Renal Hemodynamics in Essential Hypertension
Racial Differences in Response to Changes in Dietary Sodium

Robert J. Parmer, Richard A. Stone, Justine H. Cervenka

Abstract Previous studies have suggested striking racial differences in hypertension-related renal disease. To explore potential mechanisms responsible for these differences, we investigated changes in renal hemodynamics in white and black essential hypertensive patients in response to alterations in dietary sodium. Patients were untreated, age-matched, and blood pressure–matched white (n = 59) and black (n = 22) males with essential hypertension. Studies were conducted on an inpatient metabolic ward and included assessment of blood pressure, urinary sodium excretion, glomerular filtration rate, renal plasma flow, and renal blood flow after 5 days each of high and low salt diets. In response to high dietary salt intake, both white and black patients demonstrated significantly higher mean arterial pressure, renal plasma flow, and renal blood flow, and there were no racial differences in the changes in these parameters. However, whites and blacks differed significantly in glomerular filtration rate, with black hypertensive patients showing an increase in glomerular filtration rate (+17.3 ± 5.3 mL/min per 1.73 m², F = 7.586, p = .007) and white hypertensive patients showing no change (–0.2 ± 3.3 mL/min per 1.73 m²) in response to high dietary sodium. These data demonstrate racial differences in the autoregulation of glomerular filtration rate in response to changes in dietary sodium. These differences suggest that glomerular hyperfiltration in response to a high salt diet may be a mechanism contributing to the racial disparity in hypertension-related renal disease. (Hypertension. 1994;24:752-757.)

Key Words • hypertension, essential • sodium • race • hemodynamics • hyperfiltration • diet • heredity • kidney failure

Previous studies have demonstrated striking racial differences in the target-organ complications of hypertension.1–8 These differences are particularly dramatic for hypertensive renal disease, with hypertensive renal dysfunction occurring much more commonly and with greater severity in the black population. Indeed, the prevalence of end-stage renal disease resulting from hypertension is 16 to 17 times greater in blacks compared with whites.9,10

A number of factors have been proposed to account for this racial disparity in hypertension-related renal disease, including greater prevalence of hypertension, greater severity of hypertension, and cultural and socioeconomic factors resulting in less healthcare accessibility and poorer blood pressure control in the black population.11–13 However, more recent studies have indicated that the increase in hypertensive renal disease in blacks is not entirely explained by these factors and have suggested a greater intrinsic susceptibility of the kidney in blacks to the effects of elevated blood pressure.14–19 Studies have also demonstrated marked racial differences in sodium homeostasis,20–25 including a greater prevalence of sodium sensitivity20,21 and diminished ability to excrete a sodium load acutely in blacks compared with whites.22 In addition, recent investigations have suggested that alterations in intraglomerular hemodynamics may profoundly influence the initiation and rate of progression of renal insufficiency.26,27 Therefore, to explore potential mechanisms responsible for racial differences in hypertensive renal disease, we investigated renal hemodynamic responses to alterations in dietary sodium in black and white patients with essential hypertension.

Methods

Patients

We studied 81 adult male patients with uncomplicated essential hypertension, defined by at least three outpatient diastolic blood pressure recordings of greater than 90 mm Hg, in whom secondary causes of hypertension as well as evidence of hypertensive end-organ damage were ruled out by history, physical exam, and screening lab values (chest radiograph; electrocardiogram; hemogram; blood urea nitrogen; serum creatinine and electrolytes; urinalysis; and urinary catecholamine, metanephrine and vanillylmandelic acid excretion). Specifically, patients with evidence of renal dysfunction as defined by a serum creatinine level of greater than 1.5 mg/dL or proteinuria on urinalysis were excluded. The age range of these patients was 20 to 67 years. There were 59 white hypertensive patients and 22 black hypertensive patients. All subjects gave informed, written consent, and the study was approved by the Human Subjects Committee of the University of California, San Diego.

Assessment of Renal Hemodynamics

Patients were admitted to the Special Diagnostic and Treatment Unit of the San Diego Veterans Administration Medical Center for renal hemodynamic studies. At the beginning of the protocol, patients either had never been treated for hypertension or had had their antihypertensive medications withheld for at least 2 weeks. Each patient consumed 5 days of both a high salt (unrestricted in sodium content) and a low salt (approximately 40 mmol sodium per day) diet. The order of dietary periods (high salt, then low salt) was the same for all patients. On the final 2 days of each phase of the study, a 24-hour urine sample was obtained to verify attainment of stable sodium balance. Diets contained approximately 90 g protein per day, 80 mmol potassium per day, and 2300 kcal/d during both the

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Results

Patient Characteristics

Table 1 shows baseline patient characteristics for the two groups studied. There were no significant differences between white and black hypertensive patients in age, resting heart rate, body mass index, renal function as assessed by serum creatinine, or duration of hypertension. The two groups were equally hypertensive, with comparable degrees of elevation of both systolic and diastolic blood pressures. In addition, whites and blacks did not differ with regard to the presence or absence of prior antihypertensive therapy: 31 of the 59 whites and 14 of the 22 blacks had received antihypertensive medication before entry into the study ($\chi^2=0.413, P=.512$).

### Urinary Sodium Excretion

Twenty-four-hour urine samples collected on the final day of each dietary period revealed an approximately fourfold higher sodium excretion comparing the low sodium with the unrestricted sodium diet in both groups (36.±5 to 159±11 mmol/d in whites, 46.±8 to 155±11 mmol/d in blacks). Two-way ANOVA showed that there were no racial differences in sodium balance during either diet ($F=0.076, P=.784$ for race effect; $F=120.7, P<.001$ for dietary sodium effect; $F=0.387, P=.559$ for race by dietary sodium interaction). The change in body weight associated with the change in salt intake did not differ between the two groups ($2.7±0.3$ kg for whites, $2.5±0.4$ kg for blacks, $P=.697$).

### Systemic and Renal Hemodynamics

Table 2 shows MAP responses for the two patient groups after each 5-day dietary period. Two-way ANOVA revealed that MAP values were comparable for the two groups during both low and high sodium diets and that MAP was significantly higher during the high sodium diet in both white and black hypertensive patients, with a mean increase of 6 to 7 mm Hg in both groups (96±2 to 103±2 mm Hg for whites, 98±3 to 104±3 mm Hg for blacks). Two-way ANOVA showed that there were no racial differences in sodium balance during either diet ($F=0.076, P=.784$ for race effect; $F=120.7, P<.001$ for dietary sodium effect; $F=0.387, P=.559$ for race by dietary sodium interaction). The change in body weight associated with the change in salt intake did not differ between the two groups ($2.7±0.3$ kg for whites, $2.5±0.4$ kg for blacks, $P=.697$).

### Systemic and Renal Hemodynamics

Table 2 shows RPF as estimated by PAH clearance. There were no racial differences in RPF during either diet. White and black hypertensive patients exhibited comparable increases in RPF with higher sodium intake ($F=0.172, P=.680$ for race effect; $F=9.997, P=.002$ for dietary sodium effect; and $F=0.467, P=.497$ for race by dietary sodium interaction). Table 2 also shows RPF results. These results mirrored the RPF results, with significant increases during the high salt diet for both hypertensive groups and no significant racial differences ($F=0.346, P=.559$ for race effect; $F=11.671, P=.001$ for dietary sodium effect; and $F=0.054, P=.818$ for race by dietary sodium interaction).
higher MAP, RPF, and RBF, and there were no racial differences in the overall values or changes in these parameters.

The Figure shows GFR as estimated by endogenous creatinine clearance. Whereas GFR did not change in white hypertensive patients in response to the change in dietary sodium, it was significantly greater during the high salt diet than during the low salt diet in the black hypertensive group. This racial difference was reflected in the two-way ANOVA for dietary sodium (F=0.727, \( P=.009 \)) and a significant dietary sodium \( \times \) race interaction (F=7.586, \( P=.007 \)). Thus, dietary sodium significantly affected GFR but only in black hypertensive patients.

RVR values did not differ overall between black and white hypertensive patients, and RVR decreased significantly during the high salt compared with the low salt diet in white patients (b=-0.109 for white patients; b=+1.012 for black patients), although this was not statistically significant (F=0.035, \( P=.852 \) for race effect; F=0.454, \( P=.503 \) for diet effect; F=1.650, \( P=.204 \) for race \( \times \) diet interaction).

Predictors of the Change in GFR With Dietary Sodium Alteration

To control for the effects of several variables on the change in GFR in response to dietary sodium alteration, we evaluated these data using multiple regression analysis (Table 3). This analysis revealed that change in GFR was not independently affected by age, baseline MAP, body mass index, or change in body weight in response to dietary sodium alteration; also, after controlling for these variables, the effect of race on this parameter was still highly significant (\( P=.001 \)).

Additionally, as an assessment of the ability to autoregulate GFR in the face of blood pressure changes in response to dietary sodium manipulation, we performed linear regression analysis to investigate the relationship between changes in GFR and blood pressure in white and black patients separately. In white hypertensive patients, individual changes in GFR did not vary with changes in MAP in response to higher dietary sodium (\( r=-.056, P=NS \)). Conversely, in black patients, the change in GFR varied directly with the change in MAP (\( r=+.450, P<.05 \)); there was a significant difference in the slope of this relationship between white and black patients (b=-1.09 for white patients; b=+1.012 for black patients, \( P<.05 \)).

Discussion

Our results demonstrate significant racial differences in GFR in response to dietary sodium alterations as well as racial differences in the autoregulation of GFR despite similar blood pressure and RBF responses in blacks and whites. These results suggest a mechanism for the increased susceptibility of renal disease in blacks.

### Table 3. Multiple Linear Regression

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Coefficient</th>
<th>Standardized Coefficient</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.031</td>
<td>-0.011</td>
<td>-0.078</td>
<td>.938</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>-0.308</td>
<td>-0.127</td>
<td>-0.948</td>
<td>.347</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-0.391</td>
<td>-0.185</td>
<td>-1.388</td>
<td>.171</td>
</tr>
<tr>
<td>Delta body weight</td>
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<td>0.120</td>
<td>0.941</td>
<td>.351</td>
</tr>
<tr>
<td>Race</td>
<td>37.253</td>
<td>0.481</td>
<td>3.418</td>
<td>.001</td>
</tr>
</tbody>
</table>

The dependent variable was change in glomerular filtration rate in response to change in dietary sodium. n=81.
Recent studies have indicated that glomerular hyperfiltration and increased glomerular capillary pressure may result in increased transglomerular traffic of plasma proteins leading to their accumulation in the mesangium, thereby serving as a stimulus to the proliferation of mesangial cells and matrix, ultimately resulting in glomerulosclerosis.

In addition, the parallel increases in GFR and RBF in black hypertensive patients, coupled with the decrease in RVR and constancy of FF, are consistent with afferent renal arteriolar vasodilatation in response to the high sodium diet in this group. Interestingly, studies in genetic models of hypertension suggest that defective preglomerular vasoconstriction in response to increases in dietary sodium may represent an inherited abnormality that predisposes to renal injury. Dahl salt-sensitive rats respond to increases in dietary sodium by increased blood pressure and a fall in afferent renal arteriolar resistance, resulting in increased glomerular capillary pressures and progressive renal injury. By comparison, another inbred rat strain, the spontaneously hypertensive rat strain, adapts to similar blood pressure elevations by increasing preglomerular resistance, which may render these animals less susceptible to hypertensive glomerulosclerosis. Our results in hypertensive blacks are consistent with an abnormality in preglomerular vasoconstriction similar to that found in the Dahl salt-sensitive model. Recent studies by Campese et al. demonstrated increased calculated intraglomerular pressures in a group of salt-sensitive hypertensive patients (which also contained a greater percentage of blacks compared with salt-resistant hypertensive patients) in response to high dietary sodium.

Whether glomerular hyperfiltration or glomerular hypertension precedes and initiates progressive renal damage in essential hypertension in humans is unknown, but recent clinical studies by Schmieder et al. suggest that glomerular hyperfiltration may be found in the early stages of hypertensive target-organ damage. Our results also suggest that in black hypertensive patients GFR is more dependent on changes in renal hemodynamics or in cation transport mechanisms involved in sodium homeostasis than in white patients. The lack of a change in GFR in this study is consistent with normal withdrawal of angiotensin II during volume expansion. Thus, taken together with previous data, the current findings suggest reduced participation of the renin-angiotensin system in renovascular tone during dietary sodium alterations in black compared with white patients.

In addition to possible differences in the contribution of the renin-angiotensin system, racial disparities in other hormonal systems involved in sodium homeostasis and renal hemodynamics or in cation transport mechanisms could also provide a molecular or cellular mechanism for the results we have obtained. Racial differences in plasma aldosterone concentrations, plasma dopamine /3-hydroxylase activity, urinary kallikrein activity, and ouabain-sensitive red blood cell sodium transport have been described. In addition, blacks may have an increased prevalence of peripheral resistance to insulin, which may have effects on tubular reabsorption of sodium and could conceivably contribute to the results we have seen.

We used endogenous creatinine clearance to estimate GFR in this study. Previous studies have demonstrated that this method is reliable and accurate, particularly if the GFR is greater than 40 mL/min, a level well below that of the patients included in this study. However, it is possible that the observed GFR differences could be a reflection of differences in the way that tubular secretion of creatinine contributed during high versus low sodium intake. Further exploration of this issue should incorporate use of a more "pure" GFR marker such as insulin.

In the present study performed on an inpatient metabolic ward, we found no differences in the blood pressure response between the two racial groups. Previous studies showing an increase in the prevalence of salt sensitivity of blood pressure in black normotensive subjects and hypertensive patients have in general demonstrated racial differences only after extremely high dietary sodium intake or saline infusions exceeding 300 mmol sodium per day, far higher than in our patients.

It should be noted that the sodium content of the high salt diet used in the current study does not represent an extreme and is well within the range of that found in typical North American diets. Thus, it is conceivable that glomerular hyperfiltration may occur frequently and on a sustained basis in susceptible patients (black hypertensive patients), rendering the kidneys of these individuals more prone to renal damage. One might also speculate that sodium restriction might be especially beneficial in black hypertensive patients, not only for the antihypertensive effect of this maneuver but also for the potential benefit of reducing glomerular filtration.

Recently, Wilson and Grim have speculated that blacks evolved particularly keen mechanisms of sodium retention, which when sodium consumption is generous may lead to a disadvantage in the form of higher blood pressures. Our results now suggest that higher sodium intakes in black hypertensive patients may also be disadvantageous by adversely affecting renal hemodynamics.
In summary, our results demonstrate racial differences in \( GFR \) in response to changes in dietary sodium. This relatively short-term study suggests a mechanism—impaired \( GFR \) autoregulation and glomerular hyperfiltration in response to increased dietary sodium intake—that may contribute to the racial disparity in hypertensive renal disease. Longer-term longitudinal studies will be required to assess further the overall importance of this mechanism to explain the increased susceptibility of renal damage from blood pressure elevation and the increased risk of end-stage renal disease in black hypertensive patients.

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References

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