Effect of Sodium Loading/Depletion on Renal Oxygenation in Young Normotensive and Hypertensive Men

Menno Pruijm, Lucie Hofmann, Marc Maillard, Sylvie Tremblay, Nicolas Glatz, Gregoire Wuerzner, Michel Burnier, Bruno Vogt

Abstract—The goal of this study was to investigate the effect of sodium intake on renal tissue oxygenation in humans. To this purpose, we measured renal hemodynamics, renal sodium handling, and renal oxygenation in normotensive (NT) and hypertensive (HT) subjects after 1 week of a high-sodium and 1 week of a low-sodium diet. Renal oxygenation was measured using blood oxygen level–dependent magnetic resonance. Tissue oxygenation was determined by the measurement of R2* maps on 4 coronal slices covering both kidneys. The mean R2* values in the medulla and cortex were calculated, with a low R2* indicating a high tissue oxygenation. Ten male NT (mean age: 26.5±7.4 years) and 8 matched HT subjects (mean age: 28.8±5.7 years) were studied. Cortical R2* was not different under the 2 conditions of salt intake. Medullary R2* was significantly lower under low sodium than high sodium in both NT and HT subjects (28.1±0.8 versus 31.3±0.6 s⁻¹; P<0.05 in NT; and 27.9±1.5 versus 30.3±0.8 s⁻¹; P<0.05, in HT), indicating higher medullary oxygenation under low-sodium conditions. In NT subjects, medullary oxygenation was positively correlated with proximal reabsorption of sodium and negatively with absolute distal sodium reabsorption, but not with renal plasma flow. In HT subjects, medullary oxygenation correlated with the 24-hour sodium excretion but not with proximal or with the distal handling of sodium. These data demonstrate that dietary sodium intake influences renal tissue oxygenation, low sodium intake leading to an increased renal medullary oxygenation both in normotensive and young hypertensive subjects. (Hypertension. 2010;55:1116-1122.)

Key Words: BOLD-MRI ■ hypertension ■ sodium ■ renal tissue oxygenation ■ proximal tubule ■ medulla ■ inulin clearance
individuals. On theoretical grounds, we expected to find lower R2* values, indicating higher local tissue PO2, under LS conditions, in both normotensive and hypertensive individuals. The goal of this study was, therefore, to investigate the impact of changes in sodium intake on renal tissue oxygenation in young male normotensive subjects and untreated age-matched hypertensive patients.

Methods

Subjects

The study was conducted in 10 male healthy, normotensive controls (NTs) and in 8 young male untreated hypertensive patients (HTs). Inclusion criteria for all of the participants were male sex, age 18 to 50 years, no history of renal disease, no illicit drug intake, and ability to understand the study protocol. Hypertensive patients could be included if they had stage I to II hypertension (blood pressure: ≥140/90 and <180/110 mm Hg). Baseline blood pressure of HT patients was the average daytime blood pressure as recorded during 24-hour ambulatory blood pressure measurement. For the NT group, normal blood pressure was defined as an average of 6 office measurements ≤135/85 mm Hg on 2 different occasions using an automated Omron 705IT oscillometric device, as measured according to the recommendations of the European Society of Hypertension.20

Exclusion criteria for all of the participants were instable asthma, estimated glomerular filtration rate (GFR) <90 mL/min per 1.73 m² (using the Modification of Diet in Renal Disease formula),21 anemia, and/or the presence of proteinuria on dipstick testing; a known hypersensitivity to insulin, PAH, or both; claustrophobia; and the presence of a pacemaker or other metallic implanted devices. After explaining the nature and purpose of the study, informed written consent was obtained from each subject. The protocol was approved by the local institutional review committee (Ethical Committee of the Faculty of Medicine, Lausanne).

Dietary Sodium Intake

All of the participants started with a high-sodium (HS) diet (>150 mmol of NaCl per day) for 7 days. In the NT group, HS diet was obtained by adding 6 g of NaCl to their regular diet. The HT group followed the HS diet during the first study period by consuming salt-rich foods. The addition of 6 g of NaCl to their regular diet. The HT group followed the HS diet during the first study period by consuming salt-rich foods. The addition of 6 g of NaCl to their regular diet. The HT group followed the HS diet during the first study period by consuming salt-rich foods. The addition of 6 g of NaCl to their regular diet.

Clearance Studies

On day 8, participants were asked to return to our research department after fasting overnight. Insulin, p-aminohippurate (PAH), and endogenous lithium clearances were performed between 8:00 and 11:30 AM, as described previously.21 In brief, 2 intravenous catheters were inserted into antecubital veins, one for the infusion of insulin and PAH and a second into the contralateral arm for drawing blood. Participants started with an oral water load of 5 mL/kg and continued to drink 3 mL/kg hourly throughout the clearance studies. After a 2-hour equilibration period, two 1-hour insulin and PAH clearances were obtained to measure GFR and effective renal plasma flow (ERPF), respectively. Blood pressure and heart rate were measured every 30 minutes using the same automated oscillometric device (Omron 705IT) in both HT and NT participants. Plasma renin activity, plasma aldosterone, blood urea nitrogen, creatinine, hemo-

globin, and sodium were measured at baseline and at the end of the clearance studies as described previously.21 Insulin was dosed by microadaptation of a diphenylamine procedure on an autoanalyzer, PAH by photometry, and lithium by electrothermal absorption spectrophotometry.21

Calculation of Renal Parameters

The insulin, PAH, and endogenous lithium clearances (Cx) were calculated with the formula Cx = Ux × fXPx, where Ux and Px are urinary and plasma concentrations of the x solute, and V is the urine flow rate in milliliters per minute. Renal blood flow (RBF) was calculated as ERPF/[1−(hematocrit/100)]. The fractional excretions of lithium (FELi) and sodium (FENa) were calculated using the formula FENa = UNa × PNa × creatinine/(PNa × Ucreatinine). Fractional distal reabsorption of sodium was estimated as ([FENa−FENa]×SERNa)/100. Absolute distal (postproximal) sodium reabsorption (ADRNa) was estimated by the difference between the clearances of lithium and sodium multiplied by the plasma concentration of sodium.21

Blood Oxygen Level–Dependent MRI

BOLD-MRI was performed in the radiology department directly after the clearance studies between 8:00 and 2:00 PM on day 8 of each phase of the diet. Magnetic resonance measurements were carried out on a 3-T whole-body magnetic resonance system (Trio Tim, Siemens Medical Systems). Four coronal slices with good corticomedullary differentiation were selected from morphological images for functional evaluation with BOLD-MRI. Twelve TR*-weighted images were recorded within a single breath hold of 17.4 s (in inspiration) with a modified Multi Echo Data Image Combination sequence with the following parameters: repetition time of 68 ms, echo time from 6.0 to 52.2 ms (equidistant echo time spacing: 4.2 ms), flip angle of 20°, field of view of 400×400 mm², voxel size of 1.6×1.6×5 mm³, bandwidth of 700 Hz per pixel, and matrix of 256×256. The range of echo time was limited to 52.2 ms to avoid (also for voxels with a lower signal/noise ratio) getting into the area of the Rician distribution of noise. R2* maps were calculated voxel by voxel by fitting an exponential function to the signal intensities measured for each echo time. Regions of interest were selected in the medulla and cortex by the same experienced investigator, and a mean value of R2* index was estimated as validated and published previously. In brief, the reported mean R2* value of every participant was the mean of 4 slices, each slice with 8 regions of interest (4 in the cortex and 4 in the medulla). This technique has been shown to have a good reproducibility (mean coefficient of variance of 3% in the medulla and 4% in the cortex) for different slice directions (axial or coronal).22,23

Statistical Analysis

On the basis of an expected diet-induced difference in renal oxygenation (as expressed by R2*) of 10% between the 2 groups, an α of 0.05 at 2-sided significance level, and using the highest SD obtained in former studies, ≥8 patients per group were needed to have a power of 90%. Data are expressed as mean±SD. Comparisons between deoxygenhemoglobin content of medullary and cortical regions for each kidney were made by using the 2-sided paired t test and differences between groups with ANOVA. Spearman rank test and linear regression were used to examine correlations. A P value <0.05 was considered statistically significant.

Results

Normotensive Subjects

Normotensive participants (mean age: 26.5±7.4 years) were whites, except one who was of Asian descent. Baseline serum creatinine was 85.9±10.4 μmol/L, corresponding with an estimated creatinine clearance (estimated GFR, Modification of Diet in Renal Disease) of 103.2±17.0 mL/min per 1.73 m². Changes in clinical parameters and results of clearance studies under HS and LS diets are shown in Table 1.

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Cortex change. FENa, FELi, and ADRNa were, as expected, higher under HS as compared with LS conditions in the NT group shown for each normotensive participant in Figure 1.

Medullary R2*, reflecting local deoxyhemoglobin levels, are higher levels of GFR, ERPF, and RBF were found under HS as compared with LS conditions. Mean values for cortical and medullary R2*, reflecting local deoxyhemoglobin levels, are shown for each normotensive participant in Figure 1.

There were no significant changes in cortical R2* levels under HS as compared with LS conditions in the NT group (17.8±1.3 versus 18.2±0.6 s⁻¹; P=0.27). The situation was different when analyzing the renal medulla, with R2* levels significantly higher under HS versus LS conditions (31.3±0.6 versus 28.1±0.8 s⁻¹; P<0.05) corresponding with higher local PO2 levels under LS. Of note, the mean coefficient of variance for R2* values averaged over all of the participants between slices was 4.0% (range: 1.0% to 10.0%) in the medulla and 4.3% (range: 2.0% to 7.0%) in the cortex under HS conditions versus 4.1% (range: 1.0% to 10.0%) in the cortex and 4.7% (range: 1.0% to 9.0%) in the medulla under LS conditions.

To further investigate the role of renal sodium handling on renal tissue oxygenation, linear regression analyses were performed. Medullary R2* levels correlated positively with 24-hour urinary sodium excretion (r=0.55; P=0.01) and also with FENa (r=0.56; P=0.01), FELi (r=0.46; P=0.04), and ADRNa (r=0.48; P=0.04). No correlations were found between medullary R2* levels and ERPF (r=0.06; P=0.8), GFR (r=0.29; P=0.2), or fractional distal reabsorption of sodium (r=0.41; P=0.08; Figure 2). There were no correlations between cortical R2* levels and renal hemodynamics or renal sodium handling.

**Hypertensive Patients**

Eight hypertensive subjects (mean age: 28.8±5.8 years) were included; 6 were whites and 2 were black. Baseline serum creatinine was 84.0±10.7 μmol/L, corresponding with an estimated GFR of 106.9±15.6 mL/min per 1.73 m². All of the hypertensives were never treated, except 1 in whom treatment (β-blocker) was stopped 2 weeks before the study. Changes in clinical characteristics and clearance studies are shown in Table 2.

In HT subjects, there were no significant differences among GFR, ERPF, and RBF under LS or HS conditions. FENa was lower under LS conditions, but FELi was low, irrespective of salt intake. Changes in plasma renin activity and aldosterone levels were as expected. There was no difference between mean cortical R2* in the HT group when comparing HS with LS conditions (17.4±0.6 versus 17.8±0.9 s⁻¹; P=0.16). However, as in the NT group, medullary R2* levels were significantly lower under LS conditions (30.3±0.8 versus 27.9±1.5 s⁻¹; P<0.05; Figure 1).

**Table 1. Baseline Characteristics and Changes of Renal Hemodynamics in NT Individuals Under HS/LS Conditions**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NT Group, Baseline ± SD</th>
<th>HS</th>
<th>LS</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>77.9±12.8</td>
<td>76.4±13.1</td>
<td>77.4±13.2</td>
<td>0.07</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>125±8</td>
<td>122±6</td>
<td>119±5</td>
<td>0.09</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>67±7</td>
<td>67±8</td>
<td>65±5</td>
<td>0.45</td>
</tr>
<tr>
<td>24-h urinary volume, mL</td>
<td>2442±903</td>
<td>1780±683</td>
<td>0.047</td>
<td></td>
</tr>
<tr>
<td>24-h urinary sodium, mmol</td>
<td>328±96</td>
<td>20.2±14</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>P–sodium, mmol/L</td>
<td>139±1.4</td>
<td>138±1.9</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>42.9±2.6</td>
<td>43.9±1.9</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>GFR, mL/min</td>
<td>107.9±24.9</td>
<td>92.7±15.7</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>ERPF, mL/min</td>
<td>725.9±187</td>
<td>634.4±179</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>RBF, mL/min</td>
<td>1277±344</td>
<td>1134±338</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>FF, %</td>
<td>15.1±2.1</td>
<td>15.2±3.1</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>FFK, %</td>
<td>18.7±3.9</td>
<td>10.3±3.7</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>FENa, %</td>
<td>1.6±0.6</td>
<td>0.1±0.07</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>Cl, lithium, mL/min</td>
<td>20.3±6.6</td>
<td>9.4±3.0</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>Cl, sodium, mmol/min</td>
<td>1.65±0.5</td>
<td>0.1±0.07</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>ADRNa, mmol/min</td>
<td>2.6±0.9</td>
<td>1.3±0.42</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>PRA, ng/mL per h</td>
<td>0.49±0.44</td>
<td>1.98±0.62</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>Aldosterone, pg/mL</td>
<td>59.5±51</td>
<td>296±108</td>
<td>&lt;0.005</td>
<td></td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; FF, filtration fraction; Cl, clearance; PRA, plasma renin activity. Values are shown as mean±SD unless otherwise specified.

*Paired t test was performed to compare means under HS and LS conditions.

Higher levels of GFR, ERPF, and RBF were found under HS as compared with LS conditions; filtration fraction did not change. FENa, FELi, and ADRNa were, as expected, higher under the HS than the LS diet. Mean values for cortical and medullary R2*, reflecting local deoxyhemoglobin levels, are shown for each normotensive participant in Figure 1.
1). Again, dietary sodium intake, as estimated by 24-hour urinary sodium excretion, was positively correlated with medullary R2* levels (r=0.62; P=0.01). However, no correlation was found between medullary R2* levels and GFR (r=0.03; P=0.91), ERPF (r=0.20; P=0.48), FE_Li (r=0.40; P=0.15), or ADRNa (r=0.42; P=0.13). No correlations were found between cortical R2* levels and any of the previously mentioned parameters.

Table 2. Baseline Characteristics and Changes of Renal Hemodynamics in HT Individuals Under HS/LS Conditions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypertensive Group, Baseline ± SD</th>
<th>HS</th>
<th>LS</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>80.8±17.6</td>
<td>81.8±17.4</td>
<td>80.9±17.8</td>
<td>0.045</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>142±7</td>
<td>141±10</td>
<td>136±9</td>
<td>0.026</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>92±5</td>
<td>85±12</td>
<td>84±12</td>
<td>0.39</td>
</tr>
<tr>
<td>24-h urinary volume, mL</td>
<td>2036±952</td>
<td>1718±826</td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>24-h urinary sodium, mmol</td>
<td>239±126</td>
<td>76.8±87</td>
<td></td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>P sodium, mmol/L</td>
<td>139±1.3</td>
<td>139±0.5</td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>43.9±2.5</td>
<td>44.1±1.7</td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>GFR, mL/min</td>
<td>104.6±21.8</td>
<td>96.4±19.3</td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>ERPF, mL/min</td>
<td>572±152</td>
<td>567±158</td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td>RBF, mL/min</td>
<td>1018±272</td>
<td>1085±264</td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>FF, %</td>
<td>19.2±4.5</td>
<td>17.2±3.1</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>FE_Li, %</td>
<td>11.4±2.0</td>
<td>12.4±2.4</td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td>FE_Na, %</td>
<td>1.2±0.6</td>
<td>0.5±0.5</td>
<td></td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Cl lithium, mL/min</td>
<td>11.8±3.1</td>
<td>11.9±3.1</td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>Cl sodium, mmol/min</td>
<td>1.2±0.7</td>
<td>0.4±0.42</td>
<td></td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>ADRNa, mmol/L</td>
<td>1.5±0.33</td>
<td>1.6±0.45</td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>PRA, ng/mL per h</td>
<td>0.56±0.54</td>
<td>1.62±1.18</td>
<td></td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Aldosterone, pg/mL</td>
<td>53.1±37.9</td>
<td>159±91.3</td>
<td></td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; FF, filtration fraction; Cl, clearance; PRA, plasma renin activity. Values are shown as mean±SD unless otherwise specified.

*Paired t-test was performed to compare means under HS and LS conditions.

Figure 3 shows the relationship between 24-hour sodium excretion and medullary tissue oxygenation in both NT and HT subjects. Above a urinary sodium excretion of ≈300 mmol/d, medullary R2* appears to reach a plateau (Figure 3A). In addition, at each level of sodium excretion, medullary R2* levels were lower in HT than NT individuals (mean: 29.1±1.7 versus 30.5±1.7 s⁻¹; P=0.02), suggesting an increased tissue oxygenation in HT subjects. No difference was noted for cortical R2* levels (mean: 17.6±0.8 versus 18.6±1.3 s⁻¹; P=0.11; Figure 3B). When analyzing blood pressure as a continuous variable rather than a dichotomous separator of groups, and independently of salt intake, an inverse correlation between the mean arterial blood pressure, as measured on the days of clearance and MR studies, and medullary R2* values was found (r=−0.37; P=0.026).

Discussion

The main finding of this study is that variations in dietary sodium intake induce changes in the renal R2* signal measured by BOLD-MRI corresponding with changes in renal tissue oxygenation in male normotensive as well as hypertensive subjects. Our data demonstrate clearly that an LS intake is associated with an increased oxygenation of the renal medulla with no change in renal cortical oxygenation. In normotensive subjects, the changes in medullary oxygenation correlated with the salt-induced changes in sodium transport by the kidney but not with the changes in renal hemodynamics. In hypertension, renal medullary oxygenation correlated only with the 24-hour sodium excretion. Interestingly, at any sodium intake, medullary R2* levels were slightly lower for HT as compared with NT subjects, suggesting an increased medullary oxygenation in young subjects with mild hypertension when compared with young normotensives.

Previous studies using BOLD-MRI have shown that renal tissue oxygenation is affected by several factors, including age, level of hydration, use of diuretics, and hemoglobin levels. In the present study, we show for the first time in humans that dietary sodium intake also modulates renal tissue oxygenation, an LS intake increasing significantly renal medullary oxygenation without affecting the oxygenation of the renal cortex. This observation made both in normotensive
and young hypertensive subjects has several clinical implications. The first is that dietary sodium intake should now be considered as a potential confounder in BOLD-MRI studies. Today, water diuresis and the administration of furosemide are well recognized as factors lowering medullary \( R2^* \) values.\(^{18,24,25} \) Hence, despite the fact that the proximal tubules reabsorb 67% of all filtered sodium, they consume only 27% of total \( O_2 \), resulting in local \( PO_2 \) of \( \approx 50 \) mm Hg.\(^{9,10,16} \) In contrast, the Henle loops in the medulla receive 10% of RBF and reabsorb 30% of sodium at a relatively high energy cost. They use 67% of all \( O_2 \), and local \( PO_2 \) is as low as 10 to 15 mm Hg under normal circumstances, which renders them susceptible to ischemic injury.\(^{9,10} \) In our study, both renal hemodynamics and renal tubular handling of sodium were measured in parallel to the determination of renal tissue oxygenation providing opportunities to correlate the salt-induced changes in renal oxygenation with the salt-induced modifications of renal perfusion and renal sodium handling. Reported medullary \( R2^* \) values represent the average of higher oxygen levels in superficial medullary zones and lower \( PO_2 \) levels at deeper zones, so correlations describe trends without providing absolute regional \( PO_2 \) levels.

As expected from animal data,\(^{11,12} \) in NT subjects, medullary oxygenation was positively correlated with the 24-hour sodium excretion but also with the proximal and distal sodium reabsorption, as illustrated by the correlation between \( R2^* \) values and \( FE_{\text{Li}} \) and \( ADR_{\text{Na}} \). This suggests that, under LS conditions, medullary oxygen consumption decreases because the enhanced proximal sodium absorption (illustrated by the low \( FE_{\text{Li}} \)) leads to a reduced distal delivery of sodium and, hence, reduces the metabolic workload of medullary and distal segments of the nephron. Theoretically, lower oxygen consumption under LS conditions could have been counter-balanced by a lower blood flow because of the activation of the renin-angiotensin system leading to a lower oxygen delivery under LS conditions. In our salt-depleted subjects, a decrease in renal plasma flow and a stimulation of the renin-angiotensin system was observed but this did not reduce cortical or medullary oxygenation, and no correlation was found between medullary oxygenation and ERPF. This illustrates the potential of kidneys to preserve and even augment local \( PO_2 \) levels, independent of global RBF as a marker of oxygen delivery.

In healthy subjects, variations in dietary sodium intake did not influence renal cortical oxygenation. This is in line with other BOLD-MRI studies, showing little changes in cortical oxygenation in different situations,\(^{17,23} \) only extreme conditions, such as acute iatrogenic arterial obstruction in animal models, have been shown to significantly alter cortical \( R2^* \).\(^{29} \) This is explained by the technical limitation of BOLD-MRI for renal cortex analyses. BOLD-MRI is less sensitive to changes in cortical \( PO_2 \), because cortical blood \( PO_2 \) lies on the shoulder of the hemoglobin oxygenation curve, in contrast to medullary \( PO_2 \), which lies on the linear part of the curve, and delivery (a function of renal perfusion and blood oxygen content) and by the \( O_2 \) consumption, which is driven essentially by the GFR and the active tubular transport. More than 90% of all renal oxygen consumption is used for tubular sodium transport, which differs between the cortex and medulla. The well-perfused proximal tubules are mainly located in the renal cortex. Proximal sodium reabsorption is partly based on energy consuming active transport via basolateral Na\(^+\),K\(^+\)-ATPase and partly on passive transport via paracellular pathways.\(^{28} \)
is more sensitive to small changes in oxygen tension. Thus, larger differences in local PO₂ are necessary to observe similar changes in the R2* signal for the cortex as compared with the medulla.14

In young hypertensive patients, a significant increase in medullary oxygenation was found in response to the LS diet. The changes in medullary oxygenation correlated with the 24-hour urinary sodium excretion, but in contrast to normotensive subjects, no correlation was found with segmental renal sodium handling. Moreover, no correlation was found between medullary R2* values and all of the tested parameters of global renal hemodynamics. Although we do not have a clear explanation for the lack of association of sodium transport and oxygen consumption in these young hypertensives, some potential explanations might be proposed. The first is the rather small number of hypertensive subjects included in the study. The second is the lack of changes in FE₅₁ when the diet was changed from HS to LS. We have reported previously that FE₅₁ remains inappropriately low in some hypertensive patients, reflecting an enhanced proximal sodium reabsorption and salt sensitivity.7 A third possible factor is the smaller decrease in sodium excretion under the LS diet in the hypertensive participants. Although the same dietary regimen was applied to normotensive and hypertensive subjects, the compliance of the latter appears to be less than that of the former. At last, the rise in medullary PO₂ in HT subjects could be explained by changes in renal microcirculation with an intrarenal redistribution of blood flow. However, this hypothesis remains to be confirmed, with more precise measurements of intrarenal blood flow.

On the basis of animal studies, we merely expected to find higher R2* levels in the HT as compared with the NT group, reflecting more intense medullary hypoxia, both under HS and LS diets.30 Although our subjects and patients were well matched for several parameters, we rather found an increased renal tissue oxygenation in our young hypertensive patients, as presented in Figure 3 and as illustrated by the inverse relationship between blood pressure as a continuous trait and medullary R2* values.

Studies in hypertensive rats using oxygen microelectrodes found pronounced medullary hypoxia as compared with normotensive controls10,31; this has been linked to reactive oxygen species, disturbed renal microcirculation, and inefficient use of oxygen for tubular transport. To the best of our knowledge, no other studies have examined renal oxygenation in humans with essential hypertension using BOLD-MRI. One BOLD-MRI study has been performed in hypertensive patients experiencing renal artery stenosis.24 In this context, normal-sized kidneys with high-grade artery stenosis had high medullary R2* levels at baseline that fell after the administration of furosemide. Atrophic kidneys with high-grade artery stenosis had reduced R2* values at baseline that did not change after furosemide. A possible explanation for the lower medullary R2* in the HT group in our study could, thus, be increased tissue oxygen content because of less active medullar sodium transport, as an adaptation to earlier medullary hypoxia, for example, in the form of hypoxia inducible factor–induced interstitial fibrosis, or adaptations in medullar microcirculation. Recent data from rabbit studies suggest that renal tissue PO₂ is relatively independent of RBF, possibly because preglomerular diffusional shunting of oxygen from arteries to veins decreases with decreasing RBF and vice versa.32 It is, thus, possible that HT subjects present altered arterial-venous shunting as compared with NT subjects. However, this remains hypothetical, because our data on renal hemodynamics provided information on the total renal perfusion and filtration rate but not on renal microcirculation. At last, it is important to note that the study was conducted in young men with mild untreated hypertension. It is conceivable that different patterns of renal oxygenation might be seen in long-standing or more severe forms of hypertension.

**Perspectives**

This study demonstrates that an LS intake leads to increased renal medullary oxygenation as compared with HS intake in normotensive as well as in hypertensive subjects. This finding might have some clinical implications. First, it demonstrates the importance of considering sodium intake as a potential confounding factor in BOLD-MRI analyses, and it illustrates the high sensitivity of this technique to detect changes in renal oxygen content. It also provides additional positive arguments for the recommendation of an LS intake in hypertension, although the potential role of an LS intake on renal tissue oxygenation and, hence, on the progression of chronic renal diseases in normotensive and hypertensive patients, remains to be documented. Nonetheless, it has been shown that renal hypoxia is associated with the progression of several renal disease states, such as diabetes mellitus, renal artery stenosis, and analgesic nephropathy.13 However, this does not necessarily imply that high local medullar PO₂ values are renoprotective. To the best of our knowledge, no studies have examined the prognostic value of local PO₂ levels in humans. Prospective studies including other age groups with different comorbidities are, thus, needed to assess whether the beneficial effects of an LS diet can be explained by its impact on renal tissue oxygenation.

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**Disclosures**

None.

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