Blood pressure measures and risk of chronic kidney disease in men

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Abstract

**Background.** High blood pressure (BP) has been associated with a decrease in kidney function. However, it remains unclear which BP measure best predicts impaired kidney function.

**Methods.** We compared systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP) and mean arterial pressure (MAP) in predicting risk of chronic kidney disease (CKD). We prospectively followed 8093 male participants in the Physicians’ Health Study, without a known history of kidney disease at baseline, who provided BP values on the baseline and 24-month questionnaires, and for whom we had creatinine measures after 14 years of follow-up. Reported BP was averaged from both questionnaires. The main outcome was CKD, defined as an estimated glomerular filtration rate <60 mL/min/1.73 m2. We used multivariable-adjusted logistic regression to evaluate the association between BP measures and CKD and compared models using the likelihood ratio test.

**Results.** After 14 years of follow-up, 1039 men (12.8%) had CKD. An increase of 10 mmHg had corresponding multivariable-adjusted odds ratios (95% confidence intervals) of 1.11 (1.03–1.19) for SBP, 1.11 (1.00–1.23) for MAP, 1.14 (1.05–1.25) for PP and 1.05 (0.93–1.17) for DBP. SBP and PP were the strongest predictors of chronic kidney function, with equal predictive abilities. Combining BP measures did not add significantly to the prediction.

**Conclusions.** Increases in SBP, PP and MAP were significantly associated with CKD. SBP may be the most clinically useful predictor of CKD, since no further calculations are required.

**Keywords:** Blood pressure; creatinine clearance; hypertension; kidney disease; renal dysfunction

Introduction

Hypertension is among the leading causes of end-stage renal disease (ESRD) in Europe and the United States, second only to diabetes mellitus. Numerous studies have identified hypertension as an independent risk factor in the development of ESRD and in the progression of early kidney disease to ESRD [1–3]. In contrast, decline in kidney function due to elevated BP has not been extensively investigated in prospective studies. In addition, uncertainty remains as to which BP measures, either alone or in combination, best predict the risk of early stages of kidney dysfunction. Among persons receiving haemodialysis, higher PP has been consistently associated with increased mortality [4]. However, little is known about the differential effects of systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP) and mean arterial pressure (MAP) in the development of early kidney dysfunction.

Various BP measures have been evaluated in the prediction of cardiovascular disease risk [5]. Data from the Framingham Heart Study and other studies indicate that SBP increases steadily across all age groups, whereas DBP increases until age 60 years and then begins to decrease [6,7]. Among older persons, SBP and possibly PP are more strongly correlated with coronary heart disease, congestive heart failure and mortality than DBP or MAP [5,8,9]. As with cardiovascular disease risk, associations between various BP measures and risk of kidney dysfunction may also vary by age. Young et al. found that SBP strongly predicted a decline in kidney function among persons ≥70 years [10]. The association between BP components and risk of chronic kidney disease (CKD) has been evaluated using cross-sectional data from the Third National Health and Nutrition Examination Survey (NHANES) [11]. However, prospective studies on the association of various BP components with early kidney dysfunction in apparently healthy individuals are lacking.

The Physicians’ Health Study (PHS) provides an opportunity to investigate the association between different BP
measures and the risk of CKD after 14 years of follow-up in apparently healthy men without known kidney disease at baseline.

**Subjects and methods**

Study subjects were all participants in the PHS, a completed randomized trial of aspirin and beta-carotene in the primary prevention of cardiovascular disease and cancer. The Brigham and Women’s Hospital institutional review board approved the methodology and procedures of the PHS. The design and methods of the PHS have been described in detail previously [12,13]. Briefly, the study population consisted of 22 071 apparently healthy male physicians in 1982 without prior history of cardiovascular disease, cancer (except nonmelanoma skin cancer), current liver disease or renal dysfunction (defined as self-reported renal failure or insufficiency), or other major illnesses. Baseline information was self-reported and collected by a mailed questionnaire that asked about many demographic, medical history (including hypertension and diabetes mellitus) and lifestyle variables. Every 6 months for the first year and annually thereafter, participants were sent follow-up questionnaires asking about personal characteristics, medical history and health behaviors during the study period.

Among the 22 071 randomized men, creatinine analyses were available for 11 105 men after 14 years of follow-up. Information on BP measures in 1982 and creatinine measurements in 1996 were available for 9793 of these samples. Information on 2-year follow-up BP measures was missing for 1700 men, leaving a sample of 8093 participants aged 40–84 years old for this analysis.

**Blood collection and analysis**

Blood kits with Vacutainer tubes containing EDTA, complete instructions for blood draws and coldpacks were mailed between 1996 and 1998 to participants. They were asked to have their blood drawn into the Vacutainer tubes, to have the tubes centrifuged and to return the samples in a coldpack by prepaid overnight courier. Upon receipt, each sample was divided into aliquots, and stored at −82°C. Specimens were received from 11 360 of the physicians who were still under active follow-up.

Blood samples were analysed in Oxford, England, using an automated Jaffe rate method on a SYNCHRON LX20 autoanalyser (Beckman Coulter, Fullerton, CA) for quantification of creatinine. Plasma creatinine is stable in chilled next-day whole blood samples preserved with EDTA [14]. To assess quality control, blinded duplicate splits were submitted; the coefficient of variation for these blinded split samples was 7.1%. The difference in means between the study samples and the repeat quality control samples was 0.018 mg/dL (standard deviation, 0.67). Intrapatient coefficients of variation on internal quality control runs were 1.4% to 3.6%.

**Information on BP**

BP values were self-reported by the participating physicians at baseline and after 24 months of follow-up. The average of the baseline and 2-year BP values was used to reduce potential misclassification in self-reported BP. Participants were not asked to report BP values for a specific time of day. In addition to SBP and DBP, we considered PP, defined as SBP minus DBP, and MAP, defined as 1/3(SBP) + 2/3(DBP). Self-reported BP is expected to be reliable and valid, since self-reported BP in a different study of physicians was highly correlated with measured SBP ($r = 0.72$) and DBP ($r = 0.60$) [15]. Another study of agreement between measured and self-reported BP found a correlation similar to that for two measurements of BP within a year [16].

We evaluated SBP in categories defined as <120, 120 to 129, 130 to 139, and ≥140 mmHg and DBP in categories defined as <75, 75 to 84, 85 to 94, and ≥95 mmHg. PP and MAP were categorized into quartiles.

**Outcomes**

The main outcome of interest was CKD, defined as a reduced GFR of <60 ml/min/1.73 m², as estimated by the simplified Modification of Diet in Renal Disease (MDRD) Study equation: GFR (ml/min per 1.73 m² body surface area) = $[186 \times (\text{creatinine in mg/dL})^{-1.154} \times (\text{age})^{-0.203} \times 1.212 \times (\text{if black})]$, as recommended by the National Kidney Foundation [17]. We repeated all analyses using the Cockcroft–Gault equation [18] to calculate creatinine clearance as an estimate of GFR, $=(140 - \text{age}) \times (\text{weight in kilograms}) / [72 \times (\text{creatinine in mg/dL})]$.

**Statistics**

To evaluate the association between the individual BP measures and GFR <60 ml/min/1.73 m², we used logistic regression models. We incorporated a missing value indicator if the number of men with missing information was ≥100 or imputed a value otherwise. The multivariable models included as covariates age (years), body mass index (BMI) (kg/m², continuous), smoking status (never, past, current), history of diabetes mellitus (yes, no), history of hypertension (yes, no), history of hypercholesterolemia (yes, no), alcohol consumption (daily, weekly, monthly, rarely), vigorous exercise (1/week yes, no), parental history of myocardial infarction prior to age 60 (yes, no) and randomized aspirin assignment. To determine which measures of average BP best predict CKD, we compared multivariable-adjusted logistic regression models that included the main effects of SBP, DBP, PP, and MAP only with models that included the combinations of SBP and DBP, SBP and PP, and PP and MAP adjusting for the same set of potential confounders as listed above. The $-2 \log$ likelihood values of the individual models were compared using the likelihood ratio test. In a second multivariable model, we additionally included information on antihypertensive medication use at baseline or at the 24-month questionnaire. We tested for linear trend across the mean values of BP categories. All tests were two-tailed and we considered a $P < 0.05$ as statistically significant.

**Results**

Table 1 summarizes the baseline characteristics of the study participants according to SBP categories. Of the study
participants, 2148 men had SBP <120 mmHg, 3067 men had a SBP of 120 to <130 mmHg, 2037 had a SBP of 130 to <140 mmHg and 841 men had a SBP of ≥140 mmHg. Men in the highest SBP category were older, had a higher BMI and were more likely to report a history of diabetes and elevated cholesterol ≥240 mg/dL. They were also more likely to smoke cigarettes, drink more alcohol and exercise less.

After 14 years of follow-up, there were 1039 (12.8%) cases of estimated GFR <60 mL/min/173 m^2. We examined the strengths of the associations between categories of average SBP, DBP, MAP and PP and reduced estimated GFR (Table 2). Compared to the lowest BP category, the multivariable-adjusted ORs (95% CI) for estimated GFR <60 mL/min/1.73 m^2 were 1.69 (1.33–2.13) for the highest category of SBP (≥140 mmHg), 1.70 (0.85–3.38) for the highest category of DBP (≥95 mmHg), 1.87 (1.23–2.85) for the highest category of MAP (≥110 mmHg) and 1.67 (1.20–2.32) for the highest category of PP (≥60 mmHg). With the exception of DBP, we found statistically significant trends for increased risk of CKD across BP categories.

While additional adjustment for antihypertensive medication use resulted in attenuation of the effect estimates, we again found significant trends across categories of SBP and PP (data not shown).

The comparisons of the various BP measures and their combination with risk of GFR <60 mL/min/1.73 m^2 are summarized in Table 3. An increase of 10 mmHg had corresponding multivariable-adjusted ORs of 1.11 (95% CI 1.03–1.19) for average SBP, 1.11 (95% CI 1.00–1.23) for average DBP and 1.14 (95% CI 1.05–1.25) for average PP. Average DBP showed only a modest association with an OR of 1.05 (95% CI 0.93–1.17), which was not statistically significant. With regard to statistical prediction, both PP and SBP had comparable predictive abilities with −2 log likelihood values of 5722.8 for SBP and 5722.2 for PP. DBP and MAP had lower predictive values. The combination of SBP and DBP, SBP and PP, as well as PP and MAP did not improve the prediction of estimated GFR <60 mL/min/1.73 m^2 (Table 3). Similar associations were observed in stratified analyses of men <60 years of age and men ≥60 years of age (data not shown). We found similar results using the Cockcroft–Gault instead of the MDRD Study equation to estimate reduced GFR, with significant adjusted trends across categories of SBP, MAP and PP (data not shown).

**Discussion**

The results of this large prospective cohort study indicate a clear association between elevated BP and the development of CKD in initially healthy men without known kidney disease at study entry. Apart from DBP, which showed no statistically significant association, average SBP, MAP and PP were significantly associated with an increased risk for reduced GFR after adjusting for a large number of potential confounding variables. Both SBP and PP were equally strong predictors of reduced GFR of <60 mL/min/1.73 m^2, followed by MAP.

A recent analysis by Fox et al. identified predictors for new-onset kidney disease examining the community-based population of the Framingham Offspring Study [19]. Among baseline variables including age, diabetes and high-density lipoprotein cholesterol, higher SBP and hypertension (defined as SBP ≥140 mmHg, or DBP ≥90 mmHg, or history of antihypertensive medication use) were significantly related to the development of kidney disease adjusting for sex and age; however, their analyses did not differentiate between individual BP measures.
Table 2. Odds ratios (95% confidence intervals) for GFR <60 mL/min/m² at 14-year follow-up (N = 8093)

<table>
<thead>
<tr>
<th>BP Category</th>
<th>N (# cases)</th>
<th>Age-adjusted b OR (95% CI)</th>
<th>Multiple-adjusted c OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120</td>
<td>2148 (199)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>120—129</td>
<td>3067 (335)</td>
<td>1.06 (0.87–1.28)</td>
<td>1.05 (0.87–1.27)</td>
</tr>
<tr>
<td>130—139</td>
<td>2037 (305)</td>
<td>1.28 (1.05–1.56)</td>
<td>1.26 (1.03–1.53)</td>
</tr>
<tr>
<td>≥140</td>
<td>841 (200)</td>
<td>1.71 (1.36–2.15)</td>
<td>1.69 (1.33–2.13)</td>
</tr>
<tr>
<td>P for trend d</td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>2010 (225)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>75—84</td>
<td>4606 (576)</td>
<td>1.00 (0.84–1.18)</td>
<td>0.98 (0.82–1.16)</td>
</tr>
<tr>
<td>85—94</td>
<td>1426 (226)</td>
<td>1.20 (0.98–1.47)</td>
<td>1.16 (0.94–1.43)</td>
</tr>
<tr>
<td>≥95</td>
<td>51 (12)</td>
<td>1.76 (0.89–3.49)</td>
<td>1.70 (0.85–3.38)</td>
</tr>
<tr>
<td>P for trend d</td>
<td>0.053</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90</td>
<td>2202 (224)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>90—99</td>
<td>4134 (488)</td>
<td>0.99 (0.83–1.18)</td>
<td>0.97 (0.82–1.16)</td>
</tr>
<tr>
<td>100—109</td>
<td>1622 (288)</td>
<td>1.36 (1.12–1.65)</td>
<td>1.33 (1.09–1.62)</td>
</tr>
<tr>
<td>≥110</td>
<td>135 (39)</td>
<td>1.98 (1.31–2.99)</td>
<td>1.87 (1.23–2.85)</td>
</tr>
<tr>
<td>P for trend d</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

a P for trend across the mean values of blood pressure categories.
b Adjusted for age as continuous term.
c Adjusted for age, body mass index, history of diabetes, elevated cholesterol ≥240 mg/dL, smoking, alcohol consumption, exercise, randomized aspirin assignment and parental history of myocardial infarction prior to age of 60 years.

Table 3. Comparison of various average blood pressure measures with risk of GFR <60 mL/min/1.73 m²

<table>
<thead>
<tr>
<th></th>
<th>Model 1 SBP</th>
<th>Model 2 DBP</th>
<th>Model 3 SBP and DBP</th>
<th>Model 4 PP</th>
<th>Model 5 PP and SBP</th>
<th>Model 6 MAP</th>
<th>Model 7 MAP and PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>1.11 (1.03–1.19)</td>
<td>–</td>
<td>1.14 (1.05–1.25)</td>
<td>–</td>
<td>1.05 (0.94–1.18)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>DBP</td>
<td>–</td>
<td>1.05 (0.93–1.17)</td>
<td>0.92 (0.80–1.06)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PP</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.14 (1.05–1.25)</td>
<td>1.09 (0.95–1.25)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MAP</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.11 (1.00–1.23)</td>
<td>1.13 (1.02–1.24)</td>
<td>–</td>
</tr>
<tr>
<td>−2 Log likelihood</td>
<td>5722.801</td>
<td>5730.221</td>
<td>5721.415</td>
<td>5722.167</td>
<td>5721.415</td>
<td>5727.287</td>
<td>5721.415</td>
</tr>
<tr>
<td>df</td>
<td>15</td>
<td>15</td>
<td>16</td>
<td>15</td>
<td>16</td>
<td>15</td>
<td>16</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; df, degrees of freedom.

The following covariates were also included in the models: age, body mass index, history of diabetes, elevated cholesterol ≥240 mg/dL, smoking, alcohol consumption, exercise, randomized aspirin assignment and parental history of myocardial infarction prior to age of 60 years.

Only approximately 27% of US adults with hypertension who receive medication for hypertension actually achieve an SBP <140 mmHg. Moreover, almost 90% of patients with hypertension and diabetes mellitus do not reach the recommended SBP of <130 mmHg [20]. The need for greater emphasis on SBP control was examined with data from the Third NHANES, which demonstrated that SBP control rates were uniformly poorer than DBP control rates [21,22]. Elevated BP is an established risk factor for the development of ESRD [1,3]. The number of persons with ESRD has increased substantially during the past 20 years [23], but represents only a small proportion of the kidney disease burden. Identifying modifiable risk factors responsible for not only the progression but also for early stages of CKD is crucial to reducing the public health burden of kidney disease.

BP as a risk factor for incident CKD has not been studied prospectively among a population with a large age range, nor have the different components of BP measures been investigated. Whereas 'conventional' BP measures such as SBP, DBP and MAP represent the steady, static components of BP determined by cardiac output and vascular resistance, PP reflects the pulsatile nature of the cardiac cycle. Large PP reflects arterial stiffness, which can cause increased afterload and decreased coronary perfusion. This may be particularly important for ESRD patients in whom an underlying cardiac dysfunction is often present. In a large retrospective cohort of patients undergoing maintenance dialysis, Klassen et al. showed a consistent relationship between increasing PP and increasing risk of mortality [4]. Their findings are in contrast with other studies that describe a U-shaped or J-relationship between conventional BP measures and mortality in patients undergoing...
haemodialysis [24–26]. If this differentiation plays a decisive role for haemodialysis patients, it might also play a role for earlier stages of kidney disease.

Findings from NHANES indicated that the prevalence of elevated serum creatinine defined as a level of ≥1.6 mg/dL for men was 25 times greater than that of ESRD [11]. Furthermore, an elevated serum creatinine level was associated with higher SBP and DBP, presence of hypertension and antihypertensive medication use. These data and the fact that our study had a follow-up period of 14 years underscore the importance of early preventive interventions for individuals with elevated BP. Furthermore, our data may indicate that studies testing the effect of antihypertensive medication on the occurrence of early decline in kidney function should have sufficiently long follow-up periods.

A study by Youssef et al. examined the temporal relation between BP and serum creatinine in a biracial community of young black and white adults enrolled in the Bogalusa Heart Study [27]. Of 662 adults aged 19–32 years, of whom 185 were black and who were followed for 7.4 years, baseline BP was significantly associated with serum creatinine at follow-up in black men only. In this rather small cohort, only the effects of SBP and DBP were examined, and the young age range of participants did not include those at highest risk for CKD.

In a large Japanese cohort using mass screening and dialysis registries, Tozawa et al. prospectively studied BP as a risk factor for ESRD [28] and showed significant associations between hypertension and the development of ESRD in both men and women. However, their final outcome was ESRD, rather than incident decline in kidney function.

In a study of men and women >70 years of age enrolled in the placebo arm of the Systolic Hypertension in the Elderly Program, Young et al. found that the risk of kidney dysfunction was strongly associated with SBP, as compared to DBP, PP and MAP [10]. However, this study was limited to older persons and thus unable to examine variations in the associations over the range of age. Previous studies have demonstrated increases in SBP with increasing age, whereas DBP may decrease after age 60 [6,7].

Our study has several strengths, including its large size, long follow-up, prospective method of data collection and the relatively homogeneous nature of our cohort, which may reduce confounding. By using the average of baseline and 2-year BP values, we reduced potential misclassification of self-reported BP. Furthermore, we evaluated the association between BP and risk of CKD using two different equations to estimate GFR.

Several limitations should be considered. Men who participated in the PHS differ in many ways from the general population by education, ready access to medical care and socioeconomic status and thus generalizability may be limited. Furthermore, our results may not apply to women. However, there is little biological basis to postulate that the mechanisms by which elevated BP may affect kidney function should differ materially between the PHS participants and the general population. In addition, blood samples were only available for a sub-sample of the PHS cohort, and we did not have baseline creatinine values for the study participants. Furthermore, no urine samples have been collected, not allowing us to rule out microalbuminuria. Thus, it is possible that unmeasured CKD at study entry may have influenced baseline BP measurements. However, since we excluded participants reporting a history of kidney disease and our study population is healthier than the general population, this bias most likely did not substantially alter our findings. For example, in a mass-screening program of approximately 100 000 persons in Japan from 1983 until 2000, hypertension was identified as an independent risk factor for the development of ESRD [28]. The authors of this study did not have available creatinine measures at baseline, and urine measurements showed a prevalence of proteinuria of only 5%. After controlling for proteinuria, the relative risk associated with hypertension was only slightly attenuated and still statistically significant. In addition, although survivorship bias may have occurred since we measured creatinine after 14 years of follow-up, we anticipate that such bias would underestimate the associations between BP and CKD. Furthermore, we aimed to evaluate the predictive ability of four BP measures on the initiation of CKD, and we find it unlikely that these potential biases differentially influence specific BP measures.

In our study of initially healthy men without known kidney disease at study entry, SBP and PP proved to be equally strong predictors for the development of CKD. The combination of BP measures did not add to the prediction of CKD. Therefore, SBP may be the best clinically utilizable predictor of GFR <60 mL/min/1.73 m² since no further calculations are required.

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References
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