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=0.007) 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
TABLE 1. Baseline Characteristics of Hypertensive Patients

<table>
<thead>
<tr>
<th></th>
<th>Whites (n=59)</th>
<th>Blacks (n=22)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>43±2</td>
<td>41±2</td>
<td>0.575</td>
<td>.567</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>155±3</td>
<td>155±6</td>
<td>0.042</td>
<td>.967</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>96±2</td>
<td>101±3</td>
<td>-1.338</td>
<td>.185</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>75±1</td>
<td>76±3</td>
<td>-0.268</td>
<td>.790</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.7±0.7</td>
<td>29.3±1.5</td>
<td>-1.103</td>
<td>.275</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.09±0.02</td>
<td>1.14±0.04</td>
<td>-1.225</td>
<td>.229</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>7.8±1.0</td>
<td>7.5±1.3</td>
<td>0.166</td>
<td>.869</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.

high and low salt phases. Blood pressure was determined with patients in the supine position during the study periods with the use of a standard aneroid-cuff sphygmomanometer. Mean arterial pressure (MAP) was calculated as diastolic blood pressure plus one-third pulse pressure. Renal hemodynamics were assessed as previously described9,28-34 on the final day of each dietary period (after establishment of stable sodium balance) as follows: renal plasma flow (RPF) was estimated by clearance of para-aminomaleic acid (C]<p,> by the method of constant infusion of PAH without urine collection;35 with each infusion carried to steady state over a 4-hour period (this method has proved reliable in our previous studies of RPF in normotensive and hypertensive humans28,29): renal blood flow (RBF) was determined from the formula RBF=Cl<p,>/1-hematocrit; and glomerular filtration rate (GFR) was estimated by endogenous creatinine clearance (C<cre>) on 24-hour urine collections. Clearance data were corrected to a body surface area of 1.73 m². Filtration fraction (FF) was derived from the formula FF=C<cre>/Cl<p,>. Renovascular resistance (RVR) was calculated from the formula RVR=[MAP(mm Hg)/RBF(mL/min per 1.73 m²)]×80 000 and is expressed as dyne·s·cm⁻²·1.73 m².

All 81 patients (59 whites and 22 blacks) had creatinine clearance determinations, and of these, 65 patients (48 whites and 17 blacks) had PAH clearance determinations during both low and high salt diets for analysis.

Statistics

Results are expressed as mean±SEM and were analyzed by repeated measures two-way ANOVA factoring for the effects of both dietary sodium (low salt versus high salt) and race (white versus black). Simultaneous model multiple regression analysis was performed to assess the effect of several independent variables on renal hemodynamics. Linear least-squares regression analysis followed by Student's t test for differences between two slopes86 was used to compare regression line slopes between white and black groups. To ensure the validity of the correlational analysis followed by Student's t test for differences between two 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=.536 for race×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 results 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=0.014, P=.906 for race×dietary sodium interaction). There were no racial differences in sodium balance during either diet (F=0.486, P=.488 for race effect; F=21.473, P<.001 for dietary sodium effect; and F=0.406, P=.906 for race×dietary sodium interaction). There were no racial differences in 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×dietary sodium interaction).

Thus, in response to a higher dietary salt intake, both white and black patients demonstrated significantly 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 (X²=0.413, P=.512).

**Systemic and Renal Hemodynamics**

Table 2 shows RPF 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 for blacks; F=0.486, P=.488 for race effect; F=21.473, P<.001 for dietary sodium effect; and F=0.014, P=.906 for race×dietary sodium interaction). Thus, in response to a higher dietary salt intake, both white and black patients demonstrated significantly
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 by a significant effect for dietary sodium (F=7.272, P=.009) and a significant dietary sodium × 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 both groups (for whites, 967±442 to 858±411 dyne · s · cm⁻²/1.73 m²; for blacks, 10.915±11.44 to 10.074±11.84 dyne · s · cm⁻²/1.73 m² [F=1.926, P=.10] for race effect; F=6.288, P=.015 for dietary sodium; F=0.067, P=.796 for race × dietary sodium interaction)).

FF was unchanged in black hypertensive patients with dietary sodium alteration (0.19±0.02 during both low and high salt diets) and tended to fall during the high salt diet in white hypertensive patients (0.20±0.01 to 0.18±0.01), 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 × 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 = -.109 for white patients; b = +.102 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>
<thead>
<tr>
<th>Parameter</th>
<th>Whites</th>
<th>Blacks</th>
<th>Race</th>
<th>Diet</th>
<th>Race X Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Na⁺</td>
<td>High Na⁺</td>
<td>Low Na⁺</td>
<td>High Na⁺</td>
<td>F</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>96±2</td>
<td>103±2</td>
<td>98±3</td>
<td>104±3</td>
<td>0.486</td>
</tr>
<tr>
<td>RPF, mL/min per 1.73 m²</td>
<td>482±23</td>
<td>545±21</td>
<td>463±27</td>
<td>540±32</td>
<td>0.172</td>
</tr>
<tr>
<td>RBF, mL/min per 1.73 m²</td>
<td>845±40</td>
<td>1009±40</td>
<td>814±46</td>
<td>951±60</td>
<td>0.346</td>
</tr>
</tbody>
</table>

MAP indicates mean arterial pressure; RPF, renal plasma flow; and RBF, renal blood flow. For MAP, n=81 (59 whites and 22 blacks); for RPF and RBF, n=65 (48 whites and 17 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>Δ Body weight</td>
<td>2.333</td>
<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.26-27

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 vasodilation38 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.39 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.39 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 al40 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 al41 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 perfusion pressure than in white patients. GFR did not vary with change in blood pressure in white patients (r=−.05, P=NS), consistent with an intact ability to autoregulate GFR in this group. On the other hand, in black hypertensive patients, GFR varied directly with change in MAP (r=+.450, P<.05), consistent with a disturbed ability to autoregulate GFR. The autoregulation of GFR is a complex process, with several mechanisms playing important roles, including myogenic influences, RPF, and neurohumoral influences from the renin-angiotensin system, renal sympathetic nerves, and tubuloglomerular feedback.42 Studies have shown that the renin-angiotensin system may play a particularly important role in the autoregulation of GFR, in large part by affecting efferent arteriolar tone.43 Animal studies have shown that renin depletion results in marked impairment of GFR autoregulation.43 Also, recent studies in patients with hypertensive nephrosclerosis demonstrated that treatment with an angiotensin-converting enzyme inhibitor resulted in an impaired ability to autoregulate GFR, resulting in direct GFR dependence on blood pressure,44 an impairment similar to what we have found here for black hypertensive patients during dietary sodium alterations. Blacks as a group have been shown to have lower plasma renin activity compared with whites.45 The lack of a change in GFR during the higher sodium diet in white patients in the current study is consistent with normal withdrawal of angiotensin II during volume expansion.43 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,46 plasma dopamine β-hydroxylase activity,47 urinary kallikrein activity,28 and ouabain-sensitive red blood cell sodium transport have been described.48,49 In addition, blacks may have an increased prevalence of peripheral resistance to insulin, which may have effects on tubular reabsorption of sodium50 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.51-53 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 inulin.

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,20,21 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.54 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 anti-hypertensive effect of this maneuver but also for the potential benefit of reducing glomerular filtration.

Recently, Wilson and Grim55 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.

Acknowledgments

This study was supported by the National Institutes of Health (HL-50174) and the Department of Veterans Affairs. R.J.P. was an Established Investigator of the American Heart Association. We wish to thank the nursing staff of the Special Diagnostic and Treatment Unit of the San Diego Veterans Administration Medical Center for their technical assistance. Also, we thank Dr Daniel T. O'Connors his support and advice for and his critical review of the manuscript.

References


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Hypertension. 1994;24:752-757
doi: 10.1161/01.HYP.24.6.752

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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