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CARDIOVASCULAR RISK

High Central Pulse Pressure Is Independently Associated With Adverse Cardiovascular Outcome

The Strong Heart Study

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Objectives This study was designed to facilitate clinical use of central pulse pressure (PP). We sought to determine a value that might predict adverse outcome and thereby provide a target for assessment of intervention strategies.

Background We previously documented that central PP more strongly relates to carotid hypertrophy and extent of atherosclerosis and, more importantly, better predicts incident cardiovascular disease (CVD) than brachial PP.

Methods Radial applanation tonometry was performed in the third Strong Heart Study examination to determine central blood pressure. Cox regression analyses were performed using pre-specified covariates and quartiles of central and brachial PP.

Results Among 2,405 participants without prevalent CVD, 344 suffered CVD events during 5.6 ± 1.7 years. Quartiles of central PP ($p < 0.001$) predicted outcome more strongly than quartiles of brachial PP ($p = 0.052$). With adjustment for covariates, only the event rate in the fourth quartile of central PP (≥50 mm Hg) was significantly higher than that in the first quartile (hazard ratio [HR]: 1.69, 95% confidence interval [CI]: 1.20 to 2.39, $p = 0.003$). Central PP ≥50 mm Hg was related to outcome in both men (HR: 2.06, 95% CI: 1.39 to 3.04, $p < 0.001$) and women (HR: 2.03, 95% CI: 1.55 to 2.65, $p < 0.001$); in participants with (HR: 1.84, 95% CI: 1.41 to 2.39, $p < 0.001$) and without diabetes (HR: 1.91, 95% CI: 1.29 to 2.83, $p = 0.001$); and in individuals younger (HR: 2.51, 95% CI: 1.59 to 3.95, $p < 0.001$) and older (HR: 1.53, 95% CI: 1.19 to 1.97, $p = 0.001$) than the age of 60 years.

Conclusions Central PP ≥50 mm Hg predicts adverse CVD outcome and may serve as a target in intervention strategies if confirmed in other populations and in prospective studies. (J Am Coll Cardiol 2009;54:1730–4) © 2009 by the American College of Cardiology Foundation

Central (aortic) and brachial (peripheral) systolic and pulse pressures differ due to pulse wave amplification, a function of vascular compliance and wave reflection (1). The difference between central and brachial systolic and pulse pressures decreases with age and other cardiovascular disease (CVD) risk factors that cause vascular stiffening (2,3). Central arterial pressure more closely reflects the load placed on the left ventricle and the coronary and cerebral vasculature. Thus, central blood pressure (BP) should be a more accurate marker of risk and an appropriate target for assessment of efficacy of intervention strategies.

In the population-based SHS (Strong Heart Study) trial, we demonstrated that pulse pressure (PP) was more strongly related to vascular hypertrophy and extent of atherosclerosis than was systolic pressure and that central PP was more strongly related to these subclinical manifestations of CVD than was brachial PP (4). More importantly, central PP as a continuous variable better predicted incident CVD than did brachial PP. We subsequently reported similar findings in a separate population-based study of elderly community-dwelling individuals living in Dicomano, Italy (5). However, to facilitate use of central PP in intervention strategies and clinical practice, a value that may be of clinical utility in predicting adverse clinical outcome is needed. To this end, we have extended follow-up of SHS participants for an

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additional year and examined the relation of quartiles of brachial and central PPs to cardiovascular outcomes.

Methods

Study population. The SHS study is a population-based, longitudinal study of prevalent and incident CVD in American Indians that began in 1989. Details of the study design have been previously published (6). At the third examination (1997 to 1999), radial artery applanation tonometry to estimate central BP was added to the study protocol.

Blood was drawn following a 12-h fast to determine lipids, fasting plasma glucose, creatinine, and fibrinogen. Diabetes was defined by the American Diabetes Association criteria (7) as fasting plasma glucose ≥7.0 mmol/l (126 mg/dl) or by use of hypoglycemic treatment. Brachial BP was measured in triplicate in the right arm by cuff and mercury sphygmomanometer after the participant had rested in a seated position for 5 min; the average of the last 2 measurements was used as brachial BP. Then, PP was calculated as the difference between systolic and diastolic pressures. Hypertension was defined by the criteria of the Seventh Report of the Joint National Committee (8) as systolic pressure ≥140 mm Hg, diastolic pressure ≥90 mm Hg, or current use of antihypertensive medication.

Participants free of clinically overt CVD, including atrial fibrillation, at the third SHS study examination were included in analyses. The occurrence of fatal and nonfatal CVD events (myocardial infarction, coronary heart disease, sudden death, congestive heart failure, and stroke) was tabulated during follow-up, as previously described (9,10). The CVD events were determined from medical records, autopsy reports, and informant interviews; all materials were independently reviewed by physician members of the SHS study's morbidity and mortality committees. Follow-up through December 2005 was 99.8% complete for mortality and 99.2% complete for morbid events. The Indian Health Service Institutional Review Board and institutional review boards of the participating institutions and participating tribes approved the study; informed consent was obtained from all participants.

Applanation tonometry. As previously described (4), radial arterial pressure waveforms were obtained by applanation tonometry using the SphygmoCor device (AtCor Medical, Sydney, Australia). Applanation tonometry has been validated to yield accurate estimates of intra-arterial PP by comparison with simultaneous invasive pressure recordings (11,12).

Statistical analyses. Data are presented as mean ± SD. Means of continuous variables were compared using the Student *t* test for independent samples. Categorical variables were compared by chi-square analysis. Relations of quartiles of central and brachial PP to cardiovascular events were determined in Cox regression analyses. Logistic regression analysis was performed to determine the independent correlates of central PP ≥50 mm Hg. Differences in systolic and diastolic pressures across PP quartiles were assessed by analysis of variance. Two-tailed $p < 0.05$ was considered significant. Statistical analyses were performed with SPSS version 12.0 (SPSS Inc., Chicago, Illinois).

Abbreviations and Acronyms

BP = blood pressure
CVD = cardiovascular disease
PP = pulse pressure

Results

Population characteristics and CVD outcomes. Among the 2,405 participants free of prevalent CVD at the time of examination, 344 suffered fatal and nonfatal CVD events (61 myocardial infarctions, 163 definite coronary heart diseases, 49 strokes, 71 congestive heart failures) during a mean follow-up of 5.6 ± 1.7 years. Mean age was 63 ± 8 years (range 51 to 84 years), 65% were women, and body mass index was 31.3 ± 6.6 kg/m^2. Hypertension was present in 52% of the population, of whom 68% were taking antihypertensive medications. Diabetes was present in 47% of the population, and 28% were active smokers.

Quartiles of PP and CVD outcomes. Cox regression models of traditional CVD risk factors and quartiles of brachial and central PP are presented in Table 1. Quartiles of central PP ($p < 0.001$) were much more predictive of outcome than quartiles of brachial PP ($p = 0.052$). Event rates in the first to fourth quartiles of central PP were 11.0%, 9.9%, 15.0%, and 21.3% ($p < 0.001$ for trend). With adjustment for covariates, only the hazard rate in the fourth quartile (central PP ≥50 mm Hg) was significantly higher than that in the first quartile (hazard ratio [HR]: 1.69, 95% confidence interval [CI]: 1.20 to 2.39, $p = 0.003$). Event rates in the fourth quartile were likewise significantly higher than in the second quartile ($p < 0.001$) and tended to be higher than in the third quartile ($p = 0.066$). Furthermore, the hazard rate in the fourth quartile was significantly higher than that of the other quartiles combined (HR: 1.57, 95% CI: 1.22 to 2.02, $p < 0.001$). Hazards ratios for quartiles of brachial and central PPs are depicted in Figure 1. Addition of use of antihypertensive medications or substitution of high- and low-density lipoprotein cholesterol for the ratio in secondary analyses did not alter results. Furthermore, addition of indicator variables for use of either beta-blocking agents or statins did not alter results. Across both central and brachial PP quartiles, there were significant stepwise increases in systolic ($p < 0.001$) but not diastolic pressures ($p > 0.20$, data not shown).

Correlates of central PP ≥50 mm Hg. Significant differences between the fourth quartile and the other quartiles led us to perform additional analyses focusing on this quartile (Table 2). In multivariable analysis, central PP ≥50 mm Hg was independently related to female sex, age, plasma creatinine, the presence of diabetes and hypertension (or brachial systolic pressure), and lower body mass index and heart rate, but not to current smoking, fibrinogen, or cholesterol/high-

Table 1 Multivariable Cox Regression Models of Relation of Traditional Risk Factors and Central and Brachial PP Quartiles to Cardiovascular Outcome

Variable	HR (95% CI)	Variable	HR (95% CI)
Age, yrs	1.054 (1.037–1.070)*	Age, yrs	1.051 (1.035–1.067)*
Male, %	1.212 (0.948–1.50)	Male, %	1.266 (0.990–1.620)
BMI, kg/m^2	0.987 (0.968–1.006)	BMI, kg/m^2	0.990 (0.971–1.009)
Current smoking, %	1.372 (1.052–1.788)†	Current smoking, %	1.355 (1.041–1.763)†
Cholesterol/HDL	1.058 (0.988–1.133)	Cholesterol/HDL	1.062 (0.991–1.138)
Creatinine, mg/dl	1.172 (1.094–1.256)*	Creatinine, mg/dl	1.164 (1.086–1.247)*
Fibrinogen, mg/dl	1.001 (1.000–1.002)‡	Fibrinogen, mg/dl	1.001 (1.000–1.002)†
Diabetes mellitus, %	2.536 (1.974–3.258)*	Diabetes mellitus, %	2.48 (1.931–3.186)*
Heart rate, beats/min	1.014 (1.004–1.024)‡	Heart rate, beats/min	1.018 (1.008–1.029)§
Brachial PP quartiles	1.117 (0.999–1.248)	Central PP quartiles	1.229 (1.098–1.376)*
First quartile (≤45 mm Hg)		First quartile (≤31 mm Hg)	
Second quartile (46–54 mm Hg)	1.052 (0.738–1.499)	Second quartile (32–39 mm Hg)	0.89 (0.62–1.29)
Third quartile (55–66 mm Hg)	1.210 (0.860–1.704)	Third quartile (40–49 mm Hg)	1.28 (0.91–1.82)
Fourth quartile (≥67 mm Hg)	1.370 (0.967–1.942)	Fourth quartile (≥50 mm Hg)	1.69 (1.20–2.39)§

*p < 0.001; †p < 0.05; ‡p < 0.01; §p < 0.005.
BMI = body mass index; HDL = high-density lipoprotein; PP = pulse pressure.

density lipoprotein ratio. Central PP ≥50 mm Hg (compared with <50 mm Hg) was significantly related to outcome in both men and women, in participants with and without diabetes, and in individuals older and younger than the ages of both 60 and 65 years (Table 3).

Comparison of brachial and central PP quartiles. As shown in Table 1, both brachial and central PPs increased by roughly 10 mm Hg per quartile. In addition, there was a strong correlation between brachial and central PP ($r = 0.67$, $p < 0.001$). However, as shown in the box plots in Figure 2, there was substantial overlap of brachial PPs between quartiles of central PP. Furthermore, only 61% of individuals in the highest brachial PP quartile fell within the highest central PP quartile and only 58% of individuals in the lowest brachial PP quartile fell within the lowest central PP quartile.

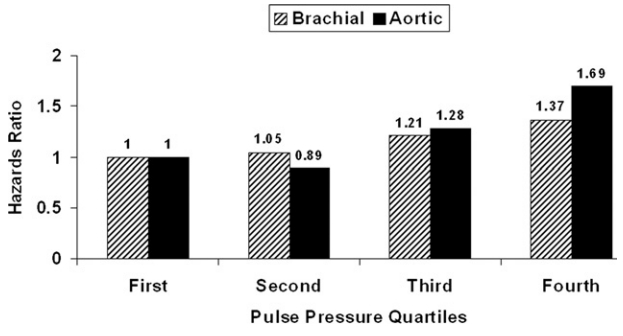

Figure 1 Hazards Ratios for Incident Cardiovascular Event

Hazards ratios for incident cardiovascular events in 2,405 individuals initially free of clinical cardiovascular disease are stratified by quartiles of brachial **(hatched bars)** and central aortic **(solid bars)** pulse pressures (PPs). Quartiles of central PP ($p < 0.001$) predicted outcome more strongly than quartiles of brachial PP ($p = 0.052$). Only the event rate in the fourth central PP quartile (PP ≥50 mm Hg) was significantly higher than in the first quartile ($p = 0.003$).

Discussion

The present study documents the superiority of central over brachial PP for prediction of cardiovascular events in the SHS study population and suggests a value that might be of clinical utility if confirmed in other populations and in prospective studies. Importantly, this value, derived from the distribution within our study population rather than from a formal, adequately-powered analysis to determine a threshold of increased risk, performed well in clinically relevant subsets of the SHS study population suggesting that it is robust and not based on skewed distribution.

From a pathophysiologic perspective, it is not surprising that central BP better correlates with target organ damage and cardiovascular outcomes than brachial BP does because it more accurately reflects vascular load on the left ventricle and cerebral and coronary vasculature. This concept has

Table 2 Comparison of Demographic Variables and Cardiovascular Disease Risk Factors in Participants With Central PP <50 mm Hg Versus ≥50 mm Hg

Variable	PP <50 mm Hg (n = 1,791)	PP ≥50 mm Hg (n = 614)	p Value
Age, yrs	61.6 ± 7.0	66.6 ± 8.0	<0.001
Male, %	38.7	23.7	<0.001
BMI, kg/m^2	31.5 ± 6.8	30.9 ± 6.1	0.049
Hypertension, %	43.3	77.2	<0.001
Diabetes mellitus, %	44.9	53.5	<0.001
Current smoking, %	29.5	22.1	<0.001
Brachial SBP, mm Hg	126 ± 16	146 ± 21	<0.001
Brachial DBP, mm Hg	75 ± 10	74 ± 11	0.126
Brachial PP, mm Hg	51 ± 13	73 ± 18	<0.001
Heart rate, beats/min	70 ± 11	66 ± 10	<0.001
Total/HDL cholesterol	4.8 ± 1.5	4.6 ± 1.5	0.016
Creatinine, mg/dl	0.8 (0.2)	0.8 (0.3)	0.004*
Fibrinogen, mg/dl	380 ± 121	396 ± 126	0.007

*Compared by Mann-Whitney *U* test and reported as median (interquartile range).
DBP = diastolic blood pressure; SBP = systolic blood pressure; other abbreviations as in Table 1.

Table 3 Performance of Central PP ≥50 mm Hg for Prediction of Cardiovascular Outcome in Population Subsets

Variable	n	HR (95% CI)	p Value	Interaction p Value
Sex				0.94
Men	838	2.06 (1.39–3.04)	<0.001	
Women	1,567	2.03 (1.55–2.65)	<0.001	
Diabetes mellitus				0.98
Absent	1,259	1.91 (1.29–2.83)	0.001	
Present	1,122	1.84 (1.41–2.39)	<0.001	
Age, yrs				
<60	994	2.51 (1.59–3.95)	<0.001	0.079
≥60	1,411	1.53 (1.19–1.97)	0.001	
<65	1,559	1.91 (1.39–2.64)	<0.001	0.47
≥65	846	1.64 (1.20–2.22)	0.002	

CI = confidence interval; PP = pulse pressure.

only recently been possible to test with the development of accurate noninvasive techniques permitting pulse wave analysis and determination of central BP (11–13). Thus, several small studies in select populations have documented stronger relations of central than brachial BP to carotid artery intima-media thickness (14), severity of coronary artery disease (15), and all-cause mortality in patients with end-stage renal disease (16). In the large, population-based SHS study, central pressure, particularly PP, was more strongly related to vascular hypertrophy and extent of atherosclerosis, as well as to incident CVD, than was brachial pressure (4). This observation has been confirmed in another population-based study (ICARe [Insufficienza Cardiaca negli Anziani Residenti] Dicomano Study) of elderly individuals (5), despite the decrease in pressure amplification with age and associated lesser difference, on average, between central and brachial pressures.

Furthermore, reduction of central pressure may add to reduction of brachial pressure in improving clinical outcome in the treatment of hypertension. In the CAFE (Conduit Artery Function Evaluation) substudy of the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) hypertension trial (17), brachial BP was reduced to a similar extent in both the atenolol with/without thiazide and amlodipine with/without perindopril arms, whereas central systolic and pulse pressures were reduced significantly more by amlodipine-based treatment. Both brachial and central PPs were similarly related (chi square = 4.1 for both) to a post-hoc–defined composite outcome (new cardiovascular events, cardiovascular procedures, renal impairment) independent of other risk factors (17). It is uncertain whether the more favorable outcome associated with the amlodipine-based arm in the overall ASCOT (18) was related to the greater central BP lowering with this regimen. This possibility, however, is supported by observations that beneficial effects of regimens based on calcium-channel and angiotensin-receptor blockade therapy on outcome were independent of lowering of brachial BP (19,20).

The findings of the current study complement the recent report from the Anglo-Cardiff Collaborative Trial II (2), wherein levels of brachial systolic pressure based on BP classifications were compared with aortic systolic pressures in 6,779 healthy normotensive or untreated hypertensive individuals. There was substantial overlap of aortic systolic pressures between individuals with normal or high normal pressures and those with stage 1 hypertension based on brachial systolic pressure, indicating that central systolic pressure cannot be inferred from brachial systolic pressure. These data also indicate the potential for undertreatment or overtreatment of hypertension based on brachial BP targets, if indeed central BP is a more accurate marker of risk. Our data provide further confirmation of the inability to accurately estimate central pressure from brachial pressure.

Study limitations. The independent prognostic utility of central PP needs to be confirmed in larger studies with more outcome events in which it will be possible to apply more formal methods for threshold estimation and to assess formally the costs and benefits of treatment based on such cut points. Whereas our study population is limited to American Indians, our findings are likely to be highly applicable to the general U.S. population given its increasing prevalence of obesity and diabetes. Furthermore, the same traditional risk factors for CVD in the general U.S. population have been shown to be operative in the SHS study population (9).

Conclusions

This and other recent studies provide strong evidence for the superiority of central BP, particularly PP, to brachial BP

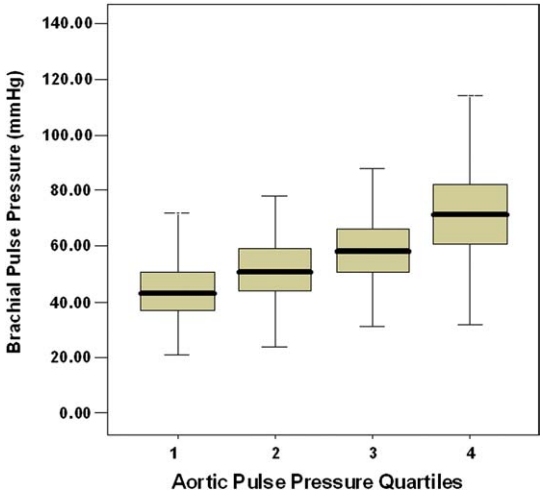

Figure 2 Box Plots of Brachial PP per Quartile of Central Aortic PP

Box plots (median, quartiles, and range) of brachial pulse pressure (PP) stratified by quartile of central aortic PP demonstrate substantial overlap of brachial PP values across quartiles and highlight the inability to accurately estimate central pressure from brachial pressure.

in correlation with subclinical vascular disease and association with CVD events. Furthermore, preliminary evidence suggests that achievement of a lower central BP for a given level of brachial BP may be more effective in reducing CVD target organ damage and morbidity and mortality. These findings lend strong support for prospective examination of central BP thresholds for prediction of CVD events and potential treatment targets in future trials (21).

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