Angiotensin II Type 2 Receptors and Nitric Oxide Sustain Oxygenation in the Clipped Kidney of Early Goldblatt Hypertensive Rats

Fredrik Palm, Stephanie G. Connors, Margarida Mendonca, William J. Welch, Christopher S. Wilcox

Abstract—Angiotensin-converting enzyme inhibitors (ACEIs) decrease the glomerular filtration rate and renal blood flow in the clipped kidneys of early 2-kidney, 1-clip Goldblatt hypertensive rats, but the consequences for oxygenation are unclear. We investigated the hypothesis that angiotensin II type 1 or angiotensin II type 2 receptors or NO synthase mediate renal oxygenation responses to ACEI. Three weeks after left renal artery clipping, kidney function, oxygen (O₂) use, renal blood flow, renal cortical blood flow, and renal cortical oxygen tension (P₀₂) were measured after acute administration of an ACEI (enalaprilat) and after acute administration of ACEI following acute administration of an angiotensin II type 1 or angiotensin II type 2 receptor blocker (candesartan or PD-123,319) or an NO synthase blocker (N⁵-nitro-l-arginine methyl ester with control of renal perfusion pressure) and compared with mechanical reduction in renal perfusion pressure to the levels after ACEI. The basal renal cortical P₀₂ of clipped kidneys was significantly lower than contralateral kidneys (35 ± 1 versus 51 ± 1 mm Hg; n=40 each). ACEI lowered renal venous P₀₂, cortical P₀₂, renal blood flow, glomerular filtration rate, and cortical blood flow and increased the renal vascular resistance in the clipped kidney, whereas mechanical reduction in renal perfusion pressure was ineffective. PD-123,319 and N⁵-nitro-l-arginine methyl ester, but not candesartan, reduced the P₀₂ of clipped kidneys and blocked the fall in P₀₂ with acute ACEI administration. In conclusion, oxygen availability in the clipped kidney is maintained by angiotensin II generation, angiotensin II type 2 receptors, and NO synthase. This discloses a novel mechanism whereby angiotensin can prevent hypoxia in a kidney challenged with a reduced perfusion pressure. (Hypertension. 2008;51:345-351.)

Key Words: Goldblatt hypertension ■ renal oxygen tension ■ renal blood flow ■ angiotensin receptor blockers ■ angiotensin-converting enzyme inhibitors

A reduced renal perfusion pressure (RPP) after clipping of a renal artery in the early (2- to 4-week) 2-kidney, 1-clip (2K,1C) rat model of Goldblatt hypertension increases angiotensin II (Ang II) concentrations in both kidneys1 and causes Ang II-dependent hypertension.2–4 A reduced renal tissue oxygen tension (P₀₂) developing during prolonged infusion of Ang II2–7 has been ascribed to reactive oxygen species and functional NO deficiency. Prolonged administration of the antioxidant drug Tempol, but not the angiotensin receptor blocker (ARB) candesartan, restores renal tissue P₀₂ in a rat model of early 2K,1C hypertension.5 This may be important, because renal hypoxia, and episodes of renal ischemia, may contribute to hypertension6 and progressive kidney disease.9

On the other hand, acute infusions of Ang II into rats increase renal NO generation and increase the dependency of renal blood flow (RBF) on NO.10,11 Moreover, studies in the early 2K,1C rat model12–14 have shown that the acute administration of an angiotensin-converting enzyme inhibitor (ACEI), or nonselective angiotensin receptor blocker with saralasin, reduces the RBF, and thereby the renal oxygen (O₂) delivery, and the glomerular filtration rate (GFR), and thereby the renal tubular sodium transport (TNa) in the clipped kidney. The consequences for renal oxygenation are not clear, because renal tissue P₀₂ should fall after a reduction in RBF but might rise after a reduction in TNa, because this determines renal O₂ usage (Q₀₂).15,16 ACEIs limit the generation of Ang II and thereby limit the activation of both Ang II type 1 (AT₁) and Ang II type 2 (AT₂) receptors, which have opposite effects on RBF and renal NO generation in renal wrap hypertension.17 In contrast, selective AT₁ receptor blockade with PD-123,319 decreases renal interstitial NO and cGMP in both kidneys in this model17 and reduces renal interstitial NO in salt-depleted rats.18 This is important, because Beierwaltes and colleagues19,20 have shown that NO maintains renal function in the clipped kidney of the 2K,1C model.

Anderson et al21 have proposed that increased plasma levels of Ang II in the early 2K,1C model are homeostatic adjustments to provide a sufficient glomerular capillary
pressure to sustain GFR. Although prolonged infusions of Ang II in normal rats may impair renal NO activity by induction of oxidative stress, more short-term infusions of Ang II into normal rats increase renal NO generation. Any increase in NO activity in the kidneys may reduce QO2 for tubular Na+ transport. The present work is designed to investigate the hypothesis that Ang II induced activation of AT2 receptors and NO synthase (NOS) sustains renal O2 availability in the clipped kidney of 2K,1C rats. This is of special importance, because the hemodynamic response to an acute challenge with ACEI is the most well-characterized clinical test of functional and reversible renovascular hypertension.

Methods

These studies were performed under guidelines recommended by the National Institutes of Health and approved by the Georgetown University Animal Care and Use Committee. As described in detail previously, young male Sprague-Dawley rats (80 to 100 g) were anesthetized with isoflurane (0.5 to 1.5%). A silver clip (0.2 mm) was placed around the left renal artery (2K,1C). Sham animals were prepared similarly without clip placement. Three weeks thereafter, the rats were anesthetized with Inactin (100 mg · kg⁻¹ · IP, Sigma-Aldrich). An endotracheal tube was inserted for spontaneous respiration.

Groups 1 to 5 assessed the effects of acute administration of ACEI using clearance and renal venous sampling methods. Rats (n=8 per group) were prepared for measurements of mean arterial pressure, GFR, renal plasma flow and RBF by collecting urine separately from each kidney. The GFR and renal plasma flow were assessed from the clearance of [14C]-inulin. Renal plasma flow was calculated from the clearance of inulin factored by the AV extraction of inulin. Twenty-four Forty-five minutes after completion of the surgery, 2K,1C or sham rats of groups 2 and 4 received an intravenous injection of either enalaprilat (0.3 mg · kg⁻¹ · body weight [bw] dissolved in 0.3 mL of 0.154 mol/L NaCl solution, followed by an infusion of 0.3 mg · kg bw⁻¹ · h⁻¹; Novaplus 1.25 mg · mL⁻¹, Baxter Healthcare Corporation) or volume-matched vehicle (group 1 and 3) or had the RPP lowered to the level recorded after enalaprilat by constricting a suprarenal aortic clamp. The RPP was adjusted by constriction of the suprarenal clamp and was monitored by a pressure catheter placed in the femoral artery below the level of the clamp. Ten minutes thereafter, there was a 30-minute clearance period with blood

<table>
<thead>
<tr>
<th>Condition, 2K,1C</th>
<th>Group</th>
<th>Body Weight, g</th>
<th>Kidney Weight, g</th>
<th>Baseline RPP, mm Hg</th>
<th>Baseline Cortical pO2, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>Left</td>
<td></td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>6</td>
<td>304±7</td>
<td>1.52±0.06</td>
<td>1.07±0.05*</td>
<td>162±6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-123,319 and</td>
<td>7</td>
<td>300±9</td>
<td>1.59±0.15</td>
<td>0.96±0.07*</td>
<td>157±2</td>
</tr>
<tr>
<td>PD-123,319+enalapril</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan and</td>
<td>8</td>
<td>297±13</td>
<td>2.03±0.19</td>
<td>0.91±0.10</td>
<td>164±6</td>
</tr>
<tr>
<td>candesartan+enalapril</td>
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<td></td>
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</tr>
<tr>
<td>L-NAME and L-NAME+enalapril</td>
<td>9</td>
<td>307±9</td>
<td>1.67±0.11</td>
<td>0.98±0.03*</td>
<td>157±2</td>
</tr>
<tr>
<td>Clamp</td>
<td>10</td>
<td>306±10</td>
<td>1.61±0.14</td>
<td>0.94±0.07*</td>
<td>158±3</td>
</tr>
</tbody>
</table>

All of the values are mean±SEM (n=8 per group).

*P<0.05 vs the contralateral nonclipped right kidney.
sampling from the femoral artery and both renal veins for measurement of blood gases and $^{18}$O activity. Blood gas and $^{18}$O content were analyzed in a co-oximeter (Instrumentation Labs Inc.).

2K,1C rats (n=8 per group) in groups of 6 to 10 had both kidneys immobilized in plastic cups, while renal cortical Po$_2$ and cortical blood flow (CBF) were measured with O$_2$ microelectrodes (Unisense) and laser Doppler needle probes (Transonic Systems Inc), as described previously. Measurements were made before and after injections of enalaprilat (0.3 mg · kg$^{-1}$ · h$^{-1}$) alone (group 6) or after PD-123,319 (1 mg · kg$^{-1}$ · h$^{-1}$), Sigma Aldrich$^\text{26}$ followed after 30 minutes by enalaprilat (group 7), after candesartan alone (1 mg · kg$^{-1}$ · bolus $+ 1$ mg · kg$^{-1}$ · h$^{-1}$), kind gift from Astra Zeneca, Södertälje, Sweden; manufacturer-recommended dose for maximal inhibition of AT$\text{1}$ receptors in vivo), followed after 30 minutes by enalaprilat (group 8), or after N$^\text{o}$-nitro-l-arginine methyl ester (L-NAME) alone (10 mg · kg$^{-1}$ · bolus $+ 10$ mg · kg$^{-1}$ · h$^{-1}$, Sigma Aldrich$^\text{9}$) group 9, followed after 30 minutes by enalaprilat or after suprarenal aortic clamp (group 10). The increased RPP caused by L-NAME was corrected by a suprarenal aortic clamp.

ANOVA was used to compare multiple data sets. When appropriate, this was followed by Bonferroni posthoc Student’s t tests.

Relative changes were analyzed using nonparametric statistics (GraphPad Prism, GraphPad Software). For all of the comparisons, P<0.05 was considered statistically significant. All of the values are expressed as mean±SEM.

## Results

The body weights did not differ among any of the groups. There was hypertrophy of the nonclipped kidney and atrophy of the clipped kidney of 2K,1C rats (Tables 1 and 2). The RPP (measured by a catheter in the femoral artery) was similar in all of the 2K,1C groups before intervention (Tables 1 and 2). The clamp in 2K,1C rats decreased RPP similarly to ACEI (Table 1). The arterial blood pH, Po$_2$, Pco$_2$, and hematocrit, measured at the completion of the studies, were similar in all of the groups (Table 1). The acute administration of ACEI reduced the GFR, RBF, T$_{na}$, and QO$_2$ of the clipped kidney significantly. There was a greater reduction in T$_{na}$ compared with QO$_2$, but the T$_{na}$/QO$_2$ ratio did not change significantly (Table 3). A similar reduction in RPP by clamping did not cause consistent or significant changes in these variables.

Basal values for renal vascular resistance were similar in all of the kidneys (data not shown). ACEI increased the renal vascular resistance substantially in clipped kidneys (Figure 1A) and reduced the renal vascular Po$_2$ below the value recorded in the other groups (Figure 1B). This accounts for the greater O$_2$ extraction (Table 3). T$_{na}$/QO$_2$ did not change significantly after any of the applied treatments.

Data from the contralateral, nonclipped kidney are shown for comparison in Table 4. The acute administration of the ACEI reduced the renal vascular Po$_2$ in this kidney as well, albeit not to the levels of the postclip kidney after ACEI. Otherwise, there were no significant changes in the function of this kidney.

ACEI reduced the CBF significantly in the clipped kidney (Figure 2A), similar to the reduction in total RBF recorded by clearance methods in rats of group 4 (Table 1). All of the treatments, except for PD-123,319, reduced RPP (Figure 2). Although all of the treatments reduced the CBF of the clipped kidney, it was reduced to a greater extent by the ACEI than by the clamp (Figure 2A).

The baseline renal cortical Po$_2$, before any intervention, was reduced uniformly in clipped kidneys (Table 2).
acute administration of enalaprilat, PD-123,319, and L-NAME all reduced the PO2 of the clipped kidney, whereas candesartan was ineffective, and the PO2 increased after clamping (Figure 2B). Enalaprilat had no additional effect on the cortical PO2 in the clipped kidney when administered 30 minutes after PD-123,319 or L-NAME. In contrast, candesartan did not reduce the PO2 of the clipped kidney and did not block the fall in PO2 produced by a subsequent infusion of enalaprilat (Figure 2B).

The responses in CBF and cortical PO2 after enalaprilat, PD-123,319, candesartan, L-NAME, or mechanically lowered RPP in the contralateral nonclipped kidney are presented in Table 5. CBF in this kidney was reduced by enalaprilat after PD-123,319 and by L-NAME. These treatments also reduced renal cortical PO2, which also fell modestly after PD-123,319 and candesartan.

**Discussion**

The main new finding is that the acute administration of an ACEI increases the renal vascular resistance and decreases the renal venous and renal cortical PO2 in the clipped kidneys of rats with early Ang II−dependent 2K,1C Goldblatt hypertension. After ACEI, the PO2 of the clipped kidney is reduced from 37 to 24 mm Hg. Remarkably, the mechanism appears to be independent of the reduction in RPP, because a similar reduction in RPP produced by a suprarenal clamp did not

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**Table 4. Renal Venous pH, pO2, pCO2, GFR, Filtration Fraction, Arteriovenous O2 Extraction, TmO2, TmO2/QmO2 and Renal Vascular Resistance in the Right (Contralateral) Nonclipped Kidney of Sham and 2K,1C Hypertensive Rats**

<table>
<thead>
<tr>
<th>Condition</th>
<th>pH</th>
<th>pO2, mm Hg</th>
<th>pCO2, mm Hg</th>
<th>GFR, mL/min per g</th>
<th>RBF mL/min per gram</th>
<th>FF</th>
<th>AV O2, μmol/mL</th>
<th>TmO2, μmol/min</th>
<th>QmO2, μmol/min</th>
<th>TmO2/QmO2</th>
<th>RVR, mm Hg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td></td>
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</tr>
<tr>
<td>Vehicle</td>
<td>7.410±0.007</td>
<td>52.5±0.8</td>
<td>47.4±1.0</td>
<td>1.48±0.10</td>
<td>8.6±1.1</td>
<td>0.31±0.03</td>
<td>1.7±0.1</td>
<td>208±16</td>
<td>14±2</td>
<td>16.6±1.8</td>
<td>13.3±1.6</td>
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<tr>
<td>Enalaprilat</td>
<td>7.395±0.006</td>
<td>52.9±0.8</td>
<td>44.5±0.5</td>
<td>1.33±0.20</td>
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<td>0.27±0.03</td>
<td>1.4±0.2</td>
<td>185±29</td>
<td>14±4</td>
<td>18.9±3.3</td>
<td>14.8±4.3</td>
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<td>Vehicle</td>
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<td>1.08±0.21</td>
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<td>150±30</td>
<td>20±5</td>
<td>10.3±1.7</td>
<td>19.5±5.5</td>
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<tr>
<td>Enalaprilat</td>
<td>7.392±0.023</td>
<td>44.3±2.1</td>
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<td>0.70±0.12</td>
<td>5.3±1.4</td>
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<td>1.6±0.3</td>
<td>100±18</td>
<td>9±3</td>
<td>19.3±5.4</td>
<td>35.2±8.2</td>
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<td>Clamp</td>
<td>7.407±0.010</td>
<td>51.4±0.5</td>
<td>47.9±1.2</td>
<td>0.75±0.10</td>
<td>4.1±0.7</td>
<td>0.37±0.02</td>
<td>2.0±0.2</td>
<td>105±14</td>
<td>8±1</td>
<td>14.1±1.4</td>
<td>37.5±7.4</td>
</tr>
</tbody>
</table>

Fi indicates filtration fraction; AV O2, arteriovenous O2 extraction; RVR, renal vascular resistance. All of the values are mean±SEM (n=8 per group).

*P<0.05 vs contralateral nonclipped right kidney.
†P<0.05 vs vehicle-treated group with similar surgery.

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**Figure 2. Changes in renal CBF (A) and cortical oxygen tension (B) in the left (clipped) kidney of 2K,1C rats.**

*P<0.05 vs baseline within the same group; †P<0.05 vs enalaprilat treatment.

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apparently prevented any further fall in the CBF of clipped circulating level of Ang II and thereby maintains blood.

there is an additional mechanism that increases renal vascular.
greater decrease in renal CBF after ACEI than after an
responses to an ACEI are blocked by PD-123,319 or L-NAME
hypertension.34 Moreover, AT2 receptor activation limits
tors is upregulated in the aorta of mice with early 2K,1C
including reduced total RBF (100%).

The acute administration of an ACEI reduces the RBF of clipped kidneys of 2K,1C rats14,27 or dogs.28 This has been ascribed to a reduction in the RPP.14,27 However, we found a greater decrease in renal CBF after ACEI than after an equivalent reduction in the RPP. Therefore, we conclude that there is an additional mechanism that increases renal vascular resistance in clipped kidneys after ACEI related to a reduction in Ang II generation. NO maintains RBF during a high circulating level of Ang II10,11 and thereby maintains blood supply to the kidney during an acute challenge with Ang II.29 However, the NO released by Ang II from isolated perfused renal afferent arterioles is mediated via AT1 receptors.29,30 In contrast, the NO released by Ang II from the kidney cortex of salt-depleted rats or rats with renal wrap hypertension is mediated via AT2 receptors.31–33 The mRNA for AT2 receptors is upregulated in the aorta of mice with early 2K,1C hypertension.34 Moreover, AT2 receptor activation limits aortic contractions to Ang II in this model by phosphorylation of endothelial NOS and increasing vascular cGMP.34

NO generation in the clipped kidney may account for our finding that blockade of AT1 or AT2 receptors or NOS apparently prevented any further fall in the CBF of clipped kidneys with enalaprilat (Figure 2A). This confirms the conclusions of Beierwaltes and colleagues30,35 that the RBF of the clipped kidney of early 2K,1C renovascular hypertensive rats is highly dependent on NOS, although this effect wanes with time. This waning over time may explain why ACEI administration in early 2K,1C hypertensive rats re-
duces RBF, whereas RBF is maintained after ACEI in some patients with unilateral renal artery stenosis, where the condition is almost always of long duration.23,36 The immediate increase in renal NO generation in rats infused with Ang II is lost after 2 weeks of Ang II infusions likely because of the development of oxidative stress in the kidneys.37 Preservation of NO signaling in the clipped kidney of early 2K,1C rats may be because of the protective effect of a reduced RPP on NO signaling38 and on upregulation of NOS-I, -II, and -III in the renal cortex and medulla in kidneys downstream from a reduction in RPP.39

In a previous study, we reported a reduced TNa/QO2 in the basal state in clipped kidneys of 2K,1C rats, whereas the TNa/QO2 was unchanged in the present study. Although the reasons for this discrepancy are not clear, in both studies there was a reduction in Po2 of the renal cortex of the clipped kidney without a change in renal venous Po2. The Po2 of the kidney cortex of the clipped kidneys is maintained by Ang II, because the acute administration of an ACEI produces a further sharp fall in renal cortical Po2, despite strictly comparable reductions in RBF (–66%), GFR (–65%), or TNa (–64%).

Laycock et al22 reported that the normally close relationship between TNa and QO2 in the dog’s kidney15 is perturbed after NOS inhibition, which increases QO2 despite a reduction in TNa. Because l-NAME blocks the fall in Po2 and CBF produced by ACEI in the clipped kidney in this study, we conclude that the generation of Ang II in the postclip kidney maintains oxygenation by the generation of NO. NO competes with O2 for terminal sites on the electron transport chain located in the mitochondrial membrane.40 The lower baseline cortical Po2 in the clipped kidney is in agreement with other states of excessive oxidative stress,5–7 which can cause functional NO deficiency in the kidney.41 The kidney in renovascular hypertension is indeed a site of increased NOO2 interaction, as shown by enhanced nitrotyrosine deposition.42 However, a reduction in RPP reduces the excretion of NO metabolites,43 reduces the directly measured NO activity in the cortex of the dog kidney,44 and reduces renal nitrotyrosine deposition, indicating a reduced NO/O2 interaction.38

Unlike the effects of acute administration of ACEI in this study, the renal cortical Po2 recorded in the clipped kidney of early 2K,1C rats was not reduced after acute administration of candesartan in this study (Figure 2B) or after 2 weeks of candesartan in the study by Welch et al.5 Presumably, AT2 receptors are still active after candesartan administration, which may account for the unchanged Po2 after the ARB, yet the fall in Po2 after acute ACEI administration, which should reduce Ang II and thereby reduce the activation of AT2 receptors. The response to an ARB depends on the model in which it is tested. Thus, 2 weeks of ARB administration to spontaneously hypertensive rats improves renal cortical oxygenation independent of RPP.24 The combination of a sharp fall in RPP and a sharp fall in AT2 receptor activation after a reduction in Ang II concentration locally within the clipped kidney by ACEI may decrease the NO levels sufficiently to reduce the Po2 of the kidney cortex. Apparently, a reduction in RPP with intact Ang II generation

Table 5. Changes in Renal CBF and CpO2 in the Right (Contralateral) Kidneys of 2K,1C Rats

<table>
<thead>
<tr>
<th>Condition, 2K,1C</th>
<th>Group</th>
<th>CBF, % Change From Baseline</th>
<th>CpO2, % Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalaprilat</td>
<td>6</td>
<td>−18 ± 12</td>
<td>−2 ± 7</td>
</tr>
<tr>
<td>PD-123,319</td>
<td>7</td>
<td>−10 ± 5</td>
<td>−9 ± 3*</td>
</tr>
<tr>
<td>PD-123,319 + enalaprilat</td>
<td>7</td>
<td>−20 ± 7*</td>
<td>−9 ± 3*</td>
</tr>
<tr>
<td>Candesartan</td>
<td>8</td>
<td>−6 ± 6</td>
<td>−5 ± 2*</td>
</tr>
<tr>
<td>Candesartan + enalaprilat</td>
<td>8</td>
<td>−18 ± 10</td>
<td>−2 ± 2</td>
</tr>
<tr>
<td>l-NAME</td>
<td>9</td>
<td>−58 ± 6*†</td>
<td>−42 ± 6*†</td>
</tr>
<tr>
<td>l-NAME + enalaprilat</td>
<td>9</td>
<td>−61 ± 7*†</td>
<td>−40 ± 6*†</td>
</tr>
<tr>
<td>Clamp</td>
<td>10</td>
<td>−9 ± 3</td>
<td>1 ± 0</td>
</tr>
</tbody>
</table>

All of the values are mean ± SEM (n = 8 per group). *P < 0.05 vs baseline within the same group. †P < 0.05 vs enalaprilat treatment.
is not itself sufficient to reduce PO2, which actually increased in the clipped kidney after clamping of its perfusion pressure to the levels accompanying ACEI administration.

Perspectives

This study has provided evidence for a novel intrarenal homeostatic role for Ang II, expressed via AT2 receptors and NO, to maintain RBF and O2 during renal ischemia caused, in this model, by a reduction in RPP in a kidney in which the blood flow capacity is limited by a renal artery clip. This is remarkable given the well-established efficacy of Ang II blood flow capacity is limited by a renal artery clip. This is remarkable given the well-established efficacy of Ang II acting on AT1 receptors to reduce RBF and PO2 in normal kidneys.10,37 Renal tissue hypoxia may be critical in the development of hypertension8-45 and the progression of chronic kidney disease.9 Therefore, this finding of a protective role for Ang II acting on AT2 receptors for maintaining renal perfusion and oxygenation raises potential concerns for the use of ACEIs in conditions of acute renal ischemia that will require further study. Indeed, the acute administration of an ACEI has been shown to reduce renal hemodynamics more than an equally antihypertensive dose ofARB in human subjects with renal artery stenosis.46

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Disclosures

None

References

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