Kidney

Preserved Oxygenation Despite Reduced Blood Flow in Poststenotic Kidneys in Human Atherosclerotic Renal Artery Stenosis

Monika L. Gloviczki, James F. Glockner, Lilach O. Lerman, Michael A. McKusick, Sanjay Misra, Joseph P. Grande, Stephen C. Textor

Abstract—Atherosclerotic renal artery stenosis reduces blood flow and perfusion pressures to the poststenotic kidney producing renovascular hypertension and threatening glomerular filtration rate. Little is known regarding regional tissue oxygenation in human renovascular disease that develops slowly. We compared stenotic and contralateral kidneys regarding volume, tissue perfusion, blood flow measured by multidetector computed tomography, and blood oxygen level–dependent magnetic resonance values in the cortex and medulla in 14 patients with unilateral stenosis (mean: 71% by quantitative computed tomography) and in 14 essential hypertensive patients during 150 mEq/d of sodium intake and renin-angiotensin blockade. Stenotic kidney volume was reduced compared with the contralateral kidney (118.6 ± 9.9 versus 155.4 ± 13.7 mL; *P*<0.01), as was total blood flow (269.7 ± 42.2 versus 383.7 ± 49; *P* = 0.02), mainly because of reduced cortical volume. Tissue perfusion was similar but lower than essential hypertension (1.5 versus 1.2 mL/min per milliliter; *P*<0.05). Blood oxygen level–dependent MR at 3 T confirmed elevated R2* values (a measure of deoxyhemoglobin) in deep medullary regions in all 3 sets of kidneys (38.9 ± 0.7 versus cortex 17.8 ± 0.36 s⁻¹; *P*<0.0001). Despite reduced blood flow, R2* values did not differ between atherosclerotic and essential hypertensive kidneys, although furosemide-suppressible fall in medullary R2* was reduced in stenotic kidneys (5.7 ± 1.8 versus 9.4 ± 1.9 s⁻¹; *P*<0.05). Renal venous oxygen levels from the stenotic kidney were higher than those from essential hypertensives (65.1 ± 2.2 versus 58.1 ± 1.2; *P* = 0.006). These data indicate that, although stenosis reduced blood flow and volume, cortical and medullary oxygenation was preserved under these conditions. (Hypertension. 2010;55:961-966.)

Key Words: renal artery stenosis ■ renovascular hypertension ■ BOLD MR ■ ischemia ■ hypertension ■ oxygen ■ renin

Atherosclerotic renal artery stenosis (ARAS) commonly reduces perfusion pressure to the affected kidney, activates the release of renin, and produces renovascular hypertension. ARAS also can lead to rarefaction of renal microvessels in experimental models associated with tubulointerstitial fibrosis that ultimately threatens kidney viability.1 Antihypertensive therapy for renovascular hypertension now often includes agents that block the renin-angiotensin system, including angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) that reduce systemic arterial pressures but also reduce poststenotic perfusion pressures to the kidney.2 Experimental studies in 2 kidney, 1-clip renovascular hypertension indicate that poststenotic cortical blood flow, oxygen levels, and renal venous oxygen levels are reduced in rats.3 Much of the hypoxia and increase in oxidative stress in this model is reversed by an ARB (candesartan) or a free radical scavenger (Tempol) but is more severe in those treated with an ACE inhibitor (enalapril).4 The authors interpret these data to suggest that oxygen availability in the poststenotic kidney is modulated in part by activation of the angiotensin II type 1 receptor that was not observed during ACE inhibition. How these findings apply to human renovascular disease is not known.

Although poststenotic pressures and blood flow are reduced, some human studies challenge the premise that renovascular disease produces whole kidney “ischemia.”5 This inference derives from the fact that erythropoietin levels are not elevated and venous oxygen saturation in the poststenotic kidney is not depressed, but actually may be higher, as compared with the levels from the contralateral kidney (CLK).6 In fact, the kidney receives more blood flow than needed for its basic metabolic function, unlike the heart or brain.7 Severe vascular occlusive disease may reduce blood flow for the whole kidney, but associated reductions in kidney volume may preserve regional

Received October 9, 2009; first decision October 23, 2009; revision accepted February 3, 2010.

From the Departments of Nephrology and Hypertension (M.L.G., L.O.L., S.C.T.) and Radiology (J.F.G., M.A.M., S.M.) and Laboratory of Medicine and Pathology (J.P.G.), Mayo Clinic, Rochester, Minn.

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

Correspondence to Stephen C. Textor, Nephrology and Hypertension, Mayo Clinic, Rochester, MN 55905. E-mail textor.stephen@mayo.edu

© 2010 American Heart Association, Inc.

Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.109.145227
perfusion (expressed as blood flow per milliliter of tissue). Whether reduced blood flow to either cortical or medullary segments of the kidneys in humans leads to a similar reduction in tissue oxygenation and/or increased overall oxygen consumption is not well understood.

Until recently, evaluation of tissue oxygenation in the human kidney in vivo was not technically feasible. Recent studies using blood oxygen level–dependent (BOLD) magnetic resonance at 1.5 T indicate that alterations in cortical and medullary deoxyhemoglobin measured as the relaxation coefficient ($R_2^*$) can provide assessment of local oxygenation in vivo. Levels of $R_2^*$ change with acute reduction in renal perfusion pressure, ureteral obstruction, acute kidney injury, or acute allograft rejection.

Studies with higher magnet field strength (3.0 T) improve differentiation between medullary and cortical oxygen consumption on the basis of inhibiting tubular solute transport.

The purpose of the current study was to examine renal blood flow, renal venous oxygen tension, and regional tissue oxygenation using BOLD magnetic resonance in post-stenotic kidneys (STKs) and CLKs from hypertensive human subjects with ARAS (ARAS group) as compared with patients with essential hypertension without renal artery stenosis (EH group). These studies were undertaken during therapy with either an ACE inhibitor or an ARB during conditions of known, stable sodium intake. Our results suggest that oxygen consumption in the post-STK beyond minimum metabolic requirements is actually reduced under these conditions.

Methods

Nondiabetic patients with either unilateral ARAS (n = 14) or essential hypertension (n = 14) participated in this study during a 3-day inpatient protocol in the clinical research unit of Saint Marys Hospital (Rochester, MN). Dietary intake was regulated at 150 mEq in sodium with an isocaloric diet prepared on site. Patients with qualifying renal artery stenosis were identified using criteria similar to those stipulated for recruitment in the Cardiovascular Outcomes in Renal Atherosclerotic Lesions Trial, with the exception of limiting sodium intake. Severity of renal artery stenosis was estimated by Doppler ultrasound measurements in tissue density produced by transit of contrast in that region.

The first study day included measurement of sodium excretion and arterial Blood Sample Syringe With Dry Lithium Heparin for gases and electrolytes and transferred immediately for analysis by the clinical laboratory. The catheter was left in place for central venous injection of contrast for transit time studies using multidetector CT (MDCT) imaging. Arterial Blood Sample Syringe With Dry Lithium Heparin for gases and electrolytes was inserted into the right, left, and infrarenal inferior vena cava to collect selective renal vein samples for venous oxygen and plasma renin activity. Samples for oxygen tension were collected in a Portex 3 mL Line Draw Arterial Blood Sample Syringe With Dry Lithium Heparin for gases and electrolytes and transferred immediately for analysis by the clinical laboratory. The catheter was left in place for central venous injection of contrast for transit time studies using multidetector CT (MDCT), as described previously. MDCT imaging was obtained using a dual-source 64-slice helical MDCT scanner (SOMATOM Definition, Siemens Medical Solutions) after a bolus injection of iopamidol 370 (0.5 mL/kg up to a maximum of 40 mL) using a power injector during respiratory suspension. Perfusion scans were performed at 120 kVp and 160 mAs (adjusted per level of signal-to-noise ratio of the scan) with 20×1.2 collimation and 0 table feed. The flow study was composed of 35 scans divided into 3 consecutive scanning sequences (each 20 seconds long) followed by 10 additional scans at 8-seconds intervals, for a total of 45 scans. The total scanning time lasted ~158 seconds. The longest breath hold was 20 seconds. Images representing the 4 slices (5-mm thickness) localized in the hilum region were acquired and reconstructed using a B40f kernel.

Fifteen minutes after completion of the perfusion study, a kidney volume study (5-mm thick slices) was performed to determine both cortical and medullary regional volumes. Additional images for quantitative vascular stenosis evaluation (quantitative CT angiography) were reconstructed at 0.6-mm slice thickness, with a 0.3-mm overlap, at either the b10f or b18f kernel setting.

Image analysis was performed using ANALYZE (Biomedical Imaging Resource Center, Mayo Clinic). Analyses of MDCT flow studies were undertaken by selecting regions of interest in cross-sectional images from the aorta, individual kidney cortex, and medulla. The computer then generated curves reflecting the change in tissue density produced by transit of contrast in that region. Regional perfusion or blood flow normalized per unit of tissue with TEs ranging from 2.5 to 32.0 ms. Imaging parameters for the BOLD acquisition included the following: repetition time at 140 ms, flip angle at 45°, slice thickness at 5 mm, imaging matrix 224×160 to 192, and field of view at 32 to 40 cm, with 0.7 to 1.0 partial phase field of view. Imaging protocols to establish TEs in normal subjects were performed in volunteers without furosemide. Image matrix and repetition time were adjusted in patients with limited breath hold capacity, and the field of view and partial phase field of view were adjusted according to patient size. Transverse slice BOLD images were acquired during suspended respiration through the midpole hilar region of each kidney. Parametric images of $R_2^*$ were then generated by fitting signal intensity versus TE data to an exponential function on a voxel-by-voxel basis. After the first BOLD acquisition, furosemide (20 mg) was administered intravenously and flushed with 20 mL of saline. BOLD measurements for each kidney were repeated 15 minutes later.

BOLD images were analyzed on an Advantage Windows workstation version 4.2 (GE Healthcare) using CineTool software (GE Healthcare). This program generates a set of parametric images of $R_2^*$ from the BOLD sequence data by fitting signal intensity data from each echo on a voxel-by-voxel basis to an exponential function describing the expected signal decay as a function of TE and solving for the unknown value of $R_2^*$ (the magnetic rate of relaxation of the tissue or the inverse of the T2* relaxation time).

For data analysis, individual anterior, lateral, and posterior region of interest were traced in the cortex and medulla manually on the 7-ms TE image or any other image yielding optimal contrast between the cortex and medulla and then implemented at the parametric $R_2^*$ image to determine average values of $R_2^*$ within the region of interest. Special care was taken to ensure that each region of interest fell within identifiable medullary and cortical sections that remained within the segment on repeat scanning after furosemide. As described previously, we considered for comparisons the mean values of $R_2^*$ of 3 areas (anterior, lateral, and posterior) for the cortex and medulla within the selected slice.

On the third day of the protocol, the common femoral vein was cannulated using a 5F Cobra catheter (Cook, Inc) inserted into the right, left, and infrarenal inferior vena cava to collect selective renal vein samples for venous oxygen and plasma renin activity. Samples for oxygen tension were collected in a Portex 3 mL Line Draw Arterial Blood Sample Syringe With Dry Lithium Heparin for gases and electrolytes and transferred immediately for analysis by the clinical laboratory. The catheter was left in place for central venous injection of contrast for transit time studies using multidetector CT (MDCT), as described previously. MDCT imaging was obtained using a dual-source 64-slice helical MDCT scanner (SOMATOM Definition, Siemens Medical Solutions) after a bolus injection of iopamidol 370 (0.5 mL/kg up to a maximum of 40 mL) using a power injector during respiratory suspension. Perfusion scans were performed at 120 kVp and 160 mAs (adjusted per level of signal-to-noise ratio of the scan) with 20×1.2 collimation and 0 table feed. The flow study was composed of 35 scans divided into 3 consecutive scanning sequences (each 20 seconds long) followed by 10 additional scans at 8-seconds intervals, for a total of 45 scans. The total scanning time lasted ~158 seconds. The longest breath hold was 20 seconds. Images representing the 4 slices (5-mm thickness) localized in the hilum region were acquired and reconstructed using a B40f kernel.

Fifteen minutes after completion of the perfusion study, a kidney volume study (5-mm thick slices) was performed to determine both cortical and medullary regional volumes. Additional images for quantitative vascular stenosis evaluation (quantitative CT angiography) were reconstructed at 0.6-mm slice thickness, with a 0.3-mm overlap, at either the b10f or b18f kernel setting.

Image analysis was performed using ANALYZE (Biomedical Imaging Resource Center, Mayo Clinic). Analyses of MDCT flow studies were undertaken by selecting regions of interest in cross-sectional images from the aorta, individual kidney cortex, and medulla. The computer then generated curves reflecting the change in tissue density produced by transit of contrast in that region. Regional perfusion or blood flow normalized per unit of tissue.
A B

Table 1. Clinical and Demographic Characteristics of Patients With EH and ARAS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EH (n=14)</th>
<th>ARAS (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.1±2.8</td>
<td>65.5±2.8</td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>7/7</td>
<td>6/8</td>
</tr>
<tr>
<td>Duration of the disease, y</td>
<td>12.6±1.7</td>
<td>12.5±5</td>
</tr>
<tr>
<td>GFR, mL/min per 1.73 m²</td>
<td>84.1±5.2</td>
<td>65.2±5.3*</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.8±0.0</td>
<td>1.2±0.1†</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.5±1.1</td>
<td>27.9±1</td>
</tr>
<tr>
<td>Median urinary sodium, mEq/24 h</td>
<td>165.9</td>
<td>159.3</td>
</tr>
<tr>
<td>No. of anti-HTN drugs</td>
<td>2.5±0.2</td>
<td>2.9±0.3</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>8/5</td>
<td>5/9</td>
</tr>
<tr>
<td>Mean SBP/DBP, mm Hg</td>
<td>139.2±5.8/74.9±3.6</td>
<td>131.9±5.0/70.4±2.2</td>
</tr>
<tr>
<td>Doppler peak systolic velocity, cm/s</td>
<td>NA</td>
<td>371.6±38.8</td>
</tr>
<tr>
<td>Degree of stenosis, %‡</td>
<td>NA</td>
<td>71±5.5</td>
</tr>
</tbody>
</table>

Data are mean±SEM. Anti-HTN indicates antihypertensive; ACEI, ACE inhibitor; SBP, systolic blood pressure; DBP, diastolic blood pressure; NA, not applicable. *P<0.05. †P<0.01. ‡Data are by quantitative CT angiography.

(milliliters of blood per minute per milliliter of tissue) was conventionally calculated as follows: perfusion = 60 × blood volume/mean transit time/(1 − blood volume), where (1 − blood volume) is a correction for dynamic changes in blood volume that occur in vivo.19

Cortical and medullary volumes were calculated using the stereology module within ANALYZE. Regions of interest for the cortical and medullary regions were defined on each successive slice and subsequently multiplied by slice width; these were then summed to obtain cortical, medullary, and total renal volume. Renal blood flow for each kidney was determined as the renal perfusion (milliliters per minute per milliliter of tissue) × kidney volume (milliliters of tissue). Quantitative evaluation of vascular stenosis was undertaken by CT angiography comparing the maximally narrowed cross-sections of the artery to proximal segments and expressed as the percentage of vascular occlusion.

Results were expressed using mean values and SEM. Comparison between groups with essential hypertension or ARAS were performed with t tests, as appropriate. Comparisons between stenotic kidneys and CLKs were performed using paired t tests.

Results

Clinical characteristics of the patients studied are summarized in Table 1. Ages ranged from 50 to 84 years, with the average age in each group approaching 66 years. Serum creatinine was higher, and measured iothalamate GFR was lower in subjects with ARAS (P<0.01). All of the subjects with ARAS and all but 1 subject with essential hypertension were taking an ACE inhibitor or ARB, and 22 of 28 were receiving a thiazide-class diuretic. Fifteen of 28 were taking statin therapy. The severity of arterial stenosis in the STKs (Figure 1) ranged between 62% and 81%, as estimated by quantitative CT angiography.

Antihypertensive therapy was similar in the EH and ARAS groups (average number of antihypertensive drugs was 2.5

Table 2. Kidney Functional Parameters in Patients With EH and ARAS

<table>
<thead>
<tr>
<th></th>
<th>EH N=28</th>
<th>Stenotic (n=14)</th>
<th>Contralateral (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total kidney volume (CT), mL</td>
<td>144.3±6.6</td>
<td>118.6±9.9*§</td>
<td>155.4±13.7</td>
</tr>
<tr>
<td>Cortical volume, mL</td>
<td>96.1±5.9</td>
<td>80.1±7.8§</td>
<td>111.8±12.1</td>
</tr>
<tr>
<td>Medullary volume, mL</td>
<td>48.2±3.5</td>
<td>38.5±4.5</td>
<td>43.6±6.1</td>
</tr>
<tr>
<td>Renal tissue perfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortex, mL/min per mL of tissue</td>
<td>3.5±0.2</td>
<td>2.7±0.3*§</td>
<td>2.9±0.3</td>
</tr>
<tr>
<td>Medulla, mL/min per mL of tissue</td>
<td>1.5±0.1</td>
<td>1.2±0.1†</td>
<td>1.2±0.1†</td>
</tr>
<tr>
<td>Total renal blood flow, mL/min</td>
<td>404.6±28.9</td>
<td>269.7±42.2§</td>
<td>383.7±49.0</td>
</tr>
<tr>
<td>Cortical flow, mL/min</td>
<td>331.6±27.2</td>
<td>219.1±35.1*§</td>
<td>330.2±44</td>
</tr>
<tr>
<td>Medullary flow, mL/min</td>
<td>68.1±5.4</td>
<td>49±8.9‡</td>
<td>55±10.2</td>
</tr>
<tr>
<td>MRI studies: BOLD magnetic resonance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal cortical R2*, s⁻¹</td>
<td>18.6±0.6</td>
<td>17.0±0.6</td>
<td>16.9±0.5</td>
</tr>
<tr>
<td>Basal medullary R2*, s⁻¹</td>
<td>38.2±1.0</td>
<td>37.5±1.5</td>
<td>41.9±1.4</td>
</tr>
<tr>
<td>Change in R2* after furosemide</td>
<td>7.0±1.1</td>
<td>5.7±1.8§</td>
<td>9.4±1.9</td>
</tr>
<tr>
<td>PRA, ng/mL per h</td>
<td>8.2±2.1</td>
<td>24.3±5.0*§</td>
<td>18.3±4.3</td>
</tr>
</tbody>
</table>

Data are mean±SEM. PRA indicates plasma renin activity. *P<0.05 vs EH. †P<0.01 vs EH. ‡P<0.08 vs EH. §P<0.05 vs contralateral. ¶Data from both kidneys were compiled. *All of the values of medullary R2* were higher than cortical values (P<0.0001).

Figure 1. A, Magnetic resonance angiogram of a patient with unilateral renal artery stenosis with reduced kidney volume in the post-STK. B, Coronal view of both kidneys enhanced by gadolinium emphasizing the difference in single kidney volume. This was associated with a reduced single-kidney blood flow and glomerular filtration (see Table 2). Single-kidney cortical and medullary perfusion (renal blood flow per milliliter of volume as measured by MDCT) were reduced in post-STKs, with elevation of renal vein renin values (see text).
and 2.9, respectively). Median urinary sodium collected on day 1 was 159.6 mEq/d.

The total volume of STKs was reduced, primarily because of a reduction in cortical volume as compared with the CLK (Table 2; P < 0.01). Both medullary and cortical perfusion (expressed as milliliters per minute per milliliter of tissue volume) tended to be reduced in the stenotic and CLKs compared with subjects identified with essential hypertension (P = 0.06) but did not differ from each other. Whole kidney blood flow was reduced in the stenotic as compared with both the CLK and essential hypertensives, primarily on the basis of reduced cortical and medullary volumes. Despite a reduction in blood flow and volume, tissue oxygenation, as reflected by cortical and medullary R2* values, did not differ in the post-STK as compared either with the contralateral or essential hypertensive kidneys (Table 2).

Examples of R2* parametric maps for cortex and medulla in stenotic and CLKs of this individual are illustrated in Figure 2A and 2B and compared with that of a patient with essential hypertension (Figure 2C). Cortical levels were lower (16.9 to 18.6 s⁻¹) as compared with the medulla (37.5 to 41.9 s⁻¹) for all of the patients (P < 0.001) and for each kidney group (Table 2). Average levels did not differ between stenotic and CLKs and essential hypertension. These values did not differ from basal levels of cortical and medullary R2* in healthy volunteers (n = 6 kidneys; cortical R2* = 16.4 ± 0.3 s⁻¹, medullary R2* = 39.7 ± 1.9 s⁻¹).

Renal vein levels of plasma renin activity from both the stenotic and CLKs were elevated as compared with essential hypertensive kidneys (Table 2; P < 0.01). Renal vein oxygen levels (in millimeters of mercury; Figure 3) from the STK were higher than those obtained from patients with essential hypertension and as compared with the CLK. No differences in renal vein oxygen levels were apparent in ARAS patients treated with ACE inhibitors (64 mm Hg; n = 5) versus ARBs (64.6 mm Hg; n = 9).

**Discussion**

In this article we present measurements of single kidney volume, blood flow, and tissue oxygenation in hypertensive patients with unilateral ARAS as compared with essential hypertension. Despite reduced blood flow to the whole organ, our results demonstrated elevation of venous oxygen levels in post-STKs. The fact that deep medullary and cortical oxygenation as measured by regional BOLD MR did not differ despite reduced blood flow suggests that loss of kidney volume was not associated with ischemia within either region under these conditions. We interpret the elevation of venous oxygen levels to likely reflect reduced oxygen consumption in the STK as compared with both the CLK and essential hypertension. Reduced furosemide-suppressible changes in medullary oxygen consumption in the STKs as compared with the CLK were consistent with this interpretation and suggest less energy-requiring solute transport in the post-STKs.

It should be emphasized that our patients had relatively preserved GFR, although lower than the 2-kidney GFR in essential hypertensives. None of the patients with renal artery
stenosis had total occlusion, and all had measurable single kidney blood flow by MDCT. The actual perfusion (blood flow per volume of tissue) was only modestly reduced in the STK (20% as compared with essential hypertension). Small differences in perfusion were apparent between the STK and CLK, consistent with the inference that long-standing small vessel changes within both kidneys may be more important than the large vessel occlusive disease evident in the STK. These results extend the observations that histological and functional changes in ARAS are present in both kidneys. On the other hand, the average difference in kidney volume between the STK and CLK was 23% in our subjects, suggesting that the difference in blood flow between ARAS kidneys was related primarily to changes in volume rather than tissue perfusion. Our results demonstrate that, despite changes in volume, both cortical and medullary R2* levels were preserved at levels not different from essential hypertension, consistent with the known excess of blood flow to the kidney as compared with its basal metabolic energy requirements.

Levels of plasma renin activity were elevated in our subjects, in part because nearly all were treated with inhibitors of the renin-angiotensin system and diuretics. As expected, the highest levels were obtained from the post-STK. The renal vein renin levels from both STKs and CLKs were higher than those from essential hypertension. We interpret this to reflect stimulation of renin from combined diuretic therapy before sampling, because long-term thiazide effects were magnified by the dose of intravenous furosemide administered the day before as part of BOLD imaging. Previous studies in experimental renovascular hypertension demonstrate that activation of the renin-angiotensin system alters levels of oxidative stress and efficiency of sodium transport within the post-STK. Administration of an ARB improves venous oxygenation in 2-kidney, 1-clip hypertension in rats after 3 weeks, whereas an ACE inhibitor leads to lower venous oxygen levels and elevated oxidative stress that can be reversed with Tempol. Studies of other experimental models of chronic kidney disease demonstrate that blockade of angiotensin alters the efficiency of sodium transport favorably to reduce oxidative stress, a mechanism that may be renoprotective. The precise role of renin-angiotensin blockade in our studies cannot be determined with the data available, but our data indicate that both ACE inhibitors and ARBs were associated with preserved oxygenation in humans under these conditions. The range of values for normal subjects not treated either with ACE/ARB therapy or diuretics overlapped those of both essential hypertension and renal artery stenosis.

These human studies differ from changes observed with more acute models of renal artery occlusion. R2* levels rise during acute, progressive renovascular occlusion that reduces blood flow in a swine model. Direct measurement of tissue oxygen tension using microelectrodes confirms that this reduction produces reductions of both cortical and medullary oxygen tensions to desaturated levels. On the other hand, our results are supported by a previous study showing little difference in basal R2* values in chronically stenotic swine kidneys. Previous studies of venous erythropoietin levels and oxygen saturation are consistent with the postulate that whole kidney ischemia is not common in human ARAS. Our interpretation of these differences is that gradual, incremental reduction in perfusion to the kidney triggers compensatory mechanisms that preserve oxygenation in both the cortex and medulla. This occurs even in the deepest medullary segments sampled in the present studies. Some compensation may be provided by the development of collateral circulation, although this could not be determined in this study. Much of the oxygen consumption in the kidney beyond minimal metabolic requirements is related to energy-dependent solute transport that may decline as a function of reduced filtration. Reduced solute filtration and transport may provide one explanation for the difference observed in the medullary R2* response after administration of furosemide in the STK as compared with either contralateral or essential hypertensive kidneys. Considerable data support the presence of preglomerular arteriovenous shunting within the kidney that affects local distribution of oxygen. We cannot exclude a role for enhanced shunting to medullary sites during long-term adaptation to reduced perfusion that may play a role in our findings. It is possible that such long-term adaptation plays a role in the functional “hibernation” that allows preservation and potential recovery of function after restoration of the renal vascular supply. Taken together, these results support the premise that ARAS can reduce kidney volume and blood flow under some conditions without evident tissue ischemia during blockade of the renin-angiotensin system. The role of large vessel occlusion in promoting renovascular hypertension and loss of kidney function continues to pose vexing challenges to clinicians caring for patients with ARAS. Determining the underlying mechanisms by which vascular occlusion begins to threaten tissue oxygenation and injury is fundamental to identifying individuals likely to benefit from restoration of renal blood flow with endovascular procedures. These studies partly explain the stability of kidney function during trials of medical therapy that include renin-angiotensin system blockade for renal vascular disease. Up to now, these trials failed to establish major benefits from renal revascularization, perhaps because the oxygenation of both the cortex and medulla for many patients can be preserved during antihypertensive therapy, similar to that used in the patients studied here. It is likely that similar strategies with more severe vascular occlusion will define more precisely those post-STKs at high risk for injury related to tissue ischemia that may benefit from restoring the circulation.

Acknowledgments

We thank all of the team that made this study possible and, in particular, Beverly Tietje, John Crane, John Woollard, Dr Hui Tang, and the Clinical Research Unit from the Saint Marys Hospital.

Sources of Funding

The project described was supported by award No. P01HL085307 from the National Heart, Lung, and Blood Institute.

Disclosures

None.
References


Preserved Oxygenation Despite Reduced Blood Flow in Poststenotic Kidneys in Human Atherosclerotic Renal Artery Stenosis
Monika L. Gloviczki, James F. Glockner, Lilach O. Lerman, Michael A. McKusick, Sanjay Misra, Joseph P. Grande and Stephen C. Textor

Hypertension. 2010;55:961-966; originally published online March 1, 2010;
doi: 10.1161/HYPERTENSIONAHA.109.145227
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
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/55/4/961

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/