Kidney Function and Systolic Blood Pressure

New Insights From Cystatin C: Data from the Heart and Soul Study

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Background: Control of hypertension is paramount in treating chronic kidney disease. The relationship between kidney function and blood pressure (BP) components has been studied in persons with diagnosed CKD, diabetes, or hypertension. Whether kidney function in the normal range is associated with systolic BP (SBP), diastolic BP (DBP), and pulse pressure is unclear.

Methods: We evaluated the association between kidney function and each BP component using cystatin C and 24-h creatinine clearance (CrCl) among 906 participants in the Heart and Soul Study.

Results: We observed that SBP was linearly associated with cystatin C concentrations (1.19 ± 0.55 mm Hg increase per 0.4 mg/L cystatin C, P = .03) across the range of kidney functions. In contrast, using CrCl, SBP was significantly associated with kidney function only in subjects with CrCl <60 mL/min (6.4 ± 2.13 mm Hg increase per 28 mL/min, P = .003) but not >60 mL/min (0.36 ± 0.77 mm Hg per 28 mL/min, P = .64). Slopes differed significantly (for spline term P = .001). We found that DBP was not associated with cystatin C (0.34 ± 0.40 mm Hg per 0.4 mg/L cystatin, P = .39) or CrCl (0.62 ± 0.44 mm Hg per 28 mL/min clearance, P = .16). Pulse pressure was linearly associated with cystatin C (1.28 ± 0.55 mm Hg per 0.4 mg/L cystatin, P = .02) and with CrCl <60 mL/min (7.27 ± 2.16 mm Hg per 28 mL/min, P = .001).

Conclusions: Both SBP and pulse pressure were significantly associated with kidney function across a wide range of cystatin C concentrations, even in subjects with presumably normal kidney function, by creatinine-based measures. Cystatin C may provide new insights into the association of CKD and hypertension, a relationship that may be an underappreciated barrier to hypertension control. Am J Hypertens 2006;19:939–946 © 2006 American Journal of Hypertension, Ltd.

Key Words: Kidney, hypertension, cystatin C, systolic blood pressure.

Hypertension is an important risk factor for the progression of chronic kidney disease (CKD) to end-stage renal disease (ESRD), and adequate control of blood pressure (BP) has been shown to attenuate decline in glomerular filtration rate (GFR).1 Hypertension is prevalent in persons with CKD, and rates of control are poor in the setting of CKD.2 Knowledge of the association between kidney function with each of the BP components (systolic, diastolic, or pulse pressure) has been mostly limited to persons with known CKD, diabetes, or hypertension.3–5 A recent study found a strong association between renal function and pulse pressure in elderly persons with isolated systolic hypertension.6 Another study found that systolic BP (SBP) was a stronger predictor of serum creatinine increases than diastolic BP (DBP), pulse pressure, or mean arterial pressure in a prospective cohort of older persons with isolated systolic hypertension.7 A meta-analysis of clinical trials of persons with clinical CKD...
Examination Survey. Although SBP, DBP, and pulse pressure according to the fourth National Health and Nutrition Examination Survey, showed that higher levels of SBP increased the risk of kidney disease progression. In addition, systolic hypertension and wide pulse pressure characterized most of the participants with CKD who had uncontrolled hypertension.

The Heart and Soul Study is a prospective cohort designed to investigate the influence of psychosocial factors on coronary artery disease. Methods have previously been described. Briefly, participants were recruited from the San Francisco Bay Area if they met one of the following inclusion criteria: history of myocardial infarction by treadmill or nuclear testing; history of coronary artery disease by an internist or cardiologist. Participants were instructed to take their BP medications on the morning of the intake appointment and not to smoke or consume caffeine 5 h before the visit. Pulse pressure was calculated as the difference between SBP and DBP.

Methods

Participants

The Heart and Soul Study is a prospective cohort designed to investigate the influence of psychosocial factors on coronary artery disease. Methods have previously been described. Briefly, participants were recruited from the San Francisco Bay Area if they met one of the following inclusion criteria: history of myocardial infarction by treadmill or nuclear testing; history of coronary artery disease by an internist or cardiologist. Participants were instructed to take their BP medications on the morning of the intake appointment and not to smoke or consume caffeine 5 h before the visit. Pulse pressure was calculated as the difference between SBP and DBP.

Outcome Variables

Both SBP and DBP were measured by sphygmomanometer at the intake appointment by a trained research personnel. The participants were instructed to take their BP medications on the morning of the intake appointment and not to smoke or consume caffeine 5 h before the visit. Pulse pressure was calculated as the difference between SBP and DBP.

Secondary Predictors

Age, ethnicity, smoking status, and income, education, and history of diabetes, myocardial infarction, and coronary revascularization were determined by self-report. Height and weight were measured at admission in the San Francisco Bay Area if they met one of the following inclusion criteria: history of myocardial infarction by treadmill or nuclear testing; history of coronary artery disease by an internist or cardiologist.

Measurement of Cystatin C

Cystatin C has also been shown to be a stronger predictor of adverse outcomes than serum creatinine. Based on the more linear relationship of cystatin C with GFR, we hypothesized that cystatin C would have a stronger association with SBP than conventional measures of kidney function, with DBP would be less strongly associated with cystatin C and computed mean SBP, DBP, and pulse pressure among participants across a wide range of kidney functions.

In addition, kidney function was evaluated using a 24-h urine collection and a particle-enhanced immunonephelometric assay (N Latex Detection, Evaluation, and Treatment of Hypertension. Catheterization Laboratories, Inc., Mountainview, CA) with a 2-MHz transducer. The ultrasound probe was placed on the right upper quadrant of the abdomen, and the measurement was taken in the fasting state. The rate of albumin excretion was measured by nephelometry and renal clearance rates (GFR) x 60 mL/min were calculated using the following formula: GFR (mL/min) = 24 h urine volume (dL) * serum creatinine (mg/dL) * 144 (umol/l) / (urine creatinine (mg/dL) * 24 h urine volume (dL)) and GFR was measured as urine creatinine (mg/dL) * 24 h urine volume (dL) / (urine creatinine (mg/dL) * 24 h urine volume (dL)) / (urine creatinine (mg/dL) * 24 h urine volume (dL)).
decile). Using multivariable linear regression we studied the association between kidney function (using either cystatin C or 24-h creatinine clearance) and each BP component (in separate models for SBP, DBP, and pulse pressures). In these analyses, each measurement was evaluated as a continuous variable per standard deviation (0.4 mg/dL for cystatin C and 28 mL/min for 24-h CrCl). We controlled for secondary variables of interest (age, sex, ethnicity, income, education, smoking status, body mass index, LVEF, history of myocardial infarction, diabetes, angioptasia, coronary artery bypass grafting (CABG), or congestive heart failure, use of HMG-CoA reductase inhibitors (statins), angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), β-blockers, diuretics, and calcium channel blockers, presence of microalbuminuria, and C-reactive protein levels). A two-tailed P value < .05 was considered significant.

To determine whether the association of kidney function with SBP appeared to be linear throughout the distribution of each measurement, we used a single-knot linear spline model. This method tests whether the slope of the predictor (kidney function) and the outcome (SBP) differs significantly above or below the chosen cutpoint. Therefore, a P value < .05 rejects the null hypothesis that the slopes are the same above and below the specified cutpoint. We initially chose a cutpoint of 60 mL/min for CrCl, per guidelines.20 We repeated the analyses with cutpoints of 50 and 70 mL/min. We repeated the spline analyses for cystatin C, choosing an initial cutpoint of 1.0 mg/L, with subsequent analyses testing cutpoints of 0.92 mg/L (25th percentile) and 1.07 mg/L (median).

We conducted a sensitivity analysis using the Modified Diet in Renal Disease equation to estimate GFR, and defined CKD as eGFR < 60 mL/min/1.73 m2. In addition, we looked for interactions with African American ethnicity, diabetes, older age (>75 years), and use of ACE/ARB and diuretics to evaluate whether these factors modify the association between kidney function and SBP. All analyses were performed using STATA software, version 8.0 (StataCorp., College Station, TX).

Results
Baseline Characteristics
Among 906 participants, the average age was 66 years (SD 11) and 82% were male. The mean CrCl was 81 mL/min (SD 28 mL/min) and mean cystatin C level was 1.17 mg/L (SD 0.42 mg/L). Mean SBP was 133 mm Hg (SD 22 mm Hg) and mean DBP 75 mm Hg (SD 11 mm Hg). Characteristics of participants by SBP are listed in Table 1. On average, subjects with higher SBP were older, more likely to be African American, and more likely to have diabetes.

Association of Kidney Function With SBP
Progressively reduced kidney function was associated with higher mean SBP across the full range of kidney functions. When participants were grouped by decile of cystatin C, mean SBP increased linearly with each increasing decile (Fig. 1). In a multivariable model, SBP was significantly associated with cystatin C (Table 2). Systolic BP increased by 1.19 ± 0.55 mm Hg per 0.4 mg/L increase in cystatin C (P = .03). We found similar results when we used 1/cystatin C in place of cystatin C, although the associations were less strong. In contrast, when using CrCl as the measure of kidney function, there was no significant association between CrCl and SBP (Table 2).

We tested whether the association of CrCl and SBP varied >60 mL/min or <60 mL/min. We found that >60 mL/min there was no association between kidney function and SBP (0.36 ± 0.77 mm Hg increase per 28 mL/min decrease in CrCl, P = .64) but that for participants with CrCl <60 mL/min there was a significant association between kidney function and SBP (6.40 ± 2.13 mm Hg increase per 28 mL/min, P = .003). The slopes of the lines above and below this cutoff were significantly different (for spline term P = .01) (Table 2). Similar results were observed using cutoffs of 70 mL/min (1.0 ± 0.87 mm Hg for >70 mL/min and 5.41 ± 1.54 mm Hg per 28 mL/min CrCl for <70 mL/min respectively; for difference in slopes P = .002) and 50 mL/min (0.17 ± 0.71 mm Hg and 7.70 ± 3.31 mm Hg respectively; for difference in slopes P = .03).

In contrast, the relationship between cystatin C and SBP remained linear across the wide range of cystatin C concentrations. Using a cutoff of 1.0 mg/L of cystatin C we found no evidence that the slope differed significantly above and below this cutoff (for spline term P = .85) (Table 2). Similar results were seen at cutoffs of 0.92 mg/L and 1.07 mg/L of cystatin C (for spline terms P = .74 and P = .80 respectively).

We tested for an independent association between microalbuminuria and SBP in a multivariable model adjusting for cystatin C. There was no significant independent relationship between microalbuminuria and SBP (1.0 ± 1.17 mm Hg increase in SBP for subjects with microalbuminuria compared with subjects without microalbuminuria, P = .41).

When we used eGFR (MDRD equation), results were similar to those using 24-h CrCl. In a multivariable model, eGFR was not linearly associated with SBP (0.57 mm Hg increase in SBP per SD of eGFR [22 mL/min/1.73 m2], P = .35). However, there was a significant linear relationship in subjects with eGFR <60 mL/min/1.73 m2 (4.79 mm Hg increase per SD of eGFR, P = .01). There was no significant linear relationship observed for subjects with eGFR >60 mL/min/173 m2 (0.50 mm Hg increase per SD eGFR, P = .51), and these slopes were significantly different (for spline term P = .03).

We also tested for interactions with African American ethnicity, diabetes, and use of ACE-I/ARB and diuretics. The relationship between cystatin C and SBP was not modified by African American ethnicity, diabetic status, advanced age, or use of ACE-I/ARB or diuretics. (For
interaction, $P = .38$ for African American ethnicity, $P = .68$ for diabetes, $P = .74$ for advanced age, $P = .89$ for use of ACE-I/ARB, and $P = .50$ for use of diuretics).

### Association of Kidney Function With DBP and Pulse Pressure

In contrast to SBP, cystatin C was not significantly associated with DBP (Fig. 1 and Table 3). The CrCl was not directly associated with DBP in unadjusted and adjusted models (Table 3).

Pulse pressure, however, appeared to be linearly associated with kidney function, and mean pulse pressure increased by decile of cystatin C (1.64 ± 0.54 mm Hg increase per 0.4 mg/L cystatin C increase, $P = .002$), and this persisted after multivariable analysis (1.28 ± 0.55 mm Hg increase per 0.4 mg/L cystatin C increase, $P = .02$). Pulse pressure was not linearly associated with CrCl (1.1 ± 0.63 mm Hg increase per 28 mL/min CrCl decrease, $P = .10$) in a multivariable model. Using spline terms to evaluate this relationship with CrCl >60 or <60 mL/min, pulse pressure was associated with kidney function in subjects with CrCl <60 mL/min (7.27 ± 2.16 mm Hg increase per 28 mL/min, $P = .001$) but not in those with CrCl >60 mL/min (0.35 ± 0.79 mm Hg increase per 28 mL/min, $P = .66$), and these slopes were significantly different (for spline term $P = .003$).

### Discussion

Our results demonstrated a strong association between kidney function and both SBP and pulse pressure in this cohort of patients with coronary artery disease throughout a wide range of kidney function levels. In contrast, kidney function was not associated with DBP. When 24-h urine creatinine clearance was used to measure kidney function, its association with SBP and pulse pressure was limited to those participants who met the criteria for established kidney disease (CrCl <60). However, by using cystatin C, we detected that small changes in kidney function within the normal range (GFR >60 mL/min) were also associated
with SBP and pulse pressure, even after adjustment for inflammatory markers. Thus, our study results imply that kidney function may be a more important determinant of adequate SBP control than previously appreciated, even among persons without clinical CKD.

The finding that kidney function is associated with SBP but not with DBP warrants further exploration. Isolated systolic hypertension has been shown to be a marker of cardiovascular risk. Systolic hypertension and wide pulse pressure have been associated with vascular stiffness, which may provide a clue to the association of kidney disease and cardiovascular disease. Previous findings showed that SBP was a stronger predictor of a rise in serum creatinine than DBP for patients with significantly reduced GFR, those with diabetes, and those with isolated systolic hypertension. In addition, a recent study found that pulse pressure was associated with renal function in an elderly cohort with untreated isolated systolic hypertension. Although the target SBP for those with CKD is still uncertain, our study extends the findings of the strong association between kidney function and SBP with a wider range of kidney function and SBP levels than previously known.

By using a more sensitive marker (cystatin C) to de-

### Table 2. Linear regression of systolic blood pressure by kidney function (N = 906)

<table>
<thead>
<tr>
<th>Measure</th>
<th>N</th>
<th>Age-adjusted</th>
<th>Multivariable adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystatin-C (per 0.4 mg/L [SD] increase)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Overall</td>
<td></td>
<td>1.75 ± 0.72</td>
<td>1.19 ± 0.55</td>
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<td>&gt;1.0</td>
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<td>2.23 ± 0.07</td>
<td>1.23 ± 0.03</td>
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<tr>
<td>&lt;1.0</td>
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<td>1.59 ± 0.04</td>
<td>0.54 ± 0.01</td>
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<tr>
<td>Spline P-value for difference in slopes</td>
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<tr>
<td>24-h CrCl (per 28 mL/min [SD] decrease)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.96 ± 0.76</td>
<td>0.91 ± 0.61</td>
</tr>
<tr>
<td>&lt;60</td>
<td></td>
<td>11.20 ± 2.74</td>
<td>6.40 ± 2.13</td>
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<tr>
<td>&gt;60</td>
<td></td>
<td>0.31 ± 0.99</td>
<td>0.36 ± 0.77</td>
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<tr>
<td>Spline P-value for difference in slopes</td>
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</tbody>
</table>

* Adjusted for age, ethnicity, income, education, prior myocardial infarction, diabetes, prior angioplasty, prior coronary artery bypass grafting, heart failure, body mass index, cholesterol, low-density lipoprotein, high-density lipoprotein, diastolic blood pressure, left ventricular ejection fraction, and use of angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, statin, aspirin, β-blocker, diuretic, calcium channel blocker, microalbuminuria, C-reactive protein.
termine kidney function, our analysis found an association of kidney function with SBP even in those without clinical CKD by the use of traditional creatinine-based methods. Cystatin C has been shown to be a more sensitive marker of GFR than either creatinine or eGFR, and it is independent of body mass, height, and weight.12,13,25,26 Using cystatin C, we found a significant linear relationship between kidney function and SBP even among persons with presumably normal renal function. These results are in accordance with findings in a small cohort of subjects with essential hypertension,27 and they suggest the presence of factors that may affect the vasculature before clinical CKD is diagnosed. Therefore, cystatin C concentrations appear to offer new insights into the importance of the relationship between kidney function and SBP, which may have been underestimated in previous studies.

These findings have important implications. Studies of large national samples still show an enormous burden of hypertension in the United States, and at best approximately 45% of persons with hypertension meet targets.28–31 Mildly reduced kidney function may be an important but underappreciated factor that contributes to the lack of hypertension control in the United States, especially in those with isolated systolic hypertension. Further research should be conducted to design new anti-hypertensive agents that are able to reduce SBP without lowering DBP in the setting of kidney dysfunction to improve hypertension control.

A particular strength of our study is the measurement of renal function with 24-h urine collections in juxtaposition with a novel filtration marker of GFR, cystatin C. Most studies of BP and kidney function have only used serum creatinine measures or estimated GFR.3,4,7,23 We believe, therefore, that our study more accurately quantifies the association between kidney disease and SBP.

Certain limitations should also be considered in interpreting our results. Because this is a cross-sectional study, we cannot determine the direction of the association or determine causality. Specifically, we cannot discern the extent to which kidney dysfunction leads to elevated SBP,

Table 3. Linear regression of diastolic blood pressure by kidney function (N = 906)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Age-adjusted</th>
<th>Multivariable adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β coefficient</td>
<td>P value</td>
</tr>
<tr>
<td>Cystatin-C (per 0.4 mg/L increase)</td>
<td>0.09 ± 0.38</td>
<td>.81</td>
</tr>
<tr>
<td>24-h CrCl (per 28 mL/min decrease)</td>
<td>0.55 ± 0.41</td>
<td>.18</td>
</tr>
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* Adjusted for age, ethnicity, income, education, prior myocardial infarction, diabetes, prior angioplasty, prior coronary artery bypass grafting, heart failure, body mass index, cholesterol, low-density lipoprotein, high-density lipoprotein, left ventricular ejection fraction, and use of angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, statin, aspirin, β-blocker, diuretic, calcium channel blocker, microalbuminuria, C-reactive protein.

FIG. 2. Mean pulse pressure by decile of kidney function measured as cystatin C.
or elevated SBP leads to kidney dysfunction. Blood pressure levels were limited to one measurement, which may affect the precision of our measures. Our study included participants taking antihypertensive medications, and thus BP levels may be lower than in those without treatment. However, the fact that the association between renal function and SBP persists despite this factor supports our hypothesis that mildly reduced kidney function may be an underappreciated contributor to the lack of systolic hypertension control in the United States. Furthermore, our study participants were mostly men of non-Hispanic white ethnicity and all had known coronary disease, which limits the generalization of our findings. Thus, our findings should be confirmed in other cohorts.

In summary, cystatin C was significantly and linearly associated with SBP and pulse pressure but not with DBP across a wide range of kidney functions. This association may have important implications in the treatment of hypertension, as mildly reduced kidney function may be an underappreciated barrier in the achievement of BP targets. Further studies are required to evaluate the pathways involved, as new therapies are urgently needed to reduce SBP in persons with either clinical or preclinical kidney disease.

References


