffness. The company uses these devices in clinical trials that evaluate the effects of diseases and interventions on vascular stiffness. The remaining authors report no conflicts.

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Novelty and Significance

What is new?

- The prevalence and prognostic significance of a mismatch between central pulse pressure and arterial stiffness (pulse wave velocity; CFPWV) in the community have not been well studied.
- Such information could be of interest to elucidate the validity of central pulse pressure (CPP) as a surrogate measure of arterial stiffness and to help clinicians understand the relative and conjoint importance of CPP and arterial stiffness in the assessment and pathogenesis of cardiovascular disease (CVD) risk.

What is relevant?

- 39% of 2119 Framingham Offspring cohort participants had discordant CPP and CFPWV status
- Only participants with a high CPP with high CFPWV experienced significantly increased CVD risk and the interaction term between CPP and CFPWV status on CVD risk was significant.

Summary

Our results demonstrate that pulse pressure-arterial stiffness mismatch is common in the community. CFPWV may modify the association of CPP with CVD risk, with greatest risk being observed in those with elevated CPP and CFPWV.

Figure Legends

Figure 1. Correlation between central pulse pressure and carotid-femoral pulse wave velocity.

Figure 2. Cumulative incidence of cardiovascular events in groups by central pulse pressure and pulse wave velocity status (truncated at 13 years after baseline). CVD, cardiovascular disease; CPP, central pulse pressure; CFPWV, pulse wave velocity. P for log-rank test <0.001. Data are for the unadjusted analysis.

Tables

Table 1. Baseline characteristics by central pulse pressure and pulse wave velocity status.

Characteristic	All	Low central PP with low CFPWV	Low central PP with high CFPWV	High central PP with low CFPWV	High central PP with high CFPWV
<i>n</i>	2119	643	417	415	644
Age, y	60.4±9.5	60.6±9.4	60.2±9.6	60.3±9.5	60.6±9.5
Women, n	1203 (56.6%)	362 (56.3%)	237 (56.8%)	237 (57.1%)	364 (56.5%)
BMI, kg/m ²	27.3±4.6	26.3±4.0	27.7±4.7	26.6±4.2	28.5±4.9
Central PP, mmHg	50.6±16.3	39.5±8.3	39.7±9.0	59.2±13.4	63.0±15.4
CFPWV, m/s	9.9±3.4	8.1±1.6	11.2±3.4	8.3±1.6	12.0±4.0
Systolic BP, mmHg	127±19	116±14	125±16	126±17	139±20
Diastolic BP, mmHg	74±10	71±9	76±10	73±8	78±10
Antihypertensive therapy, n	644 (30.4%)	142 (22.1%)	118 (28.3%)	106 (25.5%)	278 (43.2%)
Diabetes mellitus, n	186 (8.8%)	32 (5.0%)	51 (12.2%)	21 (5.1%)	82 (12.7%)
Current smoker, n	286 (13.5%)	94 (14.6%)	53 (12.7%)	57 (13.7%)	82 (12.7%)
Cholesterol, mmol/l	5.2±0.9	5.2±0.9	5.2±0.9	5.2±0.9	5.3±1.0
HDL cholesterol, mmol/l	1.4±0.4	1.5±0.5	1.4±0.4	1.5±0.4	1.4±0.4
Heart rate, 1/min	64.9±10.7	63.0±9.5	68.4±10.3	60.9±9.8	67.0±11.4

BP, elevated blood pressure; PP, pulse pressure; CFPWV; pulse wave velocity; HDL, high density lipoprotein. Values are mean±SD for continuous variables or n (%) for categorical variables.

Table 2. Odds ratios for echo- or electrocardiographic left ventricular hypertrophy in groups by central pulse pressure and pulse wave velocity status ($n=1579$).

Group	<i>n</i>	Participants with LVH (%)	Unadjusted OR (95% CI)	<i>P</i>	Multivariable OR (95% CI)	<i>P</i>
Low CPP with low CFPWV	484	57 (11.8)	1.00 (reference)		1.00 (reference)	
Low CPP with high CFPWV	313	51 (16.3)	1.46 (0.97-2.19)	0.07	1.36 (0.88-2.09)	0.16
High CPP with low CFPWV	324	50 (15.4)	1.37 (0.91-2.06)	0.13	1.35 (0.89-2.07)	0.16
High CPP with high CFPWV	458	96 (20.9)	1.99 (1.39-2.84)	<0.001	1.86 (1.27-2.72)	0.001

CFPWV, pulse wave velocity; LVH, left ventricular hypertrophy; OR, odds ratio; CI, confidence interval. Multivariable model is adjusted for age, sex, body mass index, smoking status, diabetes mellitus, heart rate, total cholesterol, and HDL cholesterol. Left ventricular hypertrophy was defined as presence of Cornell voltage > 20 mV in women and > 28 mV in men, left ventricular mass index >115 g/m² in men and >95 g/m² in women, or both.

Table 3. Risk of cardiovascular events in groups by central pulse pressure and pulse wave velocity status ($n=2119$).

Group	Number of CVD events (%)	Events per 1000 person-yrs (95% CI)	Unadjusted OR (95% CI)	Multivariable OR (95% CI)
Low CPP with low CFPWV	60 (9.3)	8.4 (6.5-10.8)	1.00 (reference)	1.00 (reference)
Low CPP with high CFPWV	56 (13.4)	12.4 (9.5-16.0)	1.48 (1.03-2.13)*	1.21 (0.83-1.76)
High CPP with low CFPWV	29 (7.0)	6.1 (4.3-8.8)	0.73 (0.47-1.14)	0.76 (0.49-1.19)
High CPP with high CFPWV	101 (15.7)	14.8 (12.2-18.0)	1.79 (1.30-2.46)†	1.52 (1.10-2.11)*

CFPWV, pulse wave velocity; CI, confidence interval; CVD, cardiovascular disease. Multivariable model adjusted for age, sex, body mass index, smoking status, diabetes mellitus, heart rate, total cholesterol and HDL cholesterol. * $P<0.05$; † $P<0.001$. The c-statistic for a model that included only the covariates was 0.777 (95% CI, 0.745-0.804). Adding the 4-category exposure variable increased the model c-statistic to 0.781 (95% CI, 0.754-0.808). The p-value for the difference between c-statistics was 0.27.