Combination of Hypercholesterolemia and Hypertension Augments Renal Function Abnormalities


Abstract—Hypercholesterolemia and hypertension are both risk factors for end-stage renal disease. This study was designed to examine whether their coexistence augmented impairment in renal function and redox status. Regional renal hemodynamics and function in response to vasoactive challenges with acetylcholine or sodium nitroprusside were quantified by using electron-beam computed tomography in pigs after 12 weeks of either a normal (n=10) or hypercholesterolemic (n=10) diet, renovascular hypertension (n=7), or combined hypercholesterolemia+hypertension (n=6). The hypercholesterolemic and hypercholesterolemic+hypertensive groups had significantly increased serum cholesterol levels, whereas in the hypertensive and hypercholesterolemic+hypertensive groups, mean arterial pressure was significantly elevated compared with the group fed a normal diet. Basal regional renal perfusion and glomerular filtration rates were similar among the groups. In response to acetylcholine, cortical perfusion increased in normal animals (15.6±4.7%, P=0.002) but not in hypercholesterolemic or hypertensive animals (8.0±7.4% and 8.2±5.9%, respectively; P>0.05). Moreover, in the hypercholesterolemic+hypertensive group, cortical perfusion response was further attenuated (2.5±4.8%, P=0.02) and significantly different from the group fed a normal diet (P<0.05). The response to sodium nitroprusside followed a similar pattern, and the impairment was augmented in the hypercholesterolemic+hypertensive group. The functional abnormalities in hypercholesterolemia or hypertension were associated with a decrease in systemic and/or renal tissue levels of oxygen radical scavengers that was again accentuated in hypercholesterolemia+hypertension. These results demonstrate that concurrent hypercholesterolemia and hypertension have a greater detrimental effect on renal perfusion responses compared with hypercholesterolemia or hypertension alone, associated with a marked pro-oxidant shift in redox status. These effects may potentially augment renal functional impairment and play a role in the initiation and progression of renal injury in hypertension and atherosclerosis. (Hypertension. 2001;37[part 2]:774-780.)

Key Words: hypertension, renal □ cholesterol □ oxidative stress □ blood flow □ imaging

Vascular nephropathies are among the leading causes of progressive renal insufficiency and end-stage renal disease in the Western world. Hypertension (HT) and hypercholesterolemia (HC) or atherosclerosis are major risk factors for renal vascular and functional abnormalities and are commonly present in combination in a clinical setting. Clinical studies have shown that the coexistence of dyslipidemia and HT greatly increases the incidence of cardiovascular morbidity and mortality and likely modulates the deterioration of renal function as well. Indeed, both antihypertensive and lipid-lowering therapies can halt the progression of renovascular disease and contribute to the preservation of renal function.

The onset of renal injury is detectable after a relatively short exposure to cardiovascular risk factors, inasmuch as experimental HC and HT have each been linked to alterations of vascular and tubular function. We have previously shown that experimental HC was associated with alterations in the renal vascular response to challenge both in vivo and in vitro and abnormal tubular dynamics in vivo. Similarly, HT has been shown to induce abnormalities of renal vascular and tubular function. One of the mechanisms by which HC and HT may induce vascular dysfunction is an increase in the production of oxygen radical species, which in turn can decrease the bioavailability of nitric oxide (NO) and increase the levels or impact of vasoconstrictors such as endothelin-1, angiotensin II, and thromboxane. Activation of oxidation-sensitive mechanisms may thus lead to initially functional and eventually structural vascular alterations. Conceivably, these deleterious effects of HC and HT may be accentuated when these risk factors coexist.
However, the potential impact of concurrent HC and HT on renal perfusion and function (and whether increased oxidative stress is involved in such effects) remains undefined. In particular, their combined impact on the intrarenal microcirculation and tubules in vivo has been difficult to assess because of the lack of reliable noninvasive techniques.

Electron-beam computed tomography (EBCT) is an ultrafast scanner, which provides accurate, reproducible, and noninvasive quantifications of single-kidney volume, perfusion, glomerular filtration rate (GFR), and segmental tubular function, which are difficult to obtain with comparable spatial and temporal resolution by use of other technologies. This technique therefore provides an opportunity to elucidate the interaction between HC and HT in the instigation of renal functional abnormalities.

Thus, the present study was designed to test the hypothesis that the combination of HC and HT is associated with more pronounced impairment of intrarenal hemodynamics and function compared with each risk factor alone and is accompanied by enhanced activation of oxidation-sensitive mechanisms.

Methods

All procedures were designed in accordance with the National Institutes of Health Guidelines and were approved by the Institutional Animal Care and Use Committee. Domestic crossbred pigs (23 to 35 kg) were divided into 4 groups (subsequently treated for 12 weeks). The first group (n=9) was fed a normal diet (normal group). Pigs in the second group (HC group, n=9) were placed on an atherogenic diet of 2% cholesterol and 15% lard by weight (TD 93296, Harlan Teklad). In animals in group 3 (HT group, n=5) was fed a normal diet (normal group). Pigs in the second group (HC group, n=9) was fed a normal diet (normal group). The first group (n=6), blood pressure was recorded, and unilateral renal artery stenosis was induced by placement of a local-irritant stent in the left renal artery with subsequent development of renovascular HT, as previously described. The animals were then maintained on a normal diet for an additional 12 weeks. In animals from group 4 (HC+HT group, n=7), initiation of an HC diet and stent placement were performed on the same day.

After 12 weeks of diet and/or intervention, the degree of stenosis in the left renal artery was determined by using selective quantitative renal angiography, as previously described. In vivo EBCT studies were then performed for the assessment of basal regional renal perfusion, renal blood flow (RBF), GFR, and tubular function. EBCT studies were then repeated during the infusion of acetycholine (ACh) and sodium nitroprusside (SNP), challenges commonly used to test endothelium-dependent and -independent vascular responses, respectively.

After the completion of in vivo studies, in vitro studies were performed in all 4 groups to determine plasma lipid profiles (Roche), plasma renin activity (PRA, New England Nuclear), and serum creatinine (spectrophotometry). Plasma oxidation was assessed spectrophotometrically by measurements of LDL lag time (propensity of LDL for oxidation) and plasma levels of the endogenous antioxidant vitamins E (α-tocopherol) and C (ascorbic acid) by high-performance liquid chromatography, as previously described. Renal tissue activities of the oxygen radical scavengers catalase, glutathione peroxidase, copper-zinc (CuZn) superoxide dismutase (SOD), and manganese SOD (Mn-SOD) were determined spectrophotometrically and normalized for protein content by the Lowry method, as previously described.

EBCT Studies

On the day of the EBCT study, each animal was anesthetized with 0.5 g of intramuscular ketamine and xylazine, intubated, and mechanically ventilated with room air. Anesthesia was maintained with a mixture of ketamine (0.2 mg/kg per minute) and xylazine (0.03 mg/kg per minute) in normal saline, which was administered via an ear vein cannula at a rate of 0.05 mL/kg per minute. This was followed by the placement of intravascular catheters, as previously described. Briefly, under sterile conditions and fluoroscopic guidance, intra-arterial and intravenous catheters were placed at the level of the suprarenal aorta and of the right atrium for the administration of vasoactive substances and contrast media, respectively. The arterial guide also served for selective renal angiography and for monitoring mean arterial pressure (MAP) throughout the experiment. ECG leads served for monitoring heart rates.

Animals were then transferred to the EBCT (Imatron C-150, Imatron Inc) scanning gantry. After a 45-minute recovery period, during which saline (5 mL/min) was administered, hemodynamic parameters were recorded, and a blood sample was collected. A baseline EBCT study of renal perfusion and function was then performed during respiratory suspension at end expiration, as previously described. After tomographic localization of the mid-hilar section of the right kidney, which in hypertensive pigs was the kidney contralateral to the stenosis (CLK), 40 consecutive scans (over 3 minutes) were obtained at variable time intervals after a bolus injection (0.5 mL/kg for 1 second) of the nonionic low-osmolar contrast medium iopamidol (Isovue-370, Squibb Diagnostics) into the right atrial catheter. After stabilization of blood pressure, hemodynamic measurements were recorded, and EBCT studies were repeated. Last, a renal volume study was performed for measurement of cortical and medullary volumes, as described previously. Urinary volume losses were replaced throughout the experiment by equivalent volumes of saline.

After the completion of all studies, the pigs were euthanized with a lethal infusion of Sleepaway (Fort Dodge Laboratories). Kidneys were removed, shock-frozen in liquid nitrogen, and stored at −80°C.

Data Analysis

All images were reconstructed by using a filtered back-projection algorithm on the EBCT workstation and then transferred and displayed on a Sun workstation for density measurements. Regions of interest were selected by manually tracing the aorta, the right (or CLK) renal cortex, medulla, and papilla, and their densities were sampled. Time-density curves were generated for each region, as previously described. From each segment of the curve, the area enclosed under this segment and its first moment (mean transit time) were calculated as previously described. Renal regional perfusion (mL/min per cm² tissue) was subsequently calculated as follows: 60×vascular blood volume/mean transit time. Normalized single-kidney GFR (mL/min per cm² tissue) was calculated as follows: 60×kidney volume×maximal slope of accumulation of contrast in the proximal tubule×(2×mean transit time)/area under aortic input curve. Single-kidney GFR (mL/min) was then calculated as normalized GFR×kidney volume.

Intratubular fluid concentration (ITC) was calculated as the ratio of the tubular curve area to the cortical vascular curve area, which normalizes ITC for concurrent RBF. This was further normalized for glomerular contrast input by division by normalized GFR.

Renal, cortical, and medullary volumes were calculated by using a statistical random-marking method, as previously described. RBF was then calculated as the sum of the products of cortical and medullary perfusions and their corresponding volumes. Renal vascular resistance (RVR) was calculated as MAP/RBF.

Statistical Analysis

Results are expressed as mean±SEM. Statistical comparisons between experimental periods within groups were performed by paired Student t test; among groups, ANOVA was used, with the Bonferroni correction for multiple comparisons and unpaired Student t test if applicable. Statistical significance was accepted at P<0.05.
**Results**

**General Characteristics**

Total and LDL cholesterol levels were significantly and similarly elevated in HC and HC+HT pigs compared with normal and HT pigs (Table 1). The degree of renal artery stenosis was similar in the HT and HC+HT groups (79.1 ± 6.0% versus 68.4 ± 8.9%, *P* = 0.37), and no obstruction was observed in the CLK renal artery. MAP was similarly and significantly increased in the HT and HC+HT groups compared with the normal and HC groups (Table 1), although the increase in MAP after the induction of renal artery stenosis was significantly greater in the HT group compared with the HC+HT group (+27.7 ± 4.7% versus +10.6 ± 3.4%, *P = 0.04). Heart rate response to ACh and SNP was similar among the 4 groups (*P* = NS, data not shown). In response to ACh, there was no change in MAP from baseline in any of the groups (normal −7.4 ± 6.6%, HC −5.2 ± 2.4%, HT −2.2 ± 2.4%, and HC+HT −4.8 ± 4.6%; ANOVA, *P = 0.86*), whereas SNP induced a small decrease in MAP that was very similar among the 4 groups (normal −9.0 ± 4.8%, HC −8.8 ± 2.6%, HT −6.9 ± 3.3%, and HC+HT −7.7 ± 2.9% compared with baseline; ANOVA, *P = 0.98*). Plasma creatinine was similarly increased in the HC, HT, and HC+HT groups (Table 1). PRA was not elevated in any of the 4 groups (ANOVA, *P = 0.75*; Table 1), as is typical for a chronic phase of renovascular HT.21

**Basal Renal Hemodynamics and Tubular Function**

Although HC animals had kidney volumes similar to those of normal animals, in HT animals the CLK was significantly larger compared with that in normal and HC animals (Table 2). In HC+HT animals, the CLK was also larger than that in control and HC animals but significantly smaller than that in HT animals (Table 2). Similarly, baseline RBF was similar in normal and HC animals (Table 2), significantly higher in HT and HC+HT animals, but lower in HC+HT animals compared with HT animals (Table 2). RVR and cortical, medullary, and papillary perfusions, as well as single-kidney GFR, were similar among the groups under basal conditions (Table 2; ANOVA, *P = NS for all parameters*). In the 3 treated experimental groups, ITC was lower than normal from Henle’s loop and distally (Table 2), suggesting decreased fluid reabsorption, although in the HC+HT group, the decrease in ITC in the CLK collecting duct had not reached statistical significance.

**Response to ACh**

In normal animals, ACh induced a significant decrease in RVR (to 0.12 ± 0.0 mm Hg/mL per minute, *P = 0.023*). This was accompanied by an increase in cortical (to 6.9 ± 0.4 mL/min per gram tissue, *P = 0.002*; Figure, bottom left) and papillary (to 7.1 ± 0.8 mL/min per gram tissue, *P = 0.007*) perfusions, RBF (to 851.4 ± 64.1 mL/min, *P = 0.004*; Figure, top left), and GFR (to 116.5 ± 13.1 mL/min, *P = 0.008*), whereas medullary perfusion remained unchanged (*P = 0.18*).

In contrast to the control group, in neither the HC nor the HT group did ACh induce a significant decrease in CLK RVR (to 0.14 ± 0.02 and 0.08 ± 0.02 mm Hg/mL per minute, respectively; both *P > 0.05*) or an increase in either RBF (to 785.5 ± 100.4 and 1196.6 ± 97.1 mL/min, respectively; both *P > 0.05*; Figure, top left) or cortical perfusion (to 6.5 ± 0.5 and 6.6 ± 0.3 mL/min per cm³ tissue, respectively; both *P > 0.12*; Figure, bottom left). Medullary and papillary perfusions remained similarly unchanged (*P = NS*).

In the HC+HT group, the attenuation in RVR response to ACh (to 0.12 ± 0.01 mm Hg/mL per minute) was more pronounced compared with that in the HC or HT group alone.

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**Table 1. Characteristics, Levels of Systemic and Tissue Endogenous Radical Scavengers, and LDL Lag Time (Propensity for Oxidation) in Normal, HC, HT, and HC+HT Pigs**

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=10)</th>
<th>HC (n=10)</th>
<th>HT (n=7)</th>
<th>HC+HT (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC, mmol/L</td>
<td>1.71±0.16</td>
<td>10.76±1.81*</td>
<td>1.78±0.23</td>
<td>9.62±0.52*</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>0.54±0.10</td>
<td>7.71±1.50*</td>
<td>1.01±0.23</td>
<td>8.48±0.83*</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>103.8±3.5</td>
<td>100.8±4.8</td>
<td>140.7±13.5*</td>
<td>122.3±6.9*</td>
</tr>
<tr>
<td>PRA, ng · mL⁻¹ · h⁻¹</td>
<td>0.40±0.01</td>
<td>0.58±0.0</td>
<td>0.30±0.1</td>
<td>0.30±0.2</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>133.48±6.19</td>
<td>162.66±7.96*</td>
<td>165.31±11.50*</td>
<td>183.87±29.17*</td>
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**Plasma**

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<tbody>
<tr>
<td>Vitamin C, μmol/L</td>
<td>60.0±4.5</td>
<td>51.6±1.1*</td>
<td>63.2±1.6</td>
<td>46.3±2.5†</td>
</tr>
<tr>
<td>Vitamin E, μmol/L</td>
<td>92.3±3.5</td>
<td>87.8±1.9*</td>
<td>87.8±1.8*</td>
<td>77.7±2.6*</td>
</tr>
<tr>
<td>LDL lag time, min</td>
<td>82.0±1.6</td>
<td>76.0±1.8*</td>
<td>81.0±1.1</td>
<td>68.5±1.8†</td>
</tr>
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</table>

**Tissue, μL/mg protein**

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<tbody>
<tr>
<td>Glut-peroxidase</td>
<td>86.8±2.7</td>
<td>87.4±2.0</td>
<td>57.5±2.0*</td>
<td>50.5±1.0†</td>
</tr>
<tr>
<td>Catalase</td>
<td>21.8±1.8</td>
<td>20.8±0.8</td>
<td>13.3±0.8*</td>
<td>10.5±0.4*</td>
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<tr>
<td>Mn-SOD</td>
<td>3.3±0.1</td>
<td>3.2±0.1</td>
<td>2.0±0.0*</td>
<td>1.5±0.1†</td>
</tr>
<tr>
<td>CuZn-SOD</td>
<td>8.1±0.2</td>
<td>8.0±0.2</td>
<td>6.5±0.1*</td>
<td>6.2±0.2*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. TC indicates total cholesterol; Glut-peroxidase, glutathione peroxidase.

*P < 0.05 compared with normal; †P < 0.05 compared with HC or HT.
TABLE 2. Basal Single-Kidney Hemodynamics and Function in Normal, HC, HT, and HC+HT Pigs

<table>
<thead>
<tr>
<th>Renal hemodynamics and function</th>
<th>Normal (n=10)</th>
<th>HC (n=10)</th>
<th>HT (n=7)</th>
<th>HC+HT (n=6)</th>
</tr>
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<tbody>
<tr>
<td><strong>Renal volume, cm³</strong></td>
<td>137.0±10.5</td>
<td>128.4±13.5</td>
<td>192.7±13.6*</td>
<td>156.6±11.05†</td>
</tr>
<tr>
<td><strong>RBF, mL/min</strong></td>
<td>791.6±54.8</td>
<td>716.9±58.9</td>
<td>1087.6±67.8*</td>
<td>919.19±85.4*†</td>
</tr>
<tr>
<td><strong>RVR, mm Hg · mL⁻¹ · min⁻¹</strong></td>
<td>0.15±0.02</td>
<td>0.16±0.02</td>
<td>0.13±0.02</td>
<td>0.13±0.01</td>
</tr>
<tr>
<td><strong>GFR, mL/min</strong></td>
<td>79.6±7.8</td>
<td>80.5±11.9</td>
<td>107.0±20.5</td>
<td>82.7±12.0</td>
</tr>
<tr>
<td><strong>Cortical perfusion, mL · min⁻¹ · cm⁻³⁻¹</strong></td>
<td>6.1±0.4</td>
<td>6.2±0.6</td>
<td>6.2±0.3</td>
<td>6.1±0.4</td>
</tr>
<tr>
<td><strong>Medullary perfusion, mL · min⁻¹ · cm⁻³⁻¹</strong></td>
<td>5.4±0.3</td>
<td>4.4±0.5</td>
<td>4.7±0.3</td>
<td>5.4±0.5</td>
</tr>
<tr>
<td><strong>Papillary perfusion, mL · min⁻¹ · cm⁻³⁻¹</strong></td>
<td>5.2±0.6</td>
<td>4.7±1.1</td>
<td>5.8±1.0</td>
<td>5.1±1.0</td>
</tr>
<tr>
<td><strong>Intratubular contrast concentration, arbitrary units</strong></td>
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<tr>
<td><strong>Proximal tubule</strong></td>
<td>5.51±0.56</td>
<td>5.14±1.13</td>
<td>4.84±0.41</td>
<td>5.93±0.66</td>
</tr>
<tr>
<td><strong>Henle’s loop</strong></td>
<td>13.04±2.39</td>
<td>7.26±2.02*</td>
<td>6.74±1.07*</td>
<td>7.83±1.47*</td>
</tr>
<tr>
<td><strong>Distal tubule</strong></td>
<td>10.10±1.39</td>
<td>6.50±1.39*</td>
<td>5.13±0.79*</td>
<td>7.07±0.57*</td>
</tr>
<tr>
<td><strong>Collecting duct</strong></td>
<td>15.31±1.67</td>
<td>10.63±1.81*</td>
<td>8.41±1.38*</td>
<td>13.43±1.34†</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
*P<0.05 compared with normal; †P<0.05 compared with HT.

and was significantly different from the ACh-induced decrease in RVR in the control group (P=0.048). Furthermore, in the HC+HT group, RBF and cortical perfusion responses were also more attenuated (to 969.5±98.7 mL/min and 6.3±0.5 mL/min per cm³ tissue, respectively; Figure, top and bottom left, respectively) than in either the HC or HT group, inasmuch as the degree of response was significantly different from that in normal animals (Figure, bottom left). Medullary and papillary perfusions were similarly unchanged in all these enzymes, although only the augmented decreases in GFR and medullary and papillary perfusions did not change in response to SNP (to 8.55.4±78.4 mL/min and 5.7±0.4 mL/min per cm³ tissue, respectively; both P<0.04; Figure, top and bottom right). GFR and medullary and papillary perfusions did not change in any group (P>0.05 for all parameters) in response to SNP.

In the proximal part of the nephron, SNP did not change ITC in the normal group (P=0.17), but it did decrease ITC in the HC, HT, and HC+HT groups (P=0.04, P=0.042, and P=0.058, respectively). In the distal part of the nephron, SNP induced a decrease in ITC in the normal, HC, and HC+HT groups (all P<0.05) but not in the HT group (P=0.14).

Redox Status

Compared with normal animals, HC animals had a decrease in plasma levels of vitamins C and E (Table 1), whereas HT animals had lower levels of vitamin E but not vitamin C (Table 1). However, in the HC+HT group, the levels of vitamins E and C were lower compared not only with the control group but also with the HC and HT groups, although only the difference in vitamin C levels reached statistical significance (Table 1). The LDL lag time was shortened (representing increased oxidizability) in the HC group but not in the HT group (Table 1) compared with the normal group. Similar to circulating vitamin levels, with concurrent HC+HT, the LDL lag time was further shortened compared with either HC or HT alone (Table 1). In addition, CLK tissue levels of the radical scavenger enzymes catalase, glutathione peroxidase, Mn-SOD, and Cu-Zn SOD were significantly lower in the HT group compared with the normal group, whereas in the HC group, these levels were not different from normal levels (Table 1). In animals with combined HC+HT, the decrease in scavenging activity was more pronounced in all these enzymes, although only the augmented decreases in...
glutathione peroxidase and Mn-SOD had reached statistically significant levels (Table 1).

**Discussion**

The present study demonstrates that the combination of the cardiovascular risk factors HC and HT is associated with a greater impairment of renal perfusion than is each risk factor alone. Furthermore, these abnormalities are associated with augmented activation of oxidation-sensitive mechanisms and reduction of endogenous scavenging activity. These alterations are likely to result in greater renal damage in a kidney exposed to both risk factors simultaneously.

HC and HT are major risk factors for the development of end-stage renal disease and are commonly present in combination. Long-standing HT induces vascular and glomerular damage, including arteriolosclerosis and glomerulosclerosis, with a progressive decline in renal function. Dyslipidemias, with subsequent lipid deposits and inflammatory infiltration, can similarly injure intrarenal vascular and glomerular structures. Nevertheless, a growing body of evidence indicates that at least some of the functional deleterious effects of HC and HT can begin after a relatively short exposure to these risk factors. One of the earliest functional alterations elicited by cardiovascular risk factors is abnormal vascular reactivity, which may result from increased release of reactive oxygen species, decreased bioavailability of NO, and increased vasoconstrictor activity. Indeed, HC and HT have been individually associated with abnormal renal vascular function, but the cross talk between them remains to be elucidated.

In the present study, we compared measurements of renal hemodynamics and function, obtained in pig models of HC and HT, with those obtained in a pig model of combined HC and HT. The HT model is characterized by a transient increase in PRA that subsequently returns to normal levels, as also observed in the present study. Single-kidney GFR of the CLK was unchanged in the HT and HC+HT groups, which may imply a decline in GFR of the total renal mass and may explain the mild increase in serum creatinine. In HC pigs, the small increase in serum creatinine may speculatively be related to an impaired homeostatic regulation of GFR in response to physiological challenges faced by the kidney.

We have previously demonstrated reliable EBCT measurements of renal volume and RBF in both normal and renovascular HT animals and humans. In the present study, EBCT showed preserved basal RVR and regional renal perfusion in the 4 groups, but both renal volume and RBF were significantly higher in all hypertensive animals compared with normal and HC animals. Hypertrophy of the CLK has been previously demonstrated in subjects with unilateral renal artery stenosis and has been suggested to represent a compensatory response of the CLK to the altered renal perfusion pressure in both kidneys. Notably, renal volume and, consequently, RBF were higher in the HT group compared with the HC+HT group, likely because the increase in MAP observed in the HT group was greater and closer to the upper limit of RBF autoregulation. We have previously shown that HC pigs had normal basal urinary sodium excretion but a greater decrease in fluid reabsorption in response to challenge. Such a propensity should not contribute to the evolution of HT at its early stage, as also demonstrated in spontaneously hypertensive rats. A subtle decreased propensity for fluid reabsorption in HC pigs and pressure natriuresis in HT and HC+HT pigs may explain the decreased basal ITC observed in our 3 experimental groups. The mechanisms underlying the enhanced tubular response to ACh and SNP remain to be elucidated but may speculatively be related to proinflammatory intrarenal changes in HC and HT.

ACh and SNP are both vasodilators and under normal conditions decrease RVR and increase RBF. Although early impairment in vascular reactivity is often observed in response to endothelium-dependent vasodilators such as ACh, previous studies have reported attenuated vasodilatory response to both endogenous and exogenous NO donors. This may involve an unbalanced increase in vasoconstrictor activity or impaired smooth muscle cell responses. In the kidney, experimental HC is associated with an abnormal response of the renal vasculature to both ACh and SNP, and this study indicates that HT is associated with similar abnormalities. The present study extends these observations and demon-
strates, for the first time, that when these 2 risk factors coexist, the deleterious effects on renal vascular function are even more accentuated. Indeed, CLK-RBF of both hypertensive groups was elevated under basal conditions, and the impaired response to vasodilators could have speculatively been related to a preexisting maximal vasodilation in these kidneys. However, basal RBF was significantly higher in the CLK of HT pigs compared with normal pigs and with those pigs with combined HT and HC, yet their responses were less impaired than those in the HT+HC group. Therefore, additional mechanisms likely played a role in the markedly impaired responses in the HT+HC group. This short exposure in pigs is known to precede signs of morphological vascular damage and is not associated with morphological glomerular damage in either HT17 or HC (authors’ unpublished data, 2000) kidneys. Hence, the impaired responses to vasodilators as observed in the present study were likely mainly functional. Although some morphological alterations in the HT+HC kidneys in the present study cannot be totally excluded, their normal basal perfusion and function suggest that the impairment observed in these kidneys was also mostly functional.

One of the mechanisms that might be involved in the renal vascular dysfunction as observed in the present study is a pro-oxidant shift in redox status, which in models of renal injury is characterized by a decrease of endogenous scavengers enzymes.24 The present study underscores the link between HC, HT, and the activation of oxidation-sensitive mechanisms. We observed that in HC, activation of these mechanisms was detectable mainly in the systemic circulation rather than in the renal tissue. However, in animals with combined HC and HT, tissue-driven oxidation-sensitive mechanisms were greatly enhanced by the HC diet, suggesting a cross talk between HC and HT that could augment the abnormalities observed in this pathophysiological state.

In the present study, HC and HT were induced almost simultaneously, inasmuch as the increase in both MAP27 and plasma cholesterol levels may be observed 1 to 2 weeks after the intervention. However, in a clinical setting, exposure to either risk factor may precede exposure to the other, and this may affect the course of renal vascular dysfunction. Nevertheless, the present study suggests that their coexistence has significant pathophysiological implications regarding the potential evolution of renal injury.

In summary, the present study demonstrates that the combination of HC and HT accentuates their individual deleterious effects on renal vascular function and activation of oxidation-sensitive mechanisms. This interaction may amplify renal injury when a kidney is exposed to both risk factors simultaneously.

Acknowledgments

This study was supported by grants HL-03621 and HL-63282 from the National Institutes of Health, by the Bruce and Ruth Rappaport Program in Vascular Biology, by the Mayo Foundation, and by grant ISNIH 99.56980 (C.N.). The authors are grateful to the staff of the EBCF for the technical assistance with performance of experiments and to Drs Yang Lee and Filomena de Nigris for their skillful technical assistance.

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_Hypertension_. 2001;37:774-780
doi: 10.1161/01.HYP.37.2.774

_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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/37/2/774

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