Accelerated Decline in Renal Perfusion With Aging in Essential Hypertension

Roland E. Schmieder, Hartmut Schächinger, Franz H. Messerli

Abstract The present cross-sectional study was designed to assess the effect of the severity of hypertensive cardiovascular disease and age on renal hemodynamics. In a homogeneous population of 157 white men (aged 15 to 87 years), we assessed renal and systemic hemodynamics by measuring mean arterial pressure invasively, renal blood flow by $^{131}$I-para-aminohippuric acid clearance, and cardiac output by the indocyanine dye dilution technique. Stepwise multiple regression analysis revealed the following independent determinants of renal blood flow: age ($\beta=-.42, P<.001$), height ($\beta=-.14, P<.03$), mean arterial pressure ($\beta=-.15, P<.02$), and cardiac output ($\beta=+.19, P<.008$). Renal blood flow corrected for height correlated inversely with age in all three groups. However, the renal fraction of cardiac output did not correlate with age in borderline hypertension ($r=.17, P=NS$) and in normotension ($r=.12, P=NS$), suggesting a parallel decline in renal blood flow and cardiac output with aging. In contrast, in established hypertension, the renal fraction of cardiac output was closely linked to age ($r=-.52, P<.001$) and significantly steeper ($P<.01$) than in normotension or borderline hypertension. We conclude that unlike in normotensive subjects or patients with borderline hypertension, patients with established hypertension have an accelerated decline in renal perfusion with aging, reflecting selective functional or structural changes or both in the renal vascular bed. (Hypertension. 1994;23:351-357.)

Key Words • renal circulation • hemodynamics • cardiac output • nephrosclerosis

Structural changes in the vascular bed of the kidneys caused by arterial hypertension, termed arteriolar nephrosclerosis, have been found to correlate with similar changes in the retina, pancreas, and salivary glands but nevertheless do occur more frequently and extensively in the kidneys than in any other organ. Studies of end-stage renal disease showed that hypertension accounted for 15% to 20% of all cases of renal failure in the United States, a percentage that increased to 30% of cases of renal failure in minority populations. In a previous report on the natural history of essential hypertension (at a time when high blood pressure frequently remained untreated), 18% of 350 patients had evidence of impaired renal function that led to end-stage renal disease in 12%.

At necropsy, 68% to 97% of patients with well-established hypertension had histologically proven renal arteriosclerosis. The severity of arteriolar renal involvement appeared to be determined by the severity of hypertensive disease. The degree of the renal vascular involvement, either structural or functional, was closely correlated with the reduction in renal blood flow. A subsequent study using selective renal arteriography confirmed a good correlation between the severity of medium-sized vessel disease and the reduction in total renal blood flow. Therefore, the assessment of renal blood flow emerged as an excellent noninvasive tool for detecting the severity of renal vascular involvement in hypertensive disease. Whereas renal perfusion may be increased in a distinct cohort of subjects strongly predisposed to developing arterial hypertension, in general it progressively declines, and renal vascular resistance rises with the natural course of untreated essential hypertension.

Changes in renal hemodynamics caused by arterial hypertension should be related to the systemic hemodynamic state. Roughly 20% of the cardiac output is distributed to the kidneys, but the fraction of cardiac output perfusing the kidneys might vary significantly. From a hemodynamic viewpoint, the initial stage of essential hypertension is predominantly characterized by an increased cardiac output and numerically normal but inappropriately high total peripheral resistance. As hypertensive disease progresses, cardiac output returns to normal and later falls below normal limits, ultimately progressing to congestive heart failure. Conversely, total peripheral resistance increases continuously with progressive hypertensive disease and is therefore considered to represent the hemodynamic hallmark for the severity of arterial hypertension.

To determine whether hemodynamic changes in the renal vascular bed parallel those in the systemic circulation or are more exaggerated in the renal than systemic circulation with progressive hypertensive disease and age, we analyzed a study population of 157 white men with a wide range in age and blood pressure in whom simultaneous renal and systemic hemodynamic findings were assessed. Our results indicate that the renal circulation is more susceptible to hypertensive pressure levels than the systemic circulation.
TABLE 1. White Men Divided According to Casual Blood Pressure: Clinical and Hemodynamic Findings

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotension (n=33)</th>
<th>Borderline Hypertension (n=56)</th>
<th>Essential Hypertension (n=68)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>36±12</td>
<td>35±12</td>
<td>46±10</td>
<td>.001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175±7</td>
<td>179±7*</td>
<td>175±7</td>
<td>.02</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85±19</td>
<td>88±16</td>
<td>87±14</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.7±5.3</td>
<td>27.4±4.6</td>
<td>28.2±4.2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>88±7</td>
<td>97±9</td>
<td>106±12</td>
<td>.001</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>6.16±1.6</td>
<td>6.93±1.4*</td>
<td>6.08±1.2</td>
<td>.002</td>
</tr>
<tr>
<td>Total peripheral resistance, U</td>
<td>15.3±4.3</td>
<td>14.6±3.4</td>
<td>18.1±4.0†§</td>
<td>.001</td>
</tr>
<tr>
<td>Renal blood flow, mL/min</td>
<td>1246±291</td>
<td>1221±278</td>
<td>1030±345§</td>
<td>.001</td>
</tr>
<tr>
<td>Renal vascular resistance, U</td>
<td>75±19</td>
<td>84±23</td>
<td>116±47‡§</td>
<td>.001</td>
</tr>
<tr>
<td>Renal fraction of cardiac output, %</td>
<td>20.8±4.5</td>
<td>18.1±4.7*</td>
<td>17.1±5.2‡</td>
<td>.002</td>
</tr>
</tbody>
</table>

Overall significance level according to ANOVA; symbols in the table represent probability value modified according to the Bonferroni method.

*P<.05, borderline hypertension vs normotension.
†P<.01, borderline hypertension vs hypertension.
‡P<.01, hypertension vs normotension.
§P<.01, hypertension vs borderline hypertension.

Methods

Study Population

The study group comprised 157 white men with various ages and blood pressure levels who were consecutively enrolled in the study protocol over the previous 3 years. Mean age was 40±12 years, and average body mass index was 27.9±5.4 kg/m². Thirty-three were considered to be normotensive, 56 to have borderline hypertension, and 68 to have established hypertension (stages I and II, Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure [JNC VI]).15 Patients were classified according to three casual blood pressure readings assessed with a standard sphygmomanometer on two different occasions after they had rested 5 minutes. Cuff size was adjusted according to arm circumference. Hypertensive patients either did not receive any cardiovascular medication or treatment was discontinued at least 4 weeks before the invasive study began and casual blood pressure measurements were taken. None of the participants followed any specific dietary guidelines before the hemodynamic evaluation. Each participant underwent a complete routine clinical workup.

TABLE 2. Determinants of Renal Blood Flow

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Explained Variance (r²)</th>
<th>Standard Correlation Coefficient (β)</th>
<th>Significance (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.33</td>
<td>- .42</td>
<td>.001</td>
</tr>
<tr>
<td>Height</td>
<td>.42</td>
<td>+ .14</td>
<td>.034</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>.40</td>
<td>- .15</td>
<td>.023</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>.38</td>
<td>+ .19</td>
<td>.008</td>
</tr>
<tr>
<td>Stroke volume/pulse pressure</td>
<td>.08</td>
<td>- .11</td>
<td>.52</td>
</tr>
<tr>
<td>Body mass index</td>
<td>.03</td>
<td>+ .04</td>
<td>.27</td>
</tr>
</tbody>
</table>

Total study population=157.

Normotensive subjects participated as volunteers or underwent hemodynamic evaluation to ensure that their cardiovascular system was normal; some patients were referred to us because of nonspecific discomfort during exercise, and others were recruited by an advertisement in the local newspaper. Clinical and extensive laboratory investigations showed completely normal results in the normotensive subjects. Patients with borderline and sustained arterial hypertension were enrolled only if secondary hypertension had been ruled out as well as World Health Organization (WHO) stage III of hypertensive disease. Therefore, exclusion criteria were advanced hypertensive fundoscopic changes, myocardial infarction or other evidence of coronary artery disease, congestive heart failure (New York Health Association classes II through IV), previous cerebrovascular event, and hepatic or renal insufficiency. In particular, 12-lead electrocardiogram, fundoscopic evaluation, chest radiograph, and two-dimensional echocardiogram were performed. Echocardiographic evidence of left ventricular hypertrophy or mild proteinuria was found in some subjects. Exercise treadmill testing or detailed evaluation of hormones and endocrine metabolites was conducted only if indicated.

The protocol for the study was approved by our clinical investigation committee, and informed written consent was obtained from each participant.

Hemodynamic Assessment

Subjects were studied in the hemodynamic laboratory of the Ochsner Medical Institutions after an overnight fast. Systemic and renal hemodynamic measurements were assessed by methods previously reported in detail.16 In brief, using the modified Seldinger procedure, catheters were inserted into a brachial artery and an antecubital vein and advanced to the ascending aorta just proximal to the subclavian artery and superior vena cava, respectively. Continuous recording of arterial pressure was obtained simultaneously with the electrocardiogram. Systolic cardiac output was determined in triplicate, using indocyanine green dye (5 mg). Mean arterial pressure was assessed...
RELATIONSHIP BETWEEN CARDIAC OUTPUT AND RENAL BLOOD FLOW IN ESSENTIAL HYPERTENSION

RELATIONSHIP BETWEEN CARDIAC OUTPUT AND RENAL BLOOD FLOW IN NORMOTENSION

HYPERTENSIVE PATIENTS

NORMOTENSIVE SUBJECTS

FIG 1. Scatterplots show correlation between cardiac output (CO) and renal blood flow (RBF) in hypertensive patients (left) and normotensive subjects (right). The regression line between RBF and CO was significantly lower in hypertension than normotension (P<.05). NT indicates normotension; EH, essential hypertension.

Renal plasma flow was determined by measuring the single-injection clearance of para-aminohippuric acid (PAH) tagged with iodine-131 (40 μCi/1.73 m²). By application of the two-compartment model, renal plasma flow was calculated from the disappearance curve of I¹³¹-PAH.18-19 Arterial blood samples were immediately centrifuged to avoid contamination of the plasma with PAH that originated from red blood cells. In normotensive subjects, the PAH extraction is approximately 90% and is not substantially reduced until renal plasma flow is

FIG 2. Scatterplots show correlation between age and renal blood flow corrected for height (RBF/HT) (left) and renal fraction of cardiac output (RBF/CO) (right) in normotensive subjects.
RENAL PERFUSION IN BORDERLINE HYPERTENSION IN AGING

Fig 3. Scatterplots show correlation between age and renal blood flow corrected for height (RBF/HT) (left) and renal fraction of cardiac output (RBF/CO) (right) in patients with borderline hypertension.

less than 300 mL/min. Renal blood flow was computed from renal plasma flow and hematocrit, renal vascular resistance by dividing mean arterial pressure by renal blood flow, and the fraction of cardiac output distributed to the kidneys by the ratio of renal blood flow to cardiac output. Of note, the single-injection technique may result in a slight but systematic overestimation of PAH clearance; most importantly, however, the single-injection technique determines renal plasma flow reliably compared with the clearance techniques that require urinary collections.

Statistics
Group data are expressed as mean±1 SD in the text. By study design, comparisons among normotensive subjects and patients with borderline and those with established hypertension were restricted to white men only. The clinical characteristics among the three groups classified according to casual blood pressure were compared by ANOVA. Significance levels were modified for multiple comparisons by the Bonferroni method. Linear regression analysis (Pearson) and multiple regression analysis were applied by using SAS programs. The slopes of the regression lines of the correlations between age and renal blood flow were compared among the three groups by ANOVA. In the multiple regression analysis, eight variables were entered. In the first step, the most powerful determinant was identified; the second and subsequent steps identified determinants that were independent of the first and explained additional variance of the dependent parameter, ie, renal blood flow.

Results

Clinical and Hemodynamic Characteristics
The clinical and hemodynamic characteristics of the 157 white men who fulfilled all study entry criteria are listed in Table 1. According to the WHO criteria, the study group consisted of 33 normotensive subjects, 56 patients with borderline hypertension, and 68 with sustained hypertension. Cardiac output was mildly but significantly elevated in borderline hypertensive patients (P<.05) but similar in normotensive control subjects and patients with established hypertension. In contrast, renal blood flow was lower in hypertensive patients than normotensive subjects (P<.01). In borderline hypertension, the renal fraction of cardiac output was mildly reduced (P<.05). As cardiac output was increased (P<.05), renal blood flow was (inappropriately) normal. In established essential hypertension, the renal fraction of cardiac output was decreased because of reduced renal blood flow (P<.01), whereas cardiac output was similar to that of normotensive control subjects (Table 1).

Multiple Regression Analyses
The following variables were entered as potential determinants of renal blood flow without priority for any: age, height, body mass index (as a parameter for obesity), mean arterial pressure, cardiac output, and stroke volume/pulse pressure as a rough estimate of distensibility of large arteries (Table 2). Age was the most powerful determinant of renal blood flow (P<.001) and explained more than one third of the variance of renal blood flow in the 157 subjects examined. In the second step, body height emerged as an independent factor of renal blood flow (P<.034). Mean arterial pressure (P<.023) and cardiac output (P<.008) were found to be additional determinants independent of age and height. The degree of obesity did not emerge as an independent determinant for renal blood flow nor did stroke volume/pulse pressure index. Because height emerged as an independent deter-
RENAL PERFUSION IN ESSENTIAL HYPERTENSION WITH AGING

**Interaction of Cardiac Output and Renal Blood Flow**

In the entire study population, cardiac output declined with progressive age ($r=-.31, P<.001$) and in normotension ($r=-.40, P<.01$), borderline hypertension ($r=-.37, P<.01$), and established hypertension ($r=-.28, P<.05$). Cardiac output correlated with renal blood flow ($r=+.40, P<.001$) in all subjects. When analyzing these correlations separately, we observed a significant correlation between cardiac output and renal blood flow in normotensive subjects ($r=+.56, P<.001$), borderline hypertensive patients ($r=+.34, P<.01$), and hypertensive patients ($r=+.34, P<.01$). Of note, the regression line of cardiac output versus renal blood flow was significantly lower in hypertensive patients than normotensive subjects ($P<.01$), indicating that at any given level of cardiac output, renal blood flow was lower in hypertensive patients than normotensive subjects (Fig 1). Hence, in various stages of essential hypertension, renal perfusion was dependent on systemic circulation.

**Interaction of Age and Renal Perfusion in Hypertension**

With increasing age, renal blood flow progressively decreased ($r=-.31, P<.001$) in subjects with normal blood pressure ($r=-.35, P<.01$; Fig 2) and in patients with borderline hypertension ($r=-.58, P<.001$; Fig 3) and established hypertension ($r=-.56, P<.001$; Fig 4). The values of renal perfusion were related to height, because height was previously identified as a powerful determinant of renal blood flow. Most importantly, the decline of renal blood flow per decade, i.e., the slope of the regression lines, was significantly different ($P<.03$) between normotension and borderline hypertension and between normotension and established hypertension (Fig 5).

We did not observe any relation between age and the renal fraction of cardiac output (renal blood flow/cardiac output) in normotension and borderline hypertension (Figs 2 and 3). This finding was obviously related to the fact that with aging, renal blood flow declined in parallel to the fall in cardiac output throughout the life span in normotension and borderline hypertension. In contrast, in established essential hypertension, age correlated inversely with the renal fraction of cardiac output ($r=-.52, P<.01$; Fig 4). Moreover, the regression line of the renal fraction of cardiac output and age was steeper in established hypertension than in normotension and borderline hypertension ($P<.01$, Fig 5).

**Discussion**

In the present analysis of 157 white men, age, cardiac output, mean arterial pressure, and height emerged as independent determinants of renal blood flow. Obesity per se (as measured by body mass index) was not found to be independently correlated with renal blood flow, a finding that is in accordance with a more specific analysis of the effect of obesity on renal function. Although the age-related decline of renal perfusion has been repeatedly documented, our results imply that values for renal blood flow should be adjusted for height in addition to age to allow comparison among groups at various levels of arterial pressure.

Whether arterial pressure is related to the decrease of renal perfusion in mild to moderate hypertension is still
AGE-RELATED CHANGES IN RENAL PERFUSION AT VARIOUS STAGES OF HYPERTENSIVE DISEASE

![Graph showing comparison of regression lines between age and renal blood flow corrected for height (RBF/HT) (left) and renal fraction of cardiac output (RBF/CO) (right) among white men with normotensive (NH), borderline hypertensive (BH), and hypertensive (EH) blood pressure values.](http://hyper.ahajournals.org/)

controversial. Some groups have reported a negative relation between arterial pressure and renal blood flow; others have claimed that no such correlation exists. Without doubt, renal blood flow is seriously impaired in malignant hypertension. To precisely assess the interaction between age and mild to moderate hypertension and renal perfusion, we restricted the present analysis to a large homogeneous study group of white men only. With this design we eliminated any potential influence of sex and race reported previously.

We found that when compared with normotensive subjects, the decline in renal perfusion was accelerated with aging if blood pressure became elevated into the borderline hypertensive range. These data would suggest that the renal vasculature already faces a double burden in mildly elevated blood pressure levels imposed by the physiological process of aging and the pathological process of hypertension. However, the assumption that renal blood flow is a dependent variable remains questionable as long as a third major determinant of renal perfusion, namely cardiac output, is not taken into account.

In the current study, cardiac output emerged as an independent determinant of renal blood flow in humans. Renal perfusion was found to be closely linked to cardiac output in normotensive, borderline hypertensive, and hypertensive states. In borderline hypertension, the fraction of cardiac output distributed to both kidneys was significantly reduced, predominantly resulting from a lack of increase in renal blood flow despite the observed increase in cardiac output. Most previous studies reported a slightly decreased renal blood flow in borderline hypertension. This pattern of a lack of increase in renal blood flow despite the hyperdynamic systemic circulation suggests vasoconstriction in the renal vasculature. With increasing age, the decline in renal blood flow paralleled the fall in cardiac output, because the renal fraction of cardiac output was similar throughout the life span and was not significantly different from the values of normotensive subjects. Thus, when changes in renal perfusion were related to those in systemic circulation, no decline of renal perfusion (expressed as renal blood flow/cardiac output) with aging was noted in borderline hypertension (Fig 5). The steeper fall in renal blood flow with aging in borderline hypertension compared with normotension (Fig 5) therefore was related to the concomitant systemic hemodynamic changes.

Quite in contrast, in established hypertension, renal blood flow and most importantly the renal fraction of cardiac output decreased excessively with aging compared with normotension and borderline hypertension. This result clearly indicates an exaggerated adaptation of the renal vascular tree caused by hypertension and age. Several studies provided evidence that this reduction in renal blood flow with hypertension is predominantly functional and not structural. The decrease in renal blood flow and the renal fraction of cardiac output with hypertension was found to be reversible with administration of centrally acting sympatholytic agents. However, structural processes in the renal vascular bed also appeared to be responsible for the age-related fall in renal perfusion, because age per se reduced the vasodilator response to administration of acetylcholine and sodium load. Furthermore, a close negative relation between renal blood flow and the severity of arteriolar nephrosclerosis was noted in a series of more than 100 renal biopsies.
We conclude from our study in white men that age, cardiac output, mean arterial pressure, and height but not obesity were independent determinants of renal perfusion. In normotension and borderline hypertension, the fall in renal blood flow with age paralleled the fall in cardiac output. In contrast, established hypertension the fall in renal perfusion with age was accelerated, reflecting selective functional or structural changes or both in the renal vascular bed.

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References


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