Atherosclerotic renal artery stenosis (ARAS) produces lumen occlusion, eventually lowering kidney perfusion and accelerating hypertension. ARAS is strongly associated with cardiovascular disease and progressive renal dysfunction. Although the kidneys can adapt to partially reduced blood flow without major loss of oxygenation and viability (as they receive more blood than needed for their metabolic activity), severe reductions in renal blood flow (RBF) eventually lead to tissue fibrosis and what has been labeled ischemic nephropathy. Recent experimental studies underscore the development of renal microvascular changes distal to a stenosis in the renal artery, and over time, rarefaction of the distal arterioles. Severe degrees of vascular occlusion lead to overt cortical hypoxia associated with fibrogenesis and loss of renal function.

The benefits of revascularization procedures to restore blood flow in ARAS remain ambiguous. Only a fraction of patients treated with renal revascularization have improved blood pressure levels or reduced medication requirements, and kidney function after revascularization infrequently improves and sometimes declines. Notably, most clinical studies in humans evaluating the response to revascularization suggest that inflammatory pathways and tubulointerstitial damage remain elevated following revascularization. These results identify potential therapeutic targets for recovery of kidney function in renovascular disease.

Key Words: anoxia ■ hypertension ■ renal artery obstruction ■ revascularization

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WHAT IS KNOWN

- Although renal artery stenosis is known to accelerate hypertension and reduce kidney function, revascularization often produces only minor benefits to blood pressure control and often fails to restore kidney function.

WHAT THE STUDY ADDS

- This article demonstrates that severe renovascular disease is associated with tissue hypoxia and increased renal venous markers of inflammatory cytokines (monocyte chemoattractant protein-1 and tumor necrosis factor-α) and tissue injury (neutrophil gelatinase–associated lipocalin).
- Revascularization can reduce hypoxia and partially restore blood flow, but failed to alter markers of inflammation, suggesting that additional measures may be needed to reverse the process of kidney injury.

The effects of restoring blood flow after revascularization on kidney tissue hypoxia, regional perfusion within the kidney, and markers of renal injury are not known.

Blood oxygen level–dependent (BOLD) MRI has been used to provide estimates of in vivo tissue oxygenation in humans noninvasively by determining local levels of deoxyhemoglobin within the kidney.14–16 Studies of patients with moderate ARAS during antihypertensive therapy showed remarkably preserved medullary and cortical oxygenation using (BOLD) MRI.17 Patients with high-grade renal artery stenosis but with preserved tissue volume demonstrate elevated medullary and cortical deoxyhemoglobin signals that fall after intravenous furosemide.18 These observations suggest that viable kidneys may show regional hypoxic changes associated with tubular transport activity. When ARAS produces more severe occlusion, overt tissue hypoxia and renal injury can be identified.17 We have previously shown elevated renal vein levels of neutrophil gelatinase–associated lipocalin (NGAL) in the poststenotic kidney (STKs) of patients with ARAS,19 as well as release of inflammatory markers from the post-STKs.19 Whether these inflammatory changes can be reversed in humans remains unknown.

The purpose of this study was to examine the effect of renovascular revascularization on regional tissue perfusion and renal tissue hypoxia in post-STKs using BOLD MRI. We sought to evaluate markers of renal injury as reflected by renal vein levels of the acute phase reactant (NGAL), the inflammatory cytokines monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor-α (TNF-α) from hypertensive human subjects with ARAS as compared with patients with essential hypertension (EH). Our hypothesis was that restoring blood flow to the stenotic kidney would reverse tissue hypoxia detected by BOLD MRI and reduce renal injury in human subjects with ARAS.

Methods

Patient Selection

Patients identified with EH (n=32) or ARAS (n=17; scheduled for renal revascularization for clinical indications) seen between January 2008 and September 2012 participated in this study during a 3-day inpatient protocol on 2 occasions (before and after renal artery revascularization) in the clinical research unit of Saint Mary’s Hospital (Rochester, MN), as previously described.20 Because 4 patients had bilateral stenosis (only 1 kidney per patient was randomly selected for analysis), and 3 atriplex kidneys were excluded, 10 nonstenotic (contralateral kidneys [CLK]) were available for analysis. Dietary intake was regulated at 150 mEq of sodium with an isocaloric diet prepared on site. Patients with ARAS were identified using criteria similar to those stipulated for recruitment in the Cardiovascular Outcomes in Renal Atherosclerotic Lesions Trial with cross-sectional luminal occlusion of ≥60% but with the requirement for serum creatinine ≤2.5 mg/dL.21 Informed, written consent was obtained as approved by the institutional review board of the Mayo Clinic. Severity of renal artery stenosis was estimated by Doppler ultrasound measurements in the affected artery and quantitative vascular imaging using computed tomography (CT) images, as described below. Patients continued previous medications, and all received agents blocking the renin-angiotensin system during these studies (angiotensin converting enzyme inhibitors or angiotensin receptors blockers). Patients with ARAS returned for repeat measurements 3 to 4 months after renal revascularization. After the stenting, to exclude any segmental or intrarenal disease, we performed a complete angiogram every time. The angiogram done after the end of the procedure showed patent peripheral arteries without small distal stenoses or occlusion.

Renal Function and Blood Pressure Measurements

The first study day included measurement of sodium excretion and of GFR by iohalamate clearance (iohalamate meglumine, Conray, Mallinckrodt) after oral hydration (20 mL/kg) during three 30-minute timed collection periods, as described previously.22 Single kidney (SK) GFR was determined by apportioning the measured iohalamate clearance by percentage of blood flow for each kidney. Blood pressure was measured by automated oscillometric recordings, including 3 values taken 3x daily (an automated oscillometric unit, Omron blood pressure, measured blood pressure at 5, 7, and 9 minutes after a 5-minute rest).

Tissue Oxygenation Determined by BOLD MRI

On the second day, BOLD MRI examinations were performed on a GE Twin Speed Signa EXCITE 3.0T system (GE Medical Systems, Waukesha, WI) using a 12-channel torso phased array coil.23 Threeplane single shot fast spin echo localizers were performed during suspended respiration followed by additional scout images (single shot fast spin echo) oriented parallel to the long axis of each kidney. These long axis scout images were then used to prescribe transverse BOLD images in a plane orthogonal to the long axis. BOLD imaging consisted of a 2-dimensional fast spoiled gradient echo sequence with multiple echo times. Twelve echoes were obtained for each section location, with echo times ranging from 2.5 to 50.0 ms. Imaging parameters for the BOLD acquisition included the following: repetition time, 140 ms; flip angle, 45°; section thickness, 5 mm; imaging matrix, 224×160 to 192; and field of view, 32 to 40 cm, with 0.7 to 1.0 partial phase field of view. Image matrix and repetition time were adjusted in patients with limited breath-hold capacity and the field of view and partial field of view adjusted according to patient size. BOLD images were prescribed transverse to the long axis of the kidney using the long axis localizers and acquired during suspended respiration through the midpole hilal region of each kidney. Parametric images of R2* were then generated by fitting signal intensity versus echo time data to an exponential function on a voxel-by-voxel basis and solving...
for $R^2*$. 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. Gadolinium-enhanced MR angiograms were obtained after BOLD imaging to confirm the presence or absence of large vessel renal arterial disease. BOLD MRI could not be performed in 1 patient because of susceptibility artifact from the patient’s endovascular aortic aneurysm stent graft.

MRI Data Analysis
Analysis of BOLD data from axial images was performed by drawing parenchymal regions of interest (ROIs) on 2 to 4 slices through the midpole hilar region of each kidney on representative T2*-weighted images and then transferring the ROI to the corresponding $R^2*$ parametric image. Two ROIs were traced: 1 which selected the renal cortex (large segment), and a second which included the entire kidney slice, including both cortex and medulla while excluding the renal collecting system and any incidental renal cysts (Figure 1). MRI BOLD data were processed using Matlab 7.10 (The MathWorks Inc, Natick, MA). To determine the portion of measured kidney area for which tissue hypoxia was present, we defined fractional tissue hypoxia by measuring the percentage of voxels from the whole kidney ROI with $R^2*$ values >30/s (mainly represents the medulla) taking the average of all available slices. Previous studies indicate that this value is well above the 95% confidence interval for $R^2*$ levels obtained in cortical (nonhypoxic) areas in subjects with either EH or nonischemic renovascular disease.

Cortical and Medullary Perfusion and Blood Flow Measured by Multidetector Computerized Tomography
On the third study day, the common femoral vein was cannulated with a 6F sheath and blood samples drawn from the right and left renal veins with a 5F pigtail Cobra catheter (Cook, Inc, Bloomington, IN) for NGAL, MCP-1, and TNF-$\alpha$. The catheter was then advanced into the right atrium for central venous injection of contrast for flow studies using multidetector computerized tomography (MDCT). 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:noise ratio of the scan) with 20x1.2 collimation and 0 table feed. The flow study was composed of 45 scans, of which the first 35 scans were divided into 3 consecutive scanning sequences (each 20 seconds long), followed by 10 additional scans at 8-second intervals. The total scanning time lasted $\approx$158 seconds, and the longest breath-hold 20 seconds. Images representing 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 in the helical mode to determine both cortical and medullary regional volumes.

CT Data Analysis
MDCT images were reconstructed and displayed with the Analyze software package (Biomedical Imaging Resource, Mayo Clinic, MN). ROI were selected from cross-sectional images from the aorta, renal cortex, and medulla. Average tissue attenuation in each region was plotted over time and fitted by curve-fitting algorithms to obtain measures of renal function as described previously. Cortical and medullary volumes were calculated by Analyze and RBF as the sum of the products of cortical and medullary perfusions and corresponding volumes.

Renal Vein and Urine Sampling
Renal vein blood samples for NGAL and inflammatory cytokine analysis were obtained from the STK renal vein of all patients, as previously described. Samples were stored at $-80^\circ$C until measurement. Collected samples were centrifuged, and the supernatant was stored. NGAL (ng/mL) was tested by ELISA according to the manufacturer’s protocol (BioPorto Diagnostics, Cat no. KIT 036). Levels of TNF-$\alpha$ and MCP-1 were measured by luminex (Millipore, cat no.: MPXHCYTO-60K). Signals were read by the Bio-plex 200 systems (BIO-RAD). All measurements were performed by a single investigator blinded to the clinical data.

Statistical Analysis
Data were analyzed using JMP software package version 8.0 (SAS Institute Inc, Cary, NC). Results were expressed as mean and SD or median (interquartile range) for quantitative data, as appropriate, or as number (percentage) for qualitative variables. Comparisons between independent groups with EH or ARAS were performed using 2 sample $t$ test with unequal variance (or the Wilcoxon rank-sum test for skewed data) and a $\chi^2$ test or Fisher exact test for categorical variables as appropriate. Comparisons between stenotic or CLKs within the same individuals (pre- and post furosemide and before and after revascularization) were performed using paired $t$ tests (or Wilcoxon signed-rank test for skewed data). No formal correction was made for multiple comparisons, and thus a significance level of 0.05 was accepted. Spearman rank correlation analysis was used to test for associations between basal fractional hypoxia, inflammatory markers and RBF, tissue perfusion, and GFR.

Results
Demographic Comparison Between Patients With ARAS and EH
Complete data were available for 17 patients in the ARAS group and for 32 patients in the EH group. The demographic and clinical features of the patients studied are summarized in Table 1. Age, weight, body mass index, and most biochemical values were not significantly different between groups. Triglyceride levels, serum creatinine, and systolic blood pressure were higher in patients with ARAS, whereas GFR was lower.
### Table 1. Clinical, Laboratory, and Demographic Data of Patients With EH and ARAS

<table>
<thead>
<tr>
<th></th>
<th>EH (n=32)</th>
<th>ARAS (n=17)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % (men)*</td>
<td>59</td>
<td>76</td>
<td>0.35</td>
</tr>
<tr>
<td>Age, y</td>
<td>63.1±16.3</td>
<td>68±8.8</td>
<td>0.17</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.96±0.26</td>
<td>1.4±0.4</td>
<td>0.0004</td>
</tr>
<tr>
<td>lothalamate clearance GFR, mL/min</td>
<td>87.9±24.3</td>
<td>65.6±31.9</td>
<td>0.01</td>
</tr>
<tr>
<td>ACE or ARBs (yes/no)*</td>
<td>31/1</td>
<td>17/0</td>
<td>1.01</td>
</tr>
<tr>
<td>Number of anti-HTN drugs†</td>
<td>3 (2–4)</td>
<td>3 (2.5–4.5)</td>
<td>0.19</td>
</tr>
<tr>
<td>Statins (yes %)*</td>
<td>16 (50%)</td>
<td>12 (71%)</td>
<td>0.23*</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>135±19</td>
<td>147±20</td>
<td>0.04</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>71±12</td>
<td>71±11.4</td>
<td>0.87</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78.3±15.6</td>
<td>86±18</td>
<td>0.14</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.3±4.3</td>
<td>28.6±3.9</td>
<td>0.19</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.96±0.26</td>
<td>1.4±0.4</td>
<td>0.0004</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>52.3±12</td>
<td>45±6.21</td>
<td>0.30</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>130.6±58</td>
<td>184±95.6</td>
<td>0.04</td>
</tr>
<tr>
<td>TC, mg/dL</td>
<td>182±30</td>
<td>181.2±36.2</td>
<td>0.97</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>40.3±4</td>
<td>38±3.7</td>
<td>0.06</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>52.3±12</td>
<td>45±6.21</td>
<td>0.30</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>63±25</td>
<td>96±28</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Values represent mean±SD. ACE indicates angiotensin converting enzyme; Anti-HTN, antihypertensive; ARAS, atherosclerotic renal artery stenosis; ARB, angiotensin receptors blockers; BMI, body mass index; DBP, diastolic blood pressure; EH, essential hypertension; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n, number of patients; and SBP, systolic blood pressure.

*Fisher exact test.
†Median (interquartile range) reported because of skewed data.
‡P value obtained from Wilcoxon rank-sum test.

### Table 2. Multidetector CT Measurements of Individual Kidney Volume, Tissue Perfusion, Blood Flow, and Iothalamate Filtration

<table>
<thead>
<tr>
<th></th>
<th>STK (n=17)</th>
<th>CLK (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single Kidney</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total kidney volume (CT), mL</td>
<td>145.9±36</td>
<td>162.4±59.9</td>
</tr>
<tr>
<td>Cortical volume, mL</td>
<td>96.7±29</td>
<td>111±47</td>
</tr>
<tr>
<td>Medullary volume, mL</td>
<td>49±14.6</td>
<td>51±17</td>
</tr>
<tr>
<td>Cortical perfusion, mL/min per mL of tissue</td>
<td>3.4±0.99</td>
<td>2.9±0.45</td>
</tr>
<tr>
<td>Medullary perfusion, mL/min per mL of tissue</td>
<td>1.3±0.48</td>
<td>1.3±0.03</td>
</tr>
<tr>
<td>Total renal blood flow, mL/min</td>
<td>399±174</td>
<td>372.3±221</td>
</tr>
<tr>
<td>Cortical flow, mL/min</td>
<td>331±161</td>
<td>313.9±195</td>
</tr>
<tr>
<td>Medullary flow, mL/min</td>
<td>63±25</td>
<td>73.8±36.7</td>
</tr>
<tr>
<td>Single kidney GFR, mL/min per kidney</td>
<td>44.3±13.5</td>
<td>40.5±21.2</td>
</tr>
</tbody>
</table>

CLK indicates contralateral kidney; CT, computed tomography; EH, essential hypertension; GFR, glomerular filtration rate; and STK, stenotic kidney.

*P<0.05 vs EH; †P<0.05 vs STK baseline; ‡P<0.05 vs EH; and §§P<0.05 vs STK baseline.

**Renal Revascularization Reduced Elevated Levels of Fractional Kidney Hypoxia in ARAS**

Tissue oxygenation levels defined by both R² values and fractional hypoxia (R²>30/s) are summarized in Table 3. Presenting basal and post-furosemide fractional hypoxia levels were higher in STK than EH kidneys as illustrated in Figure 2. Fractional tissue hypoxia fell after furosemide administration, but remained above those of EH. The fractional hypoxia levels in the stenotic kidneys fell to near normal levels when remeasured 3 to 4 months after renal artery stenting (Figure 3A). The fractional hypoxia basal levels correlated inversely with GFR (Spearman rank correlation coefficient, r=−0.38; P=0.007), RBF (r=−0.4; P=0.005) and also with cortical/medullary perfusion (r=−0.4; P=0.004).

Representative axial BOLD images (R² parametric maps) illustrating the change in hypoxia in ARAS kidney before and after revascularization are illustrated in Figure 3B.

**ARAS Was Associated With Elevated Markers of Renal Inflammation, Which Persisted After Revascularization**

Renal vein basal levels of NGAL, MCP-1, and TNF-α were elevated in ARAS compared with EH (P<0.0006, 0.005, and 0.0003, respectively; Table 4). These venous levels remained unchanged 3 months after revascularization (Figure 4). Levels of renal vein NGAL correlated inversely with GFR (r=−0.45; P=0.009). Also, MCP-1 (r=−0.4; P=0.007) and TNF-α correlated inversely with GFR (r=−0.6; P<0.0001).

The statin therapy, a potential anti-inflammatory, showed no consistent effects on the inflammation markers, RBF, R²,*}
Discussion
This study demonstrates, for the first time, the effect of renal revascularization to reduce the fractions of kidney parenchyma that were measurably hypoxic as a result of reduced blood flow. Cortical blood flows and perfusion were reduced in the poststenotic kidney and rose after technically successful revascularization, although medullary flows remained below those of EH or the nonstenotic CLKs. Hence, the levels of overall fractional tissue hypoxia were reversed by restoring blood flow in the STK. Despite these changes, no consistent changes in SK filtration (GFR) or renal venous levels of NGAL, MCP-1, and TNF-α. Measured levels of SK GFR did not change in the poststenotic kidney in these patients and combined GFR for both kidneys remained below those of EH. Our results extend the results observed in experimental swine models of ARAS that demonstrate microvascular rarefaction, oxidative stress injury, and interstitial fibrosis within the poststenotic kidney parenchyma.26 These results are consistent with increased renal inflammation in patients with ARAS, as evidenced by high levels of NGAL (which is an acute phase protein induced in inflammatory conditions and acute ischemic injury, often used as a biomarker for acute kidney injury)27,28 and proinflammatory cytokines TNF-α and MCP-1. MCP-1 is an inflammatory cytokine known to recruit macrophages to the kidney.29 We have recently shown that transforming growth factor-β expression associated with macrophage infiltration within the human kidney with ARAS is higher than normal kidneys30 and that renal vein levels of inflammatory cytokines such as interleukin-6, IF-γ, E selectins, and others are elevated in human ARAS.18,19 Studies using murine models of

Table 3. BOLD MRI for Essential Hypertension and Atherosclerotic Renal Artery Stenosis Before and After Revascularization Using Fractional Tissue Hypoxia and Cortical Regions of Interest Measurements

<table>
<thead>
<tr>
<th>Single Kidney</th>
<th>EH (n=32)</th>
<th>STK (n=17)</th>
<th>CLK (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 3 mo</td>
<td>Baseline 3 mo</td>
<td>3 mo</td>
</tr>
<tr>
<td>Fractional hypoxia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(%) R2*&gt;30/s</td>
<td>Pre furosemide</td>
<td>8.7 (3.5, 13.3)</td>
<td>21.9 (28.3)*‖</td>
</tr>
<tr>
<td></td>
<td>Post furosemide</td>
<td>2.6 (1.35, 6.4)§</td>
<td>5.2 (2.5, 12.6)†‡</td>
</tr>
<tr>
<td>Cortex R2* (s−1)</td>
<td>Pre furosemide</td>
<td>18.5±2.7</td>
<td>21±4.4</td>
</tr>
<tr>
<td></td>
<td>Post furosemide</td>
<td>16.7±2.2§</td>
<td>18.2±2§</td>
</tr>
</tbody>
</table>

Data are Mean±SD. BOLD indicates blood oxygen level–dependent; CLK, contralateral kidneys; EH, essential hypertension; and STK, stenotic kidney.

*P<0.05 vs EH; †P<0.05 vs STK baseline; ‡P<0.05 vs EH; and §P<0.001 pre (furosemide) vs post (furosemide).

Median (interquartile range) reported because of skewed data (P value derived from Wilcoxon rank-sum test or from Wilcoxon signed-rank test as appropriate).

and GFR on this studied cohort (both in renal artery stenosis and EH; Table I in the online-only Data Supplement).

Figure 2. Examples of T2* images and R2* parametric maps for a subject with essential hypertension (A and C) and a subject with atherosclerotic renal artery stenosis (ARAS; B and D) obtained using the same color scale for R2*. Fractional hypoxia >30/s in ARAS was greater than in essential hypertension (28.5% vs 11.3%).
renal artery stenosis demonstrate early and sustained activation of transforming growth factor-β in both the stenotic and the CLK as kidney injury develops. Smad3-knockout models that eliminate downstream effects of transforming growth factor-β seem to protect the poststenotic kidney from injury from reduced blood flow. We interpret all of these data to suggest activation of multiple inflammatory injury pathways in poststenotic kidneys. Although several of these are recognized to be triggered by tissue hypoxia, it is equally clear from the results of our study that removing the hypoxic stimulus failed to reverse this process once it has been established.

Perhaps relevant is the observation that reperfusion by percutaneous angioplasty in swine model of ARAS increases cytokine levels (MCP-1) for several hours and is associated 4 weeks later with multiple markers of inflammatory injury, oxidative stress, apoptosis, and interstitial fibrosis. These data suggest that inflammatory signals related to reperfusion procedures may participate in activating intracellular or mitochondrial stress injury. We cannot exclude a role for atheroembolic injury associated with renal artery stenting, although no clinical signs were evident in these patients. Our data provide further insights into human treatment trials related to recovery of renal function after revascularization. Although some patients recover some portion of reduced GFR after renal artery stenting, the majority either has no evident change or progress to further loss. As a result, average values for GFR do not change after successful revascularization, despite technical success of restoring blood flow. Hence, prospective trials, including The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) and Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function (STAR), up to now fail to demonstrate major benefits of restoring blood flow alone to alter the course of renal injury in human ARAS.

The present study provides evidence that although advanced renovascular disease does indeed lead to renal tissue hypoxia, restoring blood flow and reversing hypoxia alone regularly failed to alter local inflammatory signals reflecting active processes of tissue injury and inflammation. These data suggest that additional measures that may abrogate those pathways may be essential to halt the progression of injury and perhaps allow repair of functional renal structures. Recent experimental studies using endothelial progenitor cells or intrarenal infusion of mesenchymal stem cells indicate that recovery of renal microvessels, blood flow, and glomerular filtration is possible in the poststenotic kidney. Additional maneuvers targeting mitochondria at the time of restoring blood

**Table 4. Renal Vein Levels of NGAL, MCP-1, and TNF-α**

<table>
<thead>
<tr>
<th></th>
<th>EH</th>
<th>STK (Baseline)</th>
<th>STK (3 mo)</th>
<th>P Value vs EH</th>
<th>P Value vs Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCP-1, pg/mL</td>
<td>154±71</td>
<td>208.2±83</td>
<td>200±93.6</td>
<td>0.005</td>
<td>0.6</td>
</tr>
<tr>
<td>TNF-α, pg/mL</td>
<td>4.7±4.2</td>
<td>8.4±5.8</td>
<td>9±5.8</td>
<td>0.0003</td>
<td>0.3</td>
</tr>
<tr>
<td>NGAL, ng/mL</td>
<td>69.7±36.5</td>
<td>121.2±55</td>
<td>108.8±35</td>
<td>0.0006</td>
<td>0.6</td>
</tr>
</tbody>
</table>

EH indicates essential hypertension; MCP-1, monocyte chemoattractant protein-1; NGAL, neutrophil gelatinase–associated lipocalin; STK, stenotic kidney; and TNF-α, tumor necrosis factor-α.
flow offer the potential to protect the poststenotic kidney from reperfusion damage.34

This study has limitations. It was not a randomized study, but enrolled patients were selected for revascularization based on clinical criteria. Most of the patients were men. Our control group comprised subjects with EH of similar age, rather than normal individuals. The EH group did include some healthy individuals with normal kidney hemodynamics and function. Individuals with ARAS had lower GFR, although most had relatively preserved function and were limited to serum creatinine levels <2.5 mg/dL. Subjects with diabetes mellitus were specifically excluded.

Conclusions

Our results indicate that renal revascularization partially restored cortical and RBFs and reversed regional tissue hypoxia within the poststenotic kidneys. Despite improving blood flow, SK GFR did not recover nor did marks of tubulointerstitial injury (NGAL) and inflammatory cytokines change. These data underscore the importance of ongoing inflammatory and profibrotic injury that revascularization alone fails to reverse in patients with ARAS. They demonstrate the urgent need to identify and develop supplemental management strategies to restore kidney structure and function for patients with vascular occlusive disease.

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References


Disclosures

None.


Stent Revascularization Restores Cortical Blood Flow and Reverses Tissue Hypoxia in Atherosclerotic Renal Artery Stenosis but Fails to Reverse Inflammatory Pathways or Glomerular Filtration Rate

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SUPPLEMENTAL MATERIAL:

Table 1: comparison analysis between the two groups of patients (EH and RAS patients) with or without statins therapy.

<table>
<thead>
<tr>
<th></th>
<th>EH=32 Statin (=16)</th>
<th>No Statin (=16)</th>
<th>P value</th>
<th>RAS=17 Statin (=12)</th>
<th>No statin (=5)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBF (ml/min)</td>
<td>379.5 ± 188</td>
<td>421.6 ± 161</td>
<td>0.5</td>
<td>226.8 ± 106.8</td>
<td>247.3 ± 160</td>
<td>0.7</td>
</tr>
<tr>
<td>Single kidney GFR(ml/min)</td>
<td>42.5 ± 12.9</td>
<td>46.5 ± 14</td>
<td>0.4</td>
<td>26 ± 10.9</td>
<td>32.4 ± 25</td>
<td>0.6</td>
</tr>
<tr>
<td>Cortical R2* (sec⁻¹)</td>
<td>19.1 ± 3.2</td>
<td>17.8 ± 1.9</td>
<td>0.18</td>
<td>20.2 ± 3.1</td>
<td>24.5 ± 7.9</td>
<td>0.36</td>
</tr>
<tr>
<td>Fractional hypoxia (%R2* &gt;30 sec⁻¹)</td>
<td>10.8 ± 8.2</td>
<td>8.2 ± 5</td>
<td>0.3</td>
<td>19.4 ± 11.7</td>
<td>33.1 ± 27</td>
<td>0.38</td>
</tr>
<tr>
<td>NGAL (ng/ml)</td>
<td>69.3 ± 43.9</td>
<td>70.5 ± 18.6</td>
<td>0.9</td>
<td>133.1 ± 62</td>
<td>94.6 ± 39</td>
<td>0.3</td>
</tr>
<tr>
<td>MCP-1 (pg/ml)</td>
<td>171.7 ± 83</td>
<td>137.7 ± 55.5</td>
<td>0.2</td>
<td>238 ± 77</td>
<td>166.6 ± 47.6</td>
<td>0.1</td>
</tr>
<tr>
<td>TNF-a (pg/ml)</td>
<td>4.5 ± 2.5</td>
<td>3.7 ± 2.2</td>
<td>0.7</td>
<td>25.2 ± 15</td>
<td>7.1 ± 2.1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Mean ± SD.