Glomerular Hyperfiltration in Hypertensive African Americans


Abstract—The incidence of end-stage renal disease attributable to hypertension is 5-fold greater in African Americans than in whites. To determine whether glomerular hyperfiltration is an antecedent to renal failure, we compared responses of renal blood flow and glomerular filtration rate to graded infusions of norepinephrine (0.01, 0.025, and 0.05 μg · kg⁻¹ · min⁻¹ for 30 minutes each) in 29 African Americans and 33 age-matched French Canadian whites with essential hypertension. Renal blood flow and glomerular filtration rate were measured by using a constant-infusion technique of PAH and inulin, respectively. Studies were conducted on an inpatient clinical research center, and antihypertensive medications had been discontinued for at least 1 week. Based on 24-hour blood pressure monitoring, nighttime blood pressures decreased (P<0.01) in the French Canadians but not in the African Americans. Baseline renal blood flow was higher (P<0.05) in the African Americans (1310±127 mL · min⁻¹ per 1.73 m²) than in the French Canadians (1024±42 mL · min⁻¹ per 1.73 m²); baseline glomerular filtration rate was also higher (P<0.01) in the African Americans (140±4 versus 121±4 mL · min⁻¹ per 1.73 m²). In response to norepinephrine-induced blood pressure increases, renal blood flow was autoregulated and did not change in either patient group. In the African Americans, glomerular filtration rate increased (P<0.01) to 167 mL · min⁻¹ per 1.73 m² during the first norepinephrine infusion, without subsequent change. In contrast, glomerular filtration rate did not change with norepinephrine-induced increases of blood pressure in the French Canadians. In the African Americans, the elevation of baseline glomerular filtration rate, with a further increase in response to norepinephrine, may be indicative of glomerular hyperfiltration. Glomerular hyperfiltration and lack of nocturnal blood pressure decline may contribute to the higher incidence of end-stage renal disease in hypertensive African Americans. (Hypertension. 2000;35:822-826.)

Key Words: blood pressure monitoring, ambulatory ■ glomerular filtration rate ■ norepinephrine ■ plasma renin activity ■ renal blood flow

Elevated blood pressure and black race are strong risk factors for the development of end-stage renal disease.¹ Hypertensive African Americans have a greater rate of decline of renal function over time than do whites,²–⁴ and African American men have a 4-fold higher incidence of age-adjusted end-stage renal disease than do white men.⁵ The incidence of end-stage renal disease in African Americans attributable to hypertension has been increasing since 1980 and is >5-fold greater in African Americans than in whites.⁵,⁶ Although higher blood pressure levels may contribute to the excess risk of end-stage renal disease in African Americans,⁴,⁷ the racial disparity in hypertension-related renal disease may not be entirely explained by a greater prevalence of hypertension or inadequate hypertension control in African Americans.⁵,⁹ Alternatively, the kidneys of African Americans may be more susceptible to the adverse effects of elevated blood pressure than the kidneys of whites, possibly because of a genetic susceptibility to renal disease in African Americans.⁸–¹² Genetic susceptibility to renal failure has been demonstrated in a locus distinct from that of blood pressure in the fawn-hooded rat,¹³ and cross-transplantation studies have demonstrated that the kidney of the normotensive Brown Norway rat is inherently more susceptible to hypertension-induced damage than is the kidney of the spontaneously hypertensive rat.¹⁴ The early renal lesions of nephrosclerosis include ischemic glomerular collapse as well as focal and segmental glomerulosclerosis, and these latter changes may be related to glomerular hyperperfusion.¹⁵,¹⁶ In animal models of hypertension, glomerular hyperfiltration precedes and hastens the development of glomerulosclerosis.¹⁷–²⁰ Similarly, in patients with insulin-dependent diabetes mellitus, a high glomerular filtration rate (GFR) predicts the development of nephrosclerosis.²¹–²³ In white patients with essential hypertension, Schmieder et al²⁴ have reported that a high creatinine clearance, indicating glomerular hyperfiltration, is linked to an increase of serum creatinine during a subsequent 6-year follow-up.

The present study was undertaken to evaluate the hypothesis that glomerular hyperfiltration is an antecedent to the suscepti-
bility for renal failure in hypertensive African Americans. In conjunction with ongoing collaborative studies of the genetic determinants of hypertension, renal hemodynamic responses to acute elevations of blood pressure induced by norepinephrine infusion were compared in African Americans with essential hypertension and in a group of white French Canadians with essential hypertension.

Methods
African Americans were studied at the Medical College of Wisconsin in Milwaukee, and French Canadians were studied at Chicoutimi Hospital, located in the Saguenay–Lac St. Jean region of Canada. Identical protocols were carried out on inpatient clinical research centers at both sites. To ensure standardization of these protocols, investigators and other clinical staff conducted periodic exchange visits between the 2 sites. The protocols were approved by the appropriate Human Research Review Committees at both participating institutions.

Consenting patients, aged 18 to 55 years, with essential hypertension were potential candidates for study. In conjunction with our protocols for studying the genetic determinants of hypertension, an added inclusion criterion was a serum cholesterol concentration >200 mg/dL. Exclusion criteria included secondary hypertension, diastolic blood pressure >110 mm Hg on drug therapy, diabetes mellitus, serum creatinine concentration >2.2 mg/dL, body mass index (BMI) >34 kg/m², pregnancy, malignancy, substance abuse (including alcohol), and myocardial infarction or stroke within 6 months.

Before study, lipid-lowering medications were withdrawn for 1 month, and antihypertensive drugs were withdrawn for at least 1 week. At both sites, patients were admitted to an inpatient clinical research center 2 days before the renal hemodynamic studies and were placed on a weight-maintaining diet containing 150 mEq Na⁺ and 80 mEq K⁺. On day 1, baseline measurements included a fasting lipid profile and measurements of plasma renin activity and plasma aldosterone concentration that were taken after patients had been in the supine position for 60 minutes and again after they had been standing for 10 minutes. Also on day 1, for a 24-hour period, urine was collected for measurement of microalbumin excretion, and blood pressure was measured with an Accutracker (Suntech Medical Instruments, Inc) every 20 minutes during the day (5:00 AM to 11:00 PM) and every 45 minutes during the night (11:00 PM to 5:00 AM).

On day 2, renal blood flow (PAH clearance) and GFR (inulin clearance) were measured in response to graded infusions of norepinephrine. Intravenous catheters were inserted in both arms, with 1 catheter used for infusions and 1 used for sampling venous blood. At time 0, after catheter insertion, an infusion of normal saline, containing PAH (12 mg/min) also infused in normal saline at a rate of 125 mL/h. Blood pressures were measured with an Accutracker (Suntech Medical Instruments, Inc) every 15 minutes during the day (5:00 AM to 11:00 PM) and every 45 minutes during the night (11:00 PM to 5:00 AM).

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Table 1. Baseline Data for the 2 Patient Groups

<table>
<thead>
<tr>
<th></th>
<th>African Americans</th>
<th>French Canadians</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>46±1</td>
<td>48±1</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>33.3±1.3</td>
<td>26.7±0.6*</td>
</tr>
<tr>
<td><strong>Day SBP, mm Hg</strong></td>
<td>144±3</td>
<td>137±3†</td>
</tr>
<tr>
<td><strong>Day DBP, mm Hg</strong></td>
<td>87±2</td>
<td>85±2</td>
</tr>
<tr>
<td><strong>Night SBP, mm Hg</strong></td>
<td>142±4</td>
<td>121±3*</td>
</tr>
<tr>
<td><strong>Night DBP, mm Hg</strong></td>
<td>83±2</td>
<td>76±2†</td>
</tr>
<tr>
<td><strong>PRA, ng·mL⁻¹·h⁻¹</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Supine</strong></td>
<td>1.1±0.2</td>
<td>1.8±0.2†</td>
</tr>
<tr>
<td><strong>Standing</strong></td>
<td>1.8±0.3</td>
<td>2.9±0.3†</td>
</tr>
<tr>
<td><strong>Serum creatinine, mg/dL</strong></td>
<td>0.9±0.1</td>
<td>0.9±0.1</td>
</tr>
<tr>
<td><strong>Urine microalbumin, mg/24 h</strong></td>
<td>14.3±1.6</td>
<td>10.4±1.1†</td>
</tr>
<tr>
<td><strong>Serum cholesterol, mg/dL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>204±7</td>
<td>213±9</td>
</tr>
<tr>
<td><strong>LDL</strong></td>
<td>132±6</td>
<td>141±9</td>
</tr>
<tr>
<td><strong>HDL</strong></td>
<td>50±3</td>
<td>39±2*</td>
</tr>
<tr>
<td><strong>Serum triglycerides, mg/dL</strong></td>
<td>114±12</td>
<td>201±31†</td>
</tr>
</tbody>
</table>

Values are mean±SE. SBP and DBP indicate systolic and diastolic blood pressures, respectively; PRA, plasma renin activity. *P<0.001; †P<0.05.

Results
A total of 29 African Americans and 33 French Canadians completed the entire protocol. Mean ages of the 2 groups did not differ. BMI and body surface area were greater (P<0.01) in African Americans (Table 1). During the day, mean systolic blood pressure was higher (P<0.05) in African Americans than in the French Canadians, although mean diastolic blood pressures did not differ. Night blood pressures decreased (P<0.01) in the French Canadians but not in the African Americans, and when the 2 groups were compared, mean systolic and diastolic blood pressures during the night were lower (P<0.001 and P<0.05, respectively) in the
French Canadians. Although serum creatinine concentrations did not differ, urine microalbumin excretion was greater \( (P<0.01) \) in the African Americans than in the French Canadians. Supine and standing plasma renin activities were lower \( (P<0.05) \) in the African Americans. Total serum cholesterol and LDL cholesterol concentrations did not differ in the 2 patient groups. However, mean HDL cholesterol was higher \( (P<0.01) \) and mean serum triglyceride concentration was lower \( (P<0.05) \) in the African Americans than in the French Canadians.

Before infusion of norepinephrine, mean arterial pressure was higher \( (P<0.05) \) in the African Americans than in the French Canadians (Table 2). In response to graded infusions of norepinephrine, both systolic and diastolic blood pressures increased significantly \( (P<0.001) \) at each dose in African Americans (Figure 1). Systolic blood pressure also increased \( (P<0.001) \) progressively in French Canadians, although diastolic blood pressure did not. Overall, systolic blood pressure responses to norepinephrine did not differ in African Americans and French Canadians, whereas diastolic blood pressure increased to a significantly greater extent \( (P<0.001) \) in African Americans. Baseline heart rates in African Americans and French Canadians did not differ \( (69\pm1 \text{ versus } 70\pm2 \text{ bpm}) \). In African Americans, heart rate did not increase in response to norepinephrine; however, in French Canadians, heart rate increased \( (P<0.01) \) to \( 76\pm3 \text{ bpm} \) at the highest infusion rate.

Before infusion of norepinephrine, baseline renal blood flow and GFR were higher \( (P<0.05 \text{ and } P<0.01, \text{ respectively}) \) in African Americans than in French Canadians (Table 2). Within each of the 2 patient groups, renal blood flow and GFR did not differ in males and females. In African Americans, renal blood flow did not change significantly during norepinephrine infusion (Figure 2). However, compared with baseline, GFR increased \( (P<0.001) \) at the end of the first norepinephrine infusion, without further change at the 2 subsequent infusion rates. The increment of GFR was not correlated with the increment of arterial pressure. In French Canadians, neither renal blood flow nor GFR increased with norepinephrine infusion. Baseline RVR did not differ in African Americans and French Canadians, and no detectable changes of RVR were observed in either group during norepinephrine infusion.

**Discussion**

Among patients with essential hypertension, blood pressure level and alterations in renal hemodynamics resulting in both glomerular ischemia and increased glomerular capillary pressure level may play a vital role in the progressive decline of GFR.\(^{19,31}\) In the present study, although African Americans had slightly higher daytime systolic blood pressure levels than did whites, the blood pressure difference was magnified during the night because of a nighttime reduction of blood pressure in whites but not in African Americans. In response to graded infusions of norepinephrine, systolic blood pressure increased to a similar extent in both African Americans and French Canadians. Although serum creatinine concentrations did not differ, urine microalbumin excretion was greater \( (P<0.01) \) in the African Americans than in the French Canadians. Supine and standing plasma renin activities were lower \( (P<0.05) \) in the African Americans. Total serum cholesterol and LDL cholesterol concentrations did not differ in the 2 patient groups. However, mean HDL cholesterol was higher \( (P<0.01) \) and mean serum triglyceride concentration was lower \( (P<0.05) \) in the African Americans than in the French Canadians.

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**Table 2. Baseline Renal Hemodynamic Measurements**

<table>
<thead>
<tr>
<th></th>
<th>African Americans</th>
<th>French Canadians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>110±3</td>
<td>103±3*</td>
</tr>
<tr>
<td>Renal plasma flow, mL · min(^{-1}) per 1.73 m(^2)</td>
<td>832±82</td>
<td>589±26†</td>
</tr>
<tr>
<td>Renal blood flow, mL · min(^{-1}) per 1.73 m(^2)</td>
<td>1310±127</td>
<td>1024±42*</td>
</tr>
<tr>
<td>GFR, mL · min(^{-1}) per 1.73 m(^2)</td>
<td>140±4</td>
<td>121±4†</td>
</tr>
<tr>
<td>RVR, dyne · s(^{-1}) · cm(^{-5}) per 1.73 m(^2)</td>
<td>12 800±800</td>
<td>15 200±800</td>
</tr>
</tbody>
</table>

Values are mean ± SE.

*\(P<0.05\); †\(P<0.01\).

**Figure 1.** Systolic blood pressure (SBP) and diastolic blood pressure (DBP) responses to graded infusions of norepinephrine (NE) in African American and French Canadian patients.

+\(P<0.01\) vs control period or lower NE dose in same patient group; *\(P<0.01\) vs African Americans at same time period; **\(P<0.05\) vs African Americans at same time period.

**Figure 2.** Renal blood flow and GFR responses to graded infusions of NE in African American and French Canadian patients.

+\(P<0.01\) vs control period in same patient group; *\(P<0.01\) vs African Americans at same time period; **\(P<0.05\) vs African Americans at same time period.
whites; however, diastolic blood pressure increased only in African Americans. Renal blood flow, GFR, and microalbumin excretion rates were higher in African Americans than in whites. In response to norepinephrine, renal blood flow did not change in either whites or African Americans. However, the capacity to autoregulate GFR in response to norepinephrine-induced elevations of arterial pressure was impaired in African Americans but not in whites.

Previous studies have also demonstrated that black hypertensive patients, particularly American blacks, have an attenuated nocturnal blood pressure dip compared with white hypertensive patients.\textsuperscript{32–35} Similar observations have been made comparing black and white normotensive individuals.\textsuperscript{31,36,37} Failure of blood pressure to fall during the nighttime is associated with a higher incidence of target organ damage, including left ventricular hypertrophy, retinopathy, stroke, and cardiovascular morbidity.\textsuperscript{38–43} Previous reports have also shown that black hypertensive patients have an exaggerated pressor response to norepinephrine infusion as well as to a variety of environmental and psychological stressors.\textsuperscript{44–46}

Several earlier studies have compared renal hemodynamic measurements in black and white hypertensive patients with somewhat inconsistent results. Apparently conflicting results may be related to differences in duration and severity of hypertension and to different intakes of dietary NaCl. In patients with more advanced hypertension than reported in the present study and with angiographically documented nephrosclerosis, renal blood flow is lower in blacks.\textsuperscript{47,48} GFR has been reported as either not different in black and white patients with essential hypertension or higher in blacks.\textsuperscript{49–51} In response to a high NaCl diet, different investigators have reported that GFR either does not change or increases in black, but not white, patients with uncomplicated hypertension.\textsuperscript{50,51} Dietary salt reportedly induces a renal vasoconstrictor response with a reduction of renal blood flow and an increase in filtration fraction in salt-sensitive, but not in salt-resistant, hypertensive African Americans.\textsuperscript{51,52} Renal hemodynamic measurements may also be influenced by body weight. Renal hyperperfusion and hyperfiltration have been observed in obese individuals; however, the effect of overweight is not observed when renal blood flow and GFR are normalized for body surface area.\textsuperscript{52} In the present study, although BMI of the African American patients was higher than that of the French Canadians, renal blood flow and GFR were normalized for body surface area; consequently, it is unlikely that the racial differences of these measurements can be accounted for by differences of BMI.

The mechanisms contributing to glomerular hyperfiltration and the lack of autoregulation of GFR in these hypertensive African Americans remain to be determined. Normally, elevations of circulating norepinephrine constrict the preglomerular vasculature, thereby preventing transmission of sympathetically mediated elevations in arterial pressure from being transmitted to the glomerular capillaries. This results in near-perfect autoregulation of renal blood flow and GFR in normotensive individuals, as was seen in the present French Canadian patients with hypertension. However, similar to the observations in the African American patients, in 2 experimental models of low renin hypertension (Dahl salt-sensitive rats and dogs fed a high salt diet and treated with deoxycorticosterone acetate), renal blood flow is autoregulated in response to changes of renal perfusion pressure, whereas GFR is pressure dependent.\textsuperscript{54,55} Plasma renin activity tends to be suppressed in African Americans,\textsuperscript{56} and in the present study, plasma renin activity was lower in the African American than in the French Canadian patients. Conceivably, the low renin state may contribute to the lack of autoregulation of GFR because of an impairment of tubuloglomerular feedback control of afferent arteriolar resistance.

Several possible mechanisms may account for the apparent uncoupling of autoregulation of GFR and renal blood flow in the African American patients. The renal afferent arteriole may be less responsive to norepinephrine-induced vasoconstriction than the efferent arteriole in African Americans. Selective constriction of efferent arterioles in combination with an impaired tubuloglomerular feedback but intact myogenic response could lead to an elevation in glomerular capillary pressure and GFR but no change in renal blood flow. Another possibility is that an impairment in myogenic and/or tubuloglomerular feedback responses in African Americans leads to transmission of pressure to the glomerular capillaries. This would elicit a myogenic constriction of the efferent arteriole leading to normalization of renal blood flow but a further elevation in GFR. We have obtained direct evidence supporting this phenomenon in the fawn-hooded rat.\textsuperscript{57} Alternatively, the glomerular capillary ultrafiltration coefficient may be pressure dependent in African Americans because of mild glomerulosclerosis and expansion of the mesangial matrix in response to higher perfusion pressures.

Whatever the mechanism, the elevation of basal GFR and an impaired capacity to autoregulate GFR imply that the glomerular circulation is not protected from elevations of arterial pressure in hypertensive African Americans. Attenuated nighttime reduction of blood pressure and glomerular hyperfiltration may both contribute to the increased incidence of end-stage renal disease in African Americans with hypertension.

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References


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