Prospective Study of the Effect of Blood Pressure on Renal Function in Old Age: The Leiden 85-Plus Study

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High BP is associated with decline of renal function. Whether this is true for very old people largely is unknown. Therefore, this study assessed the effect of BP on creatinine clearance over time in very old participants. A total of 550 inhabitants (34% men) of Leiden, The Netherlands, were enrolled in a population-based study at their 85th birthday and followed until death or age 90. BP was measured twice at baseline and at age 90 yr. Creatinine clearance was estimated annually (Cockcroft-Gault formula). The mean creatinine clearance at baseline was 45.4 ml/min (SD 11.5). Systolic BP was not associated with changes in creatinine clearance during follow-up. Those with diastolic BP (DBP) <70 mmHg had an accelerated decline of creatinine clearance (1.63 ml/min per yr) compared with those with DBP between 70 and 79 mmHg (1.21 ml/min per yr; P = 0.01), 80 to 89 mmHg (1.26 ml/min per yr; P = 0.03), and >89 mmHg (1.38 ml/min per yr; P = 0.32). Participants with a decline in systolic BP during follow-up had an accelerated decline of creatinine clearance compared with those with stable BP (1.54 [SE 0.09] versus 0.98 ml/min per yr [SE 0.09]; P < 0.001). Similar results were found for a decline in DBP (1.54 [SE 0.10] versus 1.06 ml/min per yr [SE 0.08]; P < 0.001). In the oldest individual, high BP is not associated with renal function. In contrast, low DBP is associated with an accelerated decline of renal function. The clinical implications of these findings have to be studied.


In old age, renal function will be compromised as a result of progressive loss of glomeruli and decline in renal blood flow (1), especially in those with persistent high BP (2). Because BP increases with age, this implicates a possible double strike for creatinine clearance in the oldest individual (3).

In contrast with younger populations, in the oldest individuals, the association among high BP, mortality, and renal function is not straightforward. The available data suggest that BP lowering above 80 yr does not lower overall mortality (4,5). Data on the effect of BP on morbidity such as renal function are relatively scarce in the oldest individuals (6–8). One longitudinal report associated BP and renal function in a considerable group of very old Japanese individuals (7). In that report, high BP was related to an excess decline of serum creatinine. However, an important drawback was the use of serum creatinine for estimation of renal function. In addition, selection bias could have been induced as a result of exclusion of 40% of the participants, who did not attend the reexamination after 3 yr.

Although BP lowering in individuals over 80 yr might not lower mortality, it is unknown whether a high BP might be deleterious for renal function. To investigate whether high BP still is a risk factor for decline in renal function in the oldest individuals, we prospectively studied the effect of BP on changes of creatinine clearance over time in a population-based study of the general population of the oldest individuals.

Materials and Methods

Study Population

The Leiden 85-Plus Study is a prospective, population-based study of all 85-yr-old inhabitants of Leiden, The Netherlands. The study design and characteristics of the cohort were described in detail previously (9,10). In short, between September 1997 and September 1999, all 705 members of the 1912 to 1914 birth cohort in the city of Leiden were asked to participate in the month after their 85th birthday. There were no selection criteria related to health or demographic characteristics. Participants were followed until death or the age of 90. At baseline and yearly thereafter, 85-yr-old participants were visited at their place of residence. During these visits, participants were weighed, BP was measured, a venous blood sample was drawn, an electrocardiogram was recorded, and face-to-face interviews and performance tests were conducted. Information on the medical history was obtained by standardized interviews of the participants’ treating physicians. In addition, information on the use of medication was obtained from the participants’ pharmacist. Participants gave informed consent; for people who were severely cognitively impaired, a guardian gave informed consent. The Medical Ethics Commission of Leiden University approved the study.

BP

At baseline and at age 90 yr, BP was measured twice, with a mean intervening period of 2 wk. BP was measured, using a mercury sphygmomanometer, in the seated position after at least 5 min of rest and no vigorous exercise in the preceding 30 min. The systolic value was...
measured at Korotkoff sound 1, and the diastolic value was measured at Korotkoff sound 5. For the analysis of BP, we used the mean of the measured systolic and diastolic values. For the analysis of pulse pressure, we used the mean systolic (SBP) minus the mean diastolic BP (DBP). Data are presented according to four strata of SBP (<140, 140 to 149, 150 to 159, and ≥160 mmHg), four strata of DBP (<70, 70 to 79, 80 to 89, and ≥90 mmHg), and quartiles of pulse pressure. The change of SBP and DBP between ages 85 and 90 was categorized into three groups: Declining (≥10-mmHg decrease), stable (<10-mmHg increase or <10-mmHg decrease), and increasing (≥10 mmHg).

**Creatinine Clearance**

At entry and at yearly intervals thereafter, both the serum creatinine concentration and body weight were measured. Creatinine was fully automatically measured according to the Jaffe method (Hitachi 747; Hitachi, Tokyo, Japan). The creatinine clearances were estimated yearly with the Cockcroft-Gault formula as follows (11):

\[
\text{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times 1.23}{\text{serum creatinine (μmol/L)}} \times (0.85 \text{ if female})
\]

**Demographic and Clinical Characteristics**

At baseline, a research nurse collected information concerning the demographic characteristics. The presence of cardiovascular disease was defined as a history of cerebrovascular accident, angina pectoris, myocardial infarction, or peripheral vascular disease (including a history of arterial grafting, endarterectomy, and angioplasty) or an electrocardiogram revealing myocardial ischemia or infarction (Minnesota codes 1-1, 1-2, 1-3, 4-1, 4-2, 4-3, 5-1, 5-2, and 5-3) (12). The presence of chronic disease was defined as a history of diabetes, Parkinson’s disease, chronic obstructive pulmonary disease, osteoarthritis, or malignancies. Antihypertensive drugs were classified as use of angiotensin-converting enzyme inhibitor, angiotensin-1 receptor blocker, thiazide diuretic, dihydropyridine calcium channel blocker, or β-blocker with the exclusion of Sotacor. We had data on use of antihypertensive medication at the ages of 85 and 86.

**Statistical Analyses**

Data were presented as percentages for clinical characteristics and as the mean with SD for continuous variables. The differences in mean creatinine clearances between the categories of BP at baseline were compared with independent t test. The associations over time between creatinine clearance (ml/min) and categories of DBP and SBP were analyzed with a linear mixed model. The creatinine clearance was the dependent factor. The outcome was the effect on the change in creatinine clearance of the interaction between time and categories of BP. This analysis models the change over time by computing the rate of change for each participant on the basis of all data for that individual adjusted for gender and other possible confounders. Then the rate of changes for the entire group and the individual deviation from the group rate are computed. This model analyzes the unique effects of individual predictors adjusted for all other fixed and random predictors, accounts for the correlation among repeated measurements on the same participant, and is unaffected by randomly missing data. To investigate the effects of missing data as a result of mortality, we repeated all analyses with exclusion of participants who died within the first year of follow-up and repeated all analyses with inclusion only of surviving participants who participated up to age 90 yr.

**Creatinine clearance and blood pressure**

**Table 1. Baseline characteristics of 550 participants aged 85 yr**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Women</td>
<td>363 (66%)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>218 (40%)</td>
</tr>
<tr>
<td>Antihypertensive treatment</td>
<td>201 (37%)</td>
</tr>
<tr>
<td>Mean diastolic BP (mmHg [SD])</td>
<td>76.9 (9.4)</td>
</tr>
<tr>
<td>Mean systolic BP (mmHg [SD])</td>
<td>155.6 (18.4)</td>
</tr>
<tr>
<td>Mean pulse pressure (mmHg [SD])</td>
<td>78.7 (15.2)</td>
</tr>
<tr>
<td>No. of cardiovascular diseasesa</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>203 (37%)</td>
</tr>
<tr>
<td>1</td>
<td>210 (38%)</td>
</tr>
<tr>
<td>2</td>
<td>105 (19%)</td>
</tr>
<tr>
<td>≥3</td>
<td>32 (6%)</td>
</tr>
<tr>
<td>No history of chronic diseasesb</td>
<td>227 (41%)</td>
</tr>
<tr>
<td>Diagnosis of diabetes</td>
<td>87 (16%)</td>
</tr>
</tbody>
</table>

*aIncluding history of peripheral vascular disease, cerebrovascular accident, angina pectoris, myocardial infarction, or an electrocardiogram revealing myocardial ischemia or infarction.

*bHistory of diabetes, Parkinson's disease, chronic obstructive pulmonary disease, osteoarthritis, or malignancies.

![Figure 1. Number of participants during the study period.](Image)
An additional analysis was done to examine the effect of a decline in SBP and DBP between ages 85 and 90 on the decline of creatinine clearance in participants who were alive at age 90. The associations between the groups of BP and creatinine clearance were analyzed with a linear mixed model.

All analyses were done with software SPSS version 12.0 (SPSS, Inc. Chicago, IL).

Results

Of the 705 eligible participants, 14 died before they could be enrolled and 92 refused to participate, resulting in a cohort of 599 participants (87% response). Only one BP measurement was available for 27 participants, serum creatinine at baseline was missing in 11 participants, and body weight was missing in 11 participants. Therefore, in these analyses, we included 550 participants (Table 1). During follow-up, 34 participants declined further participation and 243 participants died (Figure 1). At age 86, 36 participants had started antihypertensive medication and 54 had stopped antihypertensive medication. There were no significant associations between the categories of DBP and SBP and changes of use of antihypertensive medication between ages 85 and 86 yr (data not shown).

At baseline, the mean creatinine clearance was 45.4 ml/min (SD 11.5 ml/min). Women had a 2.19 ml/min (SE 1.04 ml/min) lower creatinine clearance compared with men (P < 0.035). During follow-up, the overall decline in creatinine clearance was 1.31 ml/min per yr (SE 0.06, P < 0.001). At baseline, four participants had end-stage renal failure, defined as a creatinine clearance <15 ml/min. During follow-up, three participants progressed to end-stage renal failure: Two at age 89 yr and one at age 90 yr.

At baseline, creatinine clearance was correlated with the presence of cardiovascular disease. For every additional cardiovascular disease, creatinine clearance was 2.05 ml/min (SE 0.54, P < 0.001) lower. During follow-up, creatinine clearance declined with an extra 0.21 ml/min per yr (SE 0.07, P = 0.002) over the normal annual decline for every additional manifestation of cardiovascular disease. A history of hypertension and diabetes (Table 2) was not associated with the decline of renal function either at baseline or during follow-up.

At baseline, creatinine clearance was not dependent on SBP or pulse pressure (all comparisons between groups, P > 0.18).

In contrast, DBP at baseline was significantly associated with creatinine clearance: Creatinine clearances were significantly lower in the two lowest categories (<70 and 70 to 79 mmHg) of DBP (43.8 [SE 0.98] and 44.7 ml/min [SE 0.77]) compared with the two highest categories (80 to 89 and ≥90 mmHg) of DBP (47.5 [SE 0.97] and 46.5 ml/min [SE 1.61]; P = 0.005). The associations among SBP, DBP, and pulse pressure versus creatinine clearance were similar in men and women (data not shown).

Relations between baseline BP and changes in renal function over time were similar to those observed at the cross-sectional analyses. There was no association between baseline SBP or pulse pressure and the annual decline of creatinine clearance (Figure 2). However, baseline DBP <70 mmHg was associated with a significantly accelerated decline of creatinine clearance during follow-up when compared with higher DBP (Figure 2). These findings remained similar after exclusion of 42 participants who died within the first year of follow-up. The restricted analyses for 273 surviving participants who participated up to 90 yr did also not change the significant association between low DBP and an accelerated decline of creatinine clearance. The yearly decline in creatinine clearance was −1.58 ml/min for 53 participants with baseline DBP <70 mmHg (reference group), −1.13 for 70 to 79 mmHg (n = 112; P = 0.006), −1.13 for 80 to 89 mmHg (n = 82; P = 0.01), and −1.30 (n = 26; P = 0.24) for >89 mmHg.

During follow-up a low DBP was consistently associated with an accelerated decline of creatinine clearance in those with and those without cardiovascular disease at baseline (data not shown). Stratification according to the median of creatinine clearance at baseline did not reveal a different effect of BP on creatinine clearance over time (data not shown).

Figure 3 presents the annual decline of creatinine clearance in survivors up to 90 yr according to the change of BP from age 85 up to 90. Those with a decline in SBP had an accelerated decline of creatinine clearance—from age 85 up to 90—compared with those with a stable SBP (1.54 [SE 0.09] versus 0.98 ml/min per yr [SE 0.09]; P < 0.001). Those with a decline in DBP had an accelerated decline of creatinine clearance—from age 85 up to 90—compared with those with a stable DBP also (1.54 [SE 0.10] versus 1.07 ml/min per yr [SE 0.08]; P < 0.001). There were no

Table 2. Additional change in creatinine clearance (ml/min) per year during follow-up until death or the age of 90, according to the number of cardiovascular diseases, the history of hypertension, and the history of diabetes at baseline in 550 participants

<table>
<thead>
<tr>
<th></th>
<th>Crude Model</th>
<th>Adjusted Model</th>
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<tbody>
<tr>
<td></td>
<td>ml/min (SE)</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cardiovascular diseases</td>
<td>−0.21 (0.07)</td>
<td>0.002</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>−0.12 (0.12)</td>
<td>0.31</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>−0.18 (0.17)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*Analyses with linear mixed model with estimates plus SE of the mean. Crude model: adjusted for gender. Adjusted model: adjusted for gender and use of antihypertensive medication at ages 85 and 86.
*Change per additional number (range 0 to 5) of cardiovascular diseases present.
*Change according to positive history versus negative history of hypertension and diabetes.
associations between the presence of chronic disease, cardiovascular disease, history of hypertension, or use of antihypertensive medication at baseline and a decline versus an increase in SBP or DBP between 85 and 90 yr (data not shown).

Discussion

In our prospective, population-based study of the oldest individuals, we found no association between high SBP and decline of creatinine clearance during follow-up. Strikingly, a DBP <70 mmHg preceded an accelerated decline of creatinine clearance during follow-up. Moreover, a decline in SBP and DBP from age 85 up to 90 was related to an accelerated decline of creatinine clearance.

In younger age groups, the deleterious effect of elevated DBP and SBP on renal function is beyond doubt (13). Up to an average age of 72 yr, harmful effects of SBP on renal function has been reported (14). Intervention trials have shown that BP lowering prevents renal failure, independent of renal function at baseline (15). Therefore, it is surprising that we could not find an association between elevated BP (DBP and SBP) and creatinine clearance in our elderly participants. To date, only one published longitudinal study with a considerable amount of very old participants has shown that high BP was associated with a decline of creatinine clearance (7). However, renal function was estimated with two measurements of serum creatinine 3 yr apart. In older people, serum creatinine is less reliable as an estimate for renal function because of progressive loss of muscle mass (1,16). In addition, only 60% of the participants who attended the first examination were reexamined after 3 yr, possibly inducing selection bias. We did find an annual decline of renal function of 1.3 ml/min per yr and also gender differences in creatinine clearances, both in line with the literature.
(17–20). In addition, a strong association with cardiovascular disease and creatinine clearance existed at baseline and during follow-up (21). Therefore, we do think that our data are reliable and representative for the oldest individuals.

How can we explain the effect of a low DBP on creatinine clearance over time and the accelerated decline in creatinine clearance that is associated with a decline in BP? Possibly, a low DBP in the ninth decade is a reflection of a decline in BP in the years before. The underlying mechanism of the accelerated decline of creatinine clearance might be chronic hypoperfusion of the kidneys. The vulnerability of the kidney in the elderly could be related to an impaired autoregulatory response of the renal arteries in the presence of atherosclerosis.

Different from in middle age, high BP in the elderly has been associated with an increased, equal, or even decreased mortality (22–24). Within our prospective cohort study, high BP was not related to an increased mortality risk after age 85 yr (25). In addition, it is not established whether hypertension should be treated in the very old. A meta-analysis of treated participants of 80 yr and older included in hypertension trials had inconsistent results (5). A placebo-controlled trial for treatment of hypertension in people who are older than 80 yr is still running (26). The pilot study did not show a survival benefit for treatment; even worse, a nonsignificant trend toward excess mortality was found in the treated group (4). However, some beneficial effect was seen on the reduction of strokes. Given these considerations, our finding that an elevated BP is not a risk factor for decline of renal function in the oldest individuals is of interest.

Because our data are from a prospective, population-based study with a high response rate and virtually no dropouts during follow-up, we were able to observe the impact of BP on renal function of the oldest individuals in the population at large. Another strength is that we measured BP twice and assessed the creatinine clearance yearly for a period of 5 yr. Although the estimation of creatinine clearance with the Cockcroft-Gault formula is not the gold standard to measure renal function, this is a very widely used and validated method for estimation of creatinine clearance (11,16,17,19). Because we did not have reliable data on clinical heart failure, this might have influenced our results. The linear mixed model that was used is an accurate model that can handle random missing data. Participants who die probably will not die at random. However, our results remained similar in the additional analyses without the participants who died within the first year and also in the restricted analyses for survivors up to age 90 yr. These additional analyses show that our results are unlikely to be influenced by underlying survivor bias.

In contrast with younger age groups, elevated SBP and DBP did not influence the annual decline in renal function in the oldest individuals. A DBP <70 mmHg and a decline in SBP or DBP between ages 85 and 90 was related to an accelerated decline of creatinine clearance over time. Clinical implications of these findings have to be studied more in depth.

Acknowledgment

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References

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