Central Pulse Pressure in Chronic Kidney Disease
A Chronic Renal Insufficiency Cohort Ancillary Study


Abstract—Central pulse pressure (PP) can be noninvasively derived using the radial artery tonometric methods. Knowledge of central pressure profiles has predicted cardiovascular morbidity and mortality in several populations of patients, particularly those with known coronary artery disease and those receiving dialysis. Few data exist characterizing central pressure profiles in patients with mild-moderate chronic kidney disease who are not on dialysis. We measured central PP cross-sectionally in 2531 participants in the Chronic Renal Insufficiency Cohort Study to determine correlates of the magnitude of central PP in the setting of chronic kidney disease. Tertiles of central PP were <36 mm Hg, 36 to 51 mm Hg, and >51 mm Hg with an overall mean (±SD) of 46±19 mm Hg. Multivariable regression identified the following independent correlates of central PP: age, sex, diabetes mellitus, heart rate (negatively correlated), glycosylated hemoglobin, hemoglobin, glucose, and parathyroid hormone parathyroid hormone concentrations. Additional adjustment for brachial mean arterial pressure and brachial PP showed associations for age, sex, diabetes mellitus, weight, and heart rate. Discrete intervals of brachial PP stratification showed substantial overlap within the associated central PP values. The large size of this unique chronic kidney disease cohort provides an ideal situation to study the role of brachial and central pressure measurements in kidney disease progression and cardiovascular disease incidence. (Hypertension. 2010;56:518-524.)

Key Words: elasticity ■ epidemiology ■ diabetic nephropathies ■ hemodynamics ■ sex

Chronic kidney disease (CKD) confers a substantial risk of cardiovascular target organ damage, especially when kidney function falls below 60 mL/min per 1.73 m², corresponding with National Kidney Foundation stages 3, 4, and 5,1,2 that appears inadequately explained by traditional cardiovascular risk factors.3 One goal of the Chronic Renal Insufficiency Cohort (CRIC) Study is to examine traditional and novel risk factors for cardiovascular target organ damage and for progressive loss of kidney function in a diverse population with CKD.4 High blood pressure is known to influence the course of kidney disease progression.5 In recent years some data suggest that the pulse pressure (PP; the difference of systolic and diastolic blood pressures) as derived from the standard brachial blood pressure measurement is better correlated than traditional blood pressure measures (systolic and diastolic) to the rate at which estimated glomerular filtration rates (eGFRs) decline in CKD.6

Measurements of central PP (CPP) have been used for >2 decades in an attempt to further improve on the predictive value of standard brachial blood pressure measurements.7 Studies have shown that there is substantial variability in the level of blood pressure in the aorta between people with similar brachial blood pressure measurements that is difficult to estimate without performing either an invasive or a noninvasive assessment of aortic pressure.8 The increasing use of validated noninvasive devices that estimate central blood pressure profiles based on radial artery tonometry has facilitated the incorporation of these measurements into prospective cohort studies, such as the AngloCardiff Collaborative Trial,9 the Strong Heart Study,10 and the CRIC Study.

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M.P.J. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Correspondence to Raymond R. Townsend, University of Pennsylvania, 122 Founders Building, 3400 Spruce St, Philadelphia, PA 19104. E-mail townsend@mail.med.upenn.edu

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(which included measurements of central [aortic] PP using radial artery tonometry as an ancillary study beginning in 2005).

Aging has a marked effect on the relationship between CPP and brachial PP, as does female sex. However, little is known about the determinants of central aortic pressure pulse in the setting of CKD. Thus, we aimed to determine clinical factors independently associated with CPP in CKD and to evaluate how well brachial PP correlates with CPP in a large, ethnically diverse population of men and women with CKD.

Methods
Participants
Enrollment characteristics of the CRIC Study have been described previously in detail. Central aortic PP measurements were adopted into the CRIC protocol beginning at the second annual follow-up visit, and all of the participants enrolled in the CRIC Study were invited to become part of this ancillary protocol. The procedures were approved by the institutional review boards at the 7 clinical centers, and all of the participants provided written informed consent.

Procedures
CPP measurements were performed supine after ≥5 minutes of rest using the SphygmoCor PVx System (AtCor Medical) via the right radial artery at all of the CRIC sites. All of the personnel were trained and certified to take blood pressure measurements in the dominant arm with a Tyco aneroid sphygmomanometer using American Heart Association standards and to perform the central pressure measurements using radial artery tonometry. The operator captured 10 seconds of stable radial artery waveform. PP was defined as the difference between the systolic and the diastolic blood pressures in millimeters of mercury. When these data were derived from standard blood pressure measurement it was brachial PP; when derived by algorithm from the radial artery waveform it was CPP.

Laboratory Measures
Hemoglobin values were measured directly at the laboratories of each of the centers. Standard laboratory testing (eg, serum creatinine, glucose, uric acid, calcium, and phosphorus) was performed at the CRIC central laboratory in the University of Pennsylvania. The eGFR was determined according to the abbreviated Modification of Diet in Renal Disease formula using creatinine values calibrated to the Cleveland Clinic Laboratory. Some laboratory results were only available at the baseline visit and are noted in Table 1.

Race
Race was classified as American Indian/Alaskan Native, Asian/Asian American, black, Native Hawaiian/Other Pacific Islander, or white based on participant self-report.

CPP Data
The data reported here represent central aortic PP measures obtained on participants whose second annual follow-up visit occurred on or before March 31, 2009. The augmentation index is a ratio that reflects the portion of the CPP derived from pulse wave reflection.

Statistical Analyses
Continuous data are presented as mean±SD. Categorical variables are expressed as proportions. Independent variables were prespecified for analyses based on previous studies showing a relation to CPP (eg, age or systolic blood pressure) or because they may affect PP and are known to be affected by kidney disease (eg, calcium or hemoglobin). A plot of CPP in our population showed a substantial rightward skew, and analyses were performed on both raw CPP data and natural log-transformed data. Univariable regression models for CPP were used to assess the relationship between CPP and the selected variable. We performed multivariable linear regression to examine the associations between variables of interest and CPP. All of the parameters significant at a P≤0.20 level in univariable regression were entered into both forward and backward selection algorithms. Where variables were known to be strongly correlated with each other (eg, serum creatinine and eGFR) only the one with the stronger association was entered. Variables significant at the P≤0.05 level in the multivariable model were retained in the final model.

We considered 2 multivariable regression models: one with natural log-transformed (Ln)CPP as the outcome, without measures of brachial blood pressure as predictor and one with LnCPP as the outcome, including measures of natural log-transformed brachial PP and brachial mean arterial pressure as predictors. All of the multivariable models were adjusted for clinical site. Analyses were executed as in SAS 9.1 (SAS Institute).

Results
Demographic characteristics of all of the participants eligible for CPP measurement at the year 2 follow-up visit of the CRIC cohort are shown in Table 1, overall and stratified by those who did or did not have a successful CPP measurement. We anticipated data loss on ∼20% of participants (because of arrhythmia and other difficulties with waveform capture), and we were unable to obtain or use measurements on 746 (22.7%) of 3277 eligible participants.

Figure 1 shows the frequency distribution of CPP determinations in the overall sample and stratified by diabetes mellitus status. The tertiles of the CPP were <36 mm Hg, 36 to 51 mm Hg, and >51 mm Hg with an overall mean value of 46±19 (±SD).

Figure 2 presents mean CPP values for the cohort by strata of renal function that correspond with CKD stages. Given the large number of participants in CKD stage 3 (30 to 59.9 mL/min per 1.73 m², we divided this stage into stage 3A [45 to 59.9 mL/min per 1.73 m²] and 3B [30 to 44.9 mL/min per 1.73 m²]. Each 10 mL/min per 1.73 m² decrement in eGFR was associated with an increase in CPP of ∼2.5 mm Hg (Table 2). A CPP of 50 mm Hg was shown recently to be a significant independent predictor of cardiovascular outcomes in the Strong Heart Study, where it represented the lower boundary of the highest quartile. Figure 2 shows the increasing proportion (percentage) of those within each declining eGFR strata in CRIC that had a CPP ≥50 mm Hg.

Table 2 displays the results of univariable regression of demographic, hemodynamic, and laboratory data of our participants on CPP. The strongest univariable associations with CPP were presence of diabetes mellitus, brachial PP and brachial systolic blood pressure, decade of age, female sex, nonwhite ethnicity, serum calcium, the number of antihypertensive medications taken regularly, and lower eGFR level. Multivariable analyses are described in Tables 3 through 5. In the absence of an adjustment for brachial blood pressure (Table 3), there were independent contributions to the LnCPP that included age (10 years), sex, diabetes mellitus, heart rate, glycylsylated hemoglobin, hemoglobin, glucose, and serum parathyroid hormone concentration at baseline. When brachial PP and brachial mean arterial pressure were incorporated into the model (Table 4), sex was the strongest non-blood pressure predictor term for LnCPP followed by age (10 years), diabetes mellitus, weight (per 10 kg), and heart rate. Weight and heart rate had negative influences on LnCPP.
Glucose, glycosylated hemoglobin, hemoglobin, and parathyroid hormone concentrations were no longer independently associated with LnCPP. Table 5 shows that most of the variability in the multivariable model predicting LnCPP is explained from the natural log-transformed brachial PP. In the supplemental Table (please see the online Data Supplement at http://hyper.ahajournals.org), we expanded our multivariable regression incorporating the time to central wave reflection and augmentation index into the model to pursue these avenues as possible mechanisms by which these clinical factors might influence CPP, demonstrating that addition of augmentation index may mediate the effect of several clinical predictors of CPP, whereas aortic time to central wave reflection was not a predictor of CPP in univariate or multivariable analysis. We refer the reader to the online Data Supplement available at http://hyper.ahajournals.org for further details. When discrete intervals of brachial PPs were plotted against their corresponding levels of CPP, there was a substantial overlap within the associated CPP values (Figure 3).

Discussion

We performed central aortic pressure measurements on a population of 2531 participants recruited specifically with impaired kidney function but not on dialysis, of whom approximately half were diabetic. Our results indicate that CPP values are positively and independently correlated with increasing brachial PP, older age, female sex, and the presence of diabetes mellitus in a population of participants with CKD. In addition we found a significant, although weaker, negative correlation between weight and heart rate, as noted in some other studies of central blood pressure. Our results confirm a substantial overlap in CPPs when participants are stratified by discrete levels of brachial-derived PPs (Figure 3). This report adds to the literature, because it...
examined a uniquely large cohort with a spectrum of kidney dysfunction at high cardiovascular risk, a population infrequently studied using central pressure measures. Reproducibility of central blood pressure measurements has been shown by others in non-CKD populations.19,20 In addition, our previous work in this CKD population, as well as that of others,21,22 shows good reproducibility supporting the validity of these findings.

Central pressure measurements offer the opportunity to estimate the PP that the left ventricle and aorta actually “see.”7 As the pressure wave travels from the elastic central vessels into the muscular arterial conduits, there is a varying degree of increase (“amplification”) in the systolic pressure, whereas there is little change in diastolic or mean arterial pressure in the circulation. This rise in blood pressure is often expressed as an amplification ratio (defined as the PP in the brachial artery divided by the central aortic PP).8 As shown in our study and by others, knowledge of the brachial blood pressure is an imperfect estimate of central blood pressure levels8 (Figure 3).

Studies comparing brachial PP compared with CPP using outcomes such as left ventricular mass or the occurrence of cardiovascular target organ damage (carotid intima-media thickness or death) have shown independent predictive value for CPP measurements.10,23–26 On the other hand, a recent meta-analysis of cardiovascular outcomes in longitudinal studies in which central hemodynamic measures were incorporated showed that, whereas both CPP and the augmentation index predicted cardiovascular events and mortality, only the augmentation index did so independent of the brachial blood pressure.27 The kidney is particularly vulnerable to increased pulsatile stress, as reviewed recently by Loutzenhiser et al.28 Patients with CKD1,29 and end-stage renal disease have substantial cardiovascular risk.30,31 In a study of 349 subjects with CKD stages 4/5, a brachial PP of >80 mm Hg was an independent predictor of cardiovascular death or progression to end-stage renal disease requiring dialysis.32 In a non-CKD population, the Strong Heart Study, CPP measures were superior to brachial PP in predicting carotid intima-media thickness and cardiovascular outcomes.10 A second analysis of the Strong Heart Study data, including additional follow-up time, derived a CPP of ≥50 mm Hg as a clinical meaningful threshold for increased cardiovascular target organ damage.17 For that reason we chose to show the proportion of our populations, stratified by kidney function, with a CPP >50 mm Hg, recognizing that our study is observational, whereas the Strong Heart Study data were longitudinal (Figure 2). The recognition that reduced kidney function in CKD is related strongly to cardiovascular disease morbidity and mortality has stimulated an ongoing search for biological

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**Figure 1.** Plot of CPP in 5-mm Hg increments along x axis and number of participants in that increment on y axis. Green bars are all CRIC participants (n=2531). Yellow bars are those without (n=1343) and ochre bars are those with (n=1188) diabetes mellitus.

**Figure 2.** Top left panel plots CPP in 10-mm Hg increments among those with eGFR <30 mL/min per 1.73 m². Top right plots those with eGFR 30.0 to 44.9; bottom left plots those with eGFR of 45.0 to 59.9; and the bottom right panel depicts those with an eGFR >60.0. Arrow onset marks CPP of 50 mm Hg, and percentage indicates the portion of participants within that eGFR range with a CPP >50 mm Hg.
markers beyond traditional Framingham risk factors because these explain some but not all of the extra cardiovascular burden in CKD.1,3,3

Our study had several limitations. We were unable to successfully capture radial pulse waveforms in ~23% of our CKD participants, and there were differences in patient characteristics between those with versus without successful waveforms. Importantly, the brachial PP was identical in both groups. Some laboratory values are only available at the baseline visit, which occurred ~2 years before the first CPP measurement, and these may have changed between baseline and the second year follow-up visit. This caveat applies especially to glycosylated hemoglobin and serum parathyroid

Table 3. Multivariable Regression Model for LnCPP (No Adjustment for Brachial Blood Pressure)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (SE)</th>
<th>( R^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, /10 y</td>
<td>0.13 (0.01)</td>
<td>0.010</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, yes</td>
<td>0.09 (0.02)</td>
<td>0.020</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>-0.01 (0.00)</td>
<td>0.011</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex, Male</td>
<td>-0.08 (0.01)</td>
<td>0.014</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemoglobin A1C, %</td>
<td>0.03 (0.01)</td>
<td>0.014</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>-0.04 (0.00)</td>
<td>0.007</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>0.00 (0.00)</td>
<td>0.0079</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PTH baseline, pg/mL*</td>
<td>0.00 (0.00)</td>
<td>0.0019</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Data were available at baseline visit only.

Table 4. Multivariable Regression Model for LnCPP (Adjusted for Brachial Pulse Pressure and Mean Arterial Pressure)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (SE)</th>
<th>( R^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>LnBPP, mm Hg</td>
<td>0.98 (0.01)</td>
<td>0.020</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>0.00 (0.00)</td>
<td>0.020</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, /10 y</td>
<td>0.03 (0.00)</td>
<td>0.0079</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex, Male</td>
<td>-0.06 (0.01)</td>
<td>0.0079</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, yes</td>
<td>0.02 (0.01)</td>
<td>0.0079</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>-0.01 (0.00)</td>
<td>0.0079</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight, /10 kg</td>
<td>-0.012 (0.00)</td>
<td>0.0079</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

LnBPP indicates natural logarithm of brachial PP.
Table 5. Stepwise Change in Multivariable Model $R^2$ (From Table 4)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model $R^2$</th>
</tr>
</thead>
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<tr>
<td>LnBPP</td>
<td>0.8395081</td>
</tr>
<tr>
<td>LnBPP + MAP</td>
<td>0.8396461</td>
</tr>
<tr>
<td>LnBPP + MAP + age (/10 y)</td>
<td>0.8444102</td>
</tr>
<tr>
<td>LnBPP + MAP + age (/10 y) + diabetes mellitus (yes) + heart rate</td>
<td>0.8447113</td>
</tr>
<tr>
<td>LnBPP + MAP + age (/10 y) + diabetes mellitus (yes) + heart rate + sex</td>
<td>0.8589313</td>
</tr>
<tr>
<td>LnBPP + MAP + age (/10 y) + diabetes mellitus (yes) + heart rate + sex + weight (/10 kg)</td>
<td>0.8666858</td>
</tr>
<tr>
<td>LnBPP + MAP + age (/10 y) + diabetes mellitus (yes) + heart rate + sex + weight (/10 kg) + sex</td>
<td>0.8705188</td>
</tr>
</tbody>
</table>

LnBPP indicates natural logarithm of brachial PP; MAP, mean arterial pressure in millimeters of mercury.

References


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An erratum has been published regarding this article. Please see the attached page for:
/content/59/1/e3.full.pdf

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2010/07/23/HYPERTENSIONAHA.110.153924.DC1

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The corrected tables are below, with the discrepancies in bold.

The authors regret the errors; the basic results and conclusions of the original study are unchanged.

These corrections have been made to the current online version of the article, which is available at http://hyper.ahajournals.org/cgi/content/full/56/9/518.
### Table 1. Characteristics of CRIC Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Eligible (N=3277)</th>
<th>CPP Available</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No (N=746)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>1796 (55.0)</td>
<td>360 (48.3)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>1601 (49.1)</td>
<td>339 (45.4)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>1367 (41.9)</td>
<td>364 (48.8)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>295 (9.04)</td>
<td>43 (5.8)</td>
</tr>
<tr>
<td>Diabetes mellitus, yes, n (%)</td>
<td>1592 (48.8)</td>
<td>404 (54.2)</td>
</tr>
<tr>
<td>Age, y</td>
<td>59.7 (10.82)</td>
<td>58.2 (10.47)</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²*</td>
<td>41.3 (15.34)</td>
<td>41.2 (12.87)</td>
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<tr>
<td>Weight, kg</td>
<td>91.2 (23.02)</td>
<td>98.8 (27.09)</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>127.3 (22.11)</td>
<td>128.3 (21.5)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70.1 (12.87)</td>
<td>71.3 (12.9)</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>57.2 (19.47)</td>
<td>57.0 (19.0)</td>
</tr>
<tr>
<td>Augmentation index, male (SD)/female (SD), %</td>
<td>. . . . . .</td>
<td>24 (13)/31 (11)</td>
</tr>
<tr>
<td>Amplification ratio, male (SD)/female (SD), %</td>
<td>. . . . . .</td>
<td>1.33 (0.23)/1.25 (0.19)</td>
</tr>
<tr>
<td>Seated heart rate, bpm</td>
<td>67.9 (11.35)</td>
<td>68.9 (11.4)</td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>9.2 (0.51)</td>
<td>9.2 (0.52)</td>
</tr>
<tr>
<td>Phosphate, mg/dL</td>
<td>3.7 (0.66)</td>
<td>3.8 (0.67)</td>
</tr>
<tr>
<td>Ca²⁺phosphate product</td>
<td>33.9 (6.24)</td>
<td>34.9 (6.22)</td>
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<td>PTH, pg/mL†</td>
<td>73.1 (67.64)</td>
<td>80.9 (77.37)</td>
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<td>Urine protein, g/24H†</td>
<td>0.94 (2.09)</td>
<td>1.19 (2.63)</td>
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<tr>
<td>Hemoglobin A₁C, %†</td>
<td>6.6 (1.54)</td>
<td>6.7 (1.64)</td>
</tr>
<tr>
<td>Uric acid, mg/dL†</td>
<td>7.3 (1.9)</td>
<td>7.7 (1.9)</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>1520 (47.0)</td>
<td>385 (52)</td>
</tr>
<tr>
<td>ARB</td>
<td>918 (28.4)</td>
<td>203 (27.4)</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>1351 (41.8)</td>
<td>339 (45.8)</td>
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<tr>
<td>β-Blocker</td>
<td>1645 (50.9)</td>
<td>418 (56.5)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>1883 (58.2)</td>
<td>520 (70.3)</td>
</tr>
<tr>
<td>Other blood pressure medication</td>
<td>673 (20.8)</td>
<td>173 (23.4)</td>
</tr>
</tbody>
</table>

* Data were available at baseline only.

### Table 2. Multivariable Regression Model for LnCPP (No Adjustment for Brachial Blood Pressure)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (SE)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, /10 y</td>
<td>0.13 (0.01)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, yes</td>
<td>0.10 (0.02)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>0.08 (0.01)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex, Male</td>
<td>0.02 (0.01)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemoglobin A₁C, %</td>
<td>0.04 (0.00)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>0.00 (0.00)</td>
<td>0.0107</td>
</tr>
<tr>
<td>PTH baseline, pg/mL*</td>
<td>0.00 (0.00)</td>
<td>0.0031</td>
</tr>
</tbody>
</table>

### Table 3. Multivariable Regression Model for LnCPP (Adjusted for Brachial Pulse and Mean Arterial Pressure)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (SE)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>LnBPP, mm Hg</td>
<td>0.98 (0.01)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>0.00 (0.00)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, /10 y</td>
<td>0.03 (0.00)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex, Male</td>
<td>0.06 (0.01)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, yes</td>
<td>0.02 (0.01)</td>
<td>0.0026</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>0.00 (0.00)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight, /10 kg</td>
<td>0.012 (0.00)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

LnBPP indicates natural logarithm of brachial PP.

* Data were available at baseline only.
Table 5. Stepwise Change in Multivariable Model $R^2$
(From Table 4)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LnBPP</td>
<td>0.820781</td>
</tr>
<tr>
<td>LnBPP + MAP</td>
<td>0.8208165</td>
</tr>
<tr>
<td>LnBPP + MAP + age (/10 y)</td>
<td>0.843678</td>
</tr>
<tr>
<td>LnBPP + MAP + age (/10 y) + diabetes mellitus (yes)</td>
<td>0.8438822</td>
</tr>
<tr>
<td>LnBPP + MAP + age (/10 y) + diabetes mellitus (yes) + heart rate</td>
<td>0.8583589</td>
</tr>
<tr>
<td>LnBPP + MAP + age (/10 y) + diabetes mellitus (yes) + heart rate + sex</td>
<td>0.8664545</td>
</tr>
<tr>
<td>LnBPP + MAP + age (/10 y) + diabetes mellitus (yes) + heart rate + sex + weight (/10 kg)</td>
<td>0.8699979</td>
</tr>
</tbody>
</table>

LnBPP indicates natural logarithm of brachial PP; MAP, mean arterial pressure in millimeters of mercury.
Online Supplement

**TITLE:** Central Pulse Pressure in Chronic Kidney Disease: A CRIC Ancillary Study

**Authors:** Raymond R. Townsend\(^a\), Julio A. Chirinos\(^a\), Afshin Parsa\(^b\), Matthew A. Weir\(^b\), Stephen M. Sozio\(^c\), James P. Lash\(^d\), Jing Chen\(^e\), Susan P. Steigerwalt\(^f\), Alan S. Go\(^g\), Chi-yuan Hsu\(^g,h\), Mohammed Rafey\(^i\), Jackson T. Wright Jr.\(^j\), Mark J. Duckworth\(^a\), Crystal A. Gadegbeku\(^k\), Marshall P. Joffe\(^a,l\)

On behalf of the Chronic Renal Insufficiency Cohort (CRIC) Investigators

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\(^g\)-Division of Research, Kaiser Permanente of Northern California, Oakland, CA
\(^h\)-Division of Nephrology, Department of Medicine, University of California, San Francisco, CA
\(^i\)-Division of Nephrology and Hypertension, Cleveland Clinic Foundation, Cleveland, OH
\(^j\)-Division of Nephrology and Hypertension, University Hospitals Case Medical Center
\(^k\)-University of Michigan Health System, Department of Internal Medicine, Division of Nephrology, Ann Arbor, MI
\(^l\)-Center for Clinical Epidemiology & Biostatistics, University of Pennsylvania, Philadelphia, PA

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Supplemental Methods

Central pulse pressure measurements were performed supine after at least 5 minutes of rest using the Sphygmocor PVx System (AtCor Medical, West Ryde, Australia) via the right radial artery at all CRIC sites (1). All personnel were trained and certified to take blood pressure measurements in the dominant arm with a Tyco aneroid sphygmomanometer using American Heart Association standards and to perform the central pressure measurements using radial artery tonometry (2) (3). The operator captured 10 seconds of stable radial artery waveform. Pulse pressure was defined as the difference between the systolic and the diastolic blood pressure in mmHg. When this data was derived from standard blood pressure measurement it was brachial PP; when derived by algorithm from the radial artery waveform it was CPP. The augmentation index (AIX) was derived from the aortic pressure profile. It was defined as the ratio of the contribution of the reflected wave (in mmHg) to the aortic pressure profile divided by the central pulse pressure (and is unitless). The aortic time to wave reflection (Tr) was determined by a transformation algorithm within Sphygmocor PVx software based on detecting the time to an inflection in the aortic systolic upstroke and is presented in milliseconds. The other factors in Table 2 were determined by standard methods and direct participant query as detailed in the primary manuscript.

Supplemental Results

Supplemental Table S1 shows the univariate correlations as presented in the primary manuscript and now supplemented by the addition of the Tr (not significant) and the AIX (statistically significant), shown by gender (+SD) (new data lightly shaded for emphasis).

Supplemental Table S2 shows the same analysis as presented in Table 3b of the primary manuscript but now includes both Tr and AIX in the multivariable model. When compared with Table 3b in the primary manuscript Aortic Tr was not significant. However, the incorporation of AIX into the model appeared to account for the contributions of mean arterial pressure, age, gender, diabetes and weight in the primary manuscript.

Supplemental Table S3 shows the same analysis as presented in Table 3c of the primary manuscript. The incorporation of AIX into the model increased the estimation of CPP variability by the model from 0.87 in the primary manuscript to 0.92 in the Supplemental data.

Supplemental References


**Supplemental Table S1: Factors associated with Central Pulse Pressure**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Central Pulse Pressure</th>
<th>*Ln Central Pulse Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Est (StdErr)</td>
<td>R²</td>
</tr>
<tr>
<td>Female Sex</td>
<td>3.787 (0.75)</td>
<td>0.010</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>4.847 (0.79)</td>
<td>0.020</td>
</tr>
<tr>
<td>Other</td>
<td>6.527 (1.28)</td>
<td>0.020</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>4.700 (2.12)</td>
<td>0.025</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10.449 (0.72)</td>
<td>0.076</td>
</tr>
<tr>
<td>Age (/10 years)</td>
<td>6.083 (0.33)</td>
<td>0.123</td>
</tr>
<tr>
<td>†eGFR (/10 mL/min/1.73m²)</td>
<td>-2.483 (0.23)</td>
<td>0.045</td>
</tr>
<tr>
<td>Weight (/10 Kg)</td>
<td>-0.769 (0.18)</td>
<td>0.008</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>0.032 (0.06)</td>
<td>0.566</td>
</tr>
<tr>
<td>Waist (/10 cm)</td>
<td>0.262 (0.23)</td>
<td>0.256</td>
</tr>
<tr>
<td>‡MAP (/10 mmHg)</td>
<td>4.656 (0.26)</td>
<td>0.118</td>
</tr>
<tr>
<td>§SBP (/10 mmHg)</td>
<td>6.160 (0.12)</td>
<td>0.535</td>
</tr>
<tr>
<td>†DBP (/10 mm Hg)</td>
<td>-1.200 (0.29)</td>
<td>0.007</td>
</tr>
<tr>
<td>†Aortic Tr (msec)</td>
<td>-0.000 (0.00)</td>
<td>0.916</td>
</tr>
<tr>
<td>Augmentation Index</td>
<td>0.673 (0.03)</td>
<td>0.200</td>
</tr>
<tr>
<td>Heart Rate (/10 beats/min)</td>
<td>-3.187 (0.33)</td>
<td>0.037</td>
</tr>
<tr>
<td>Brachial PP (/10 mmHg)</td>
<td>8.574 (0.09)</td>
<td>0.795</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>-3.098 (0.21)</td>
<td>0.083</td>
</tr>
<tr>
<td>Glucose (/10 mg/dL)</td>
<td>0.575 (0.08)</td>
<td>0.021</td>
</tr>
<tr>
<td>Triglycerides (/10 mg/dL)</td>
<td>-0.060 (0.03)</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL-Cholesterol (/10 mg/dL)</td>
<td>-0.237 (0.11)</td>
<td>0.002</td>
</tr>
<tr>
<td>HDL-Cholesterol (/10 mg/dL)</td>
<td>0.333 (0.24)</td>
<td>0.001</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>-3.709 (0.75)</td>
<td>0.010</td>
</tr>
<tr>
<td>#Phosphate (mg/dL)</td>
<td>1.979 (1.43)</td>
<td>0.005</td>
</tr>
<tr>
<td>#Calcium-Phosphate (product)</td>
<td>0.324 (0.06)</td>
<td>0.011</td>
</tr>
<tr>
<td>#Parathyroid Hormone (/10 pg/mL)</td>
<td>0.343 (0.06)</td>
<td>0.014</td>
</tr>
<tr>
<td>#Urine Protein (g/day)</td>
<td>1.439 (0.21)</td>
<td>0.021</td>
</tr>
<tr>
<td>#Urine Albumin (g/day)</td>
<td>1.191 (0.26)</td>
<td>0.009</td>
</tr>
<tr>
<td>#HemoglobinA1C (%)</td>
<td>2.870 (0.24)</td>
<td>0.054</td>
</tr>
<tr>
<td>#Uric Acid (mg/dL)</td>
<td>0.848 (0.20)</td>
<td>0.007</td>
</tr>
<tr>
<td>Number of Antihypertensive Drugs</td>
<td>3.495 (0.24)</td>
<td>0.083</td>
</tr>
</tbody>
</table>

*Ln = Natural logarithm transformation of Central Pulse Pressure; †eGFR=estimated Glomerular Filtration Rate; ‡MAP=Mean Arterial Pressure; §SBP=Systolic Blood Pressure; †DBP=Diastolic Blood Pressure; †Aortic Tr = Time to reflected wave in aortic pressure profile; #Available at baseline visit only
Supplemental Table S2: Multivariable regression model for *LnCPP (adjusted for brachial pulse pressure [natural log transformed], and brachial mean arterial pressure, †AIX and Aortic ‡Tr)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (StdErr)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{LnBPP (mmHg)}$</td>
<td>0.965 (0.009)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>0.002 (0.002)</td>
<td>0.2242</td>
</tr>
<tr>
<td>Age (/10 years)</td>
<td>0.004 (0.003)</td>
<td>0.1284</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>-0.009 (0.005)</td>
<td>0.0805</td>
</tr>
<tr>
<td>Diabetes (Yes)</td>
<td>0.006 (0.005)</td>
<td>0.2413</td>
</tr>
<tr>
<td>Heart Rate (beats/minute)</td>
<td>-0.019 (0.002)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Weight (/10 Kg)</td>
<td>-0.001 (0.001)</td>
<td>0.3554</td>
</tr>
<tr>
<td>†AIX</td>
<td>0.008 (0.000)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>‡Aortic Tr</td>
<td>0.000 (0.000)</td>
<td>0.3134</td>
</tr>
</tbody>
</table>

* = Natural logarithm transformation of Central Pulse Pressure; † = Augmentation Index; ‡ = Time to Aortic reflected wave detection; § = Natural Logarithm transformation of Brachial Pulse Pressure

Supplemental Table S3: Stepwise change in multivariable model R² (from Table S2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>*LnBPP</td>
<td>0.820781</td>
</tr>
<tr>
<td>LnBPP + Mean Arterial Pressure (/10 mmHg; ‘MAP’)</td>
<td>0.820817</td>
</tr>
<tr>
<td>LnBPP + MAP + Age (/10yrs)</td>
<td>0.843678</td>
</tr>
<tr>
<td>LnBPP + MAP + Age (/10yrs) + Diabetes</td>
<td>0.843882</td>
</tr>
<tr>
<td>LnBPP + MAP + Age (/10yrs) + Diabetes + Heart Rate (/10beats/min)</td>
<td>0.858931</td>
</tr>
<tr>
<td>LnBPP + MAP + Age (/10yrs) + Diabetes + Heart Rate (/10beats/min) + Sex</td>
<td>0.866866</td>
</tr>
<tr>
<td>LnBPP + MAP + Age (/10yrs) + Diabetes + Heart Rate (/10beats/min) + Sex + Weight (/10kg)</td>
<td>0.870519</td>
</tr>
<tr>
<td>LnBPP + MAP + Age (/10yrs) + Diabetes + Heart Rate (/10beats/min) + Sex + Weight (/10kg) + †AIX</td>
<td>0.915581</td>
</tr>
<tr>
<td>LnBPP + MAP + Age (/10yrs) + Diabetes + Heart Rate (/10beats/min) + Sex + Weight (/10kg) + AIX + Aortic Tr</td>
<td>0.915616</td>
</tr>
</tbody>
</table>

* = Natural logarithm transformation of Central Pulse Pressure; † = Augmentation Index; ‡ = Time to Aortic reflected wave detection; § = Natural Logarithm transformation of Brachial Pulse Pressure