Laboratory Studies

Effect of Captopril on \(^{99m}\text{Tc-DTPA}\) Renograms in Two-Kidney, One Clip Hypertension

JOSEPH V. NALLY, JR, HARRY S. CLARKE, JR., GEORGE P. GRECOS, MARK SAUNDERS, MICHAEL L. GROSS, WILLIAM J. POTVIN, AND JOE P. WINDHAM

SUMMARY In an effort to improve on the noninvasive detection of renal artery stenosis, we investigated the effect of angiotensin converting enzyme inhibition on computer-assisted \(^{99m}\text{Tc-DTPA}\) renal flow studies in a canine model of two-kidney, one clip hypertension and compared these findings with clearances of inulin and \(p\)-aminohippuric acid in the stenotic and contralateral kidney before and after converting enzyme inhibition. The \(^{99m}\text{Tc-DTPA}\) renal flow study with the converting enzyme inhibitor captopril (1.5 mg/kg bolus with 1.5 mg/min infusion) showed an increased sensitivity in the detection of unilateral renal artery stenosis over the use of the \(^{99m}\text{Tc-DTPA}\) study alone. Captopril induced striking alterations that were most evident in the 15-minute \(^{99m}\text{Tc-DTPA}\) renal flow study, in which all nine curves exhibited severely blunted uptake and excretion of the radionuclide. These changes were reversed during a recovery study without converting enzyme inhibition and were not seen when blood pressure was lowered with nitroprusside to a level similar to that observed during converting enzyme inhibition. The changes shown by the \(^{99m}\text{Tc-DTPA}\) study during converting enzyme inhibition correlated with a decrease in the glomerular filtration rate of the stenotic kidney. Captopril infusion significantly decreased the glomerular filtration rate of the stenotic kidney (16.0 ± 3.1 vs 11.0 ± 2.5 mg/min, \(p<0.03\)) but not of the contralateral kidney (32.4 ± 2.6 vs 28.4 ± 2.8 mg/min). Captopril did not result in significant changes in the effective renal plasma flow of either the stenotic (42.4 ± 8 vs 41.0 ± 10 ml/min) or the contralateral (86.8 ± 10 vs 106 ± 15 ml/min) kidney. These results suggest that, in this model of acute unilateral renal artery stenosis, the \(^{99m}\text{Tc-DTPA}\) renal flow study coupled with captopril challenge unmasks angiotensin II-dependent renal functional and hemodynamic changes of the stenotic kidney and may offer promise in the detection of renovascular hypertension. (Hypertension 8: 685-693, 1986)

KEY WORDS • renovascular hypertension • \(^{99m}\text{Tc-DTPA}\) • captopril

SCREENING and detection of correctable renovascular hypertension (RVHT) have received renewed interest given the recent advances in surgical and percutaneous angioplasty techniques.\(^1\)\(^,\)\(^2\) We reported the development of a computer-assisted \(^{99m}\text{Tc-DTPA}\) renal flow study in a group of patients with angiographically proven RVHT and preserved renal function\(^3\) and in a canine model of two-kidney, one clip (2K1C) hypertension.\(^4\) During the course of the latter studies, we observed a subset of hypertensive animals with a milder degree of renal artery stenosis that did not exhibit consistent changes in \(^{99m}\text{Tc-DTPA}\) renal flow studies.

The purpose of the present study was to evaluate the effect of angiotensin converting enzyme inhibition (CEI) on the \(^{99m}\text{Tc-DTPA}\) renal flow study as well as on individual kidney glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) in a model of 2K1C hypertension. This provocative captopril challenge, which pharmacologically blocks the renin-angiotensin system, was studied for two reasons. First, orally administered angiotensin converting enzyme inhibitors have been reported to result in acute renal insufficiency in selected patients with RVHT.\(^5\)\(^,\)\(^6\) It has been postulated that the existing data regarding the

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Results

Creation of unilateral renal artery stenosis resulted in a 47.3 ± 7% decrease in ipsilateral PAH clearance and an increase in mean arterial pressure from 128 ± 4 to 140 ± 4 mm Hg (p < 0.02). Baseline clearances of...
inulin and PAH were 47.5 ± 4 and 140 ± 10 ml/min, respectively, with a filtration fraction of 0.36 ± 0.04. Split function clearance studies following stenosis are shown in Table 1. There were parallel changes in the GFR and ERPF of the stenotic and contralateral kidneys such that the filtration fraction did not change significantly from control for either the stenotic or the contralateral kidney.

Visual analysis of the 99mTc-DTPA renal flow studies showed that the 90-second and 15-minute studies without captopril were diagnostic of renal artery stenosis in five of nine and seven of nine dogs, respectively. The nondiagnostic studies occurred in the four animals with milder stenosis, in which reduction in ipsilateral renal flow studies during captopril infusion were not seen during nitroprusside infusion.

Infusion of captopril during the subsequent 99mTc-DTPA renal flow studies resulted in a decrease in mean arterial pressure (from 140 ± 4 to 106 ± 4 mm Hg; p < 0.02) that was maintained throughout the radionuclide infusion, while the remaining three were all considered diagnostic of unilateral renal artery stenosis. These changes reversed after captopril infusion, while the remaining three were all considered diagnostic of unilateral renal artery stenosis. These changes reversed after captopril infusion, while the remaining three were all considered diagnostic of unilateral renal artery stenosis.

### Table 1. Studies of the Stenotic and Contralateral Kidneys Before and After Captopril Treatment

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>MAP (mm Hg)</th>
<th>Cfa (ml/min)</th>
<th>FF</th>
<th>CpAH (ml/min)</th>
<th>Cfa (ml/min)</th>
<th>FF</th>
<th>CpAH (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
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<tr>
<td>9</td>
<td>132</td>
<td>100</td>
<td>23</td>
<td>13</td>
<td>0.36</td>
<td>0.22</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>128</td>
<td>107</td>
<td>13</td>
<td>9</td>
<td>0.45</td>
<td>0.26</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>123</td>
<td>105</td>
<td>16</td>
<td>15</td>
<td>0.34</td>
<td>0.29</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>147</td>
<td>97</td>
<td>6</td>
<td>2</td>
<td>0.33</td>
<td>0.50</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>167</td>
<td>119</td>
<td>22</td>
<td>16</td>
<td>0.41</td>
<td>0.29</td>
<td>54</td>
</tr>
<tr>
<td>Mean</td>
<td>139</td>
<td>106</td>
<td>16.0</td>
<td>11.0</td>
<td>0.38</td>
<td>0.31</td>
<td>42.4</td>
</tr>
<tr>
<td>± SEM</td>
<td>± 6</td>
<td>± 4 *</td>
<td>± 3.1</td>
<td>± 2.5</td>
<td>± 0.02</td>
<td>± 0.05 *</td>
<td>± 8</td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure; Cfa = inulin clearance; FF = filtration fraction; CpAH = p-aminohippuric acid clearance; Pre = before captopril; Post = after captopril.

*p < 0.02, t < 0.03, t' < 0.01, compared with pretreatment values.
To quantitate the individual kidney hemodynamic and functional changes in unilateral renal artery stenosis suggested by the $^{99m}$Tc-DTPA renal flow studies, split function clearances of PAH and inulin were performed before and during a similar captopril infusion in each of the last six animals (see Table 1; Figure 9). Captopril induced a significant reduction in mean arterial pressure in the six animals even when Dog 4 was excluded because of severe, albeit transient, hypotension. Converting enzyme inhibition in these animals with unilateral renal artery stenosis resulted in a significant decrease in GFR of the stenotic kidney (16.0 ± 3.1 vs 11.0 ± 2.5 ml/min; p < 0.03) and an insignificant fall in GFR of the contralateral kidney (32.4 ± 2.6 vs 28.4 ± 2.8 ml/min). Total GFR was reduced from 48.4 ± 4 to 38.4 ± 3 ml/min (p < 0.02). There was no change in the ERPF of the stenotic kidney, but ERPF increased 22% in the contralateral kidney at a time when mean arterial pressure was reduced by 24%, although this trend did not reach statistical significance. The filtration fraction of both the stenotic and the contralateral kidney fell during CEI. The reduction of filtration fraction of the stenotic kidney resulted from a significant fall in GFR, whereas the reduction in the contralateral kidney was derived from a small decrease in the GFR with a concomitant increase in ERPF.

Discussion

In the present study, CEI induced reproducible alterations in the $^{99m}$Tc-DTPA renal flow studies of the stenotic kidney performed on animals with 2K1C hypertension such that detection of renal artery stenosis was enhanced during captopril infusion. The most evident changes seen in the 15-minute $^{99m}$Tc-DTPA time-activity curves during CEI were noted only in the stenotic kidney and correlated with the significant decrease in GFR of the stenotic kidney. There were no significant changes in either GFR or ERPF of the contr-
tralateral kidney during CEI, and no changes in the time-activity curves of the contralateral kidney were obvious. Hence, the changes in the 15-minute \(^{99m}\)Tc-DTPA time-activity curves were severely blunted or absent uptake and excretory phases observed during CEI appear to be related to CEI-induced deterioration of GFR of the stenotic kidney. These observations are consistent with the hypothesis that GFR and intrarenal resistance of the stenotic kidney are mediated by angiotensin II-dependent, efferent arteriolar constriction and suggest that CEI may unmask angiotensin II-dependent renal hemodynamic and functional changes of renal artery stenosis.

\(^{99m}\)Tc-DTPA is a Tc-labeled chelate that is minimally protein-bound and is excreted almost completely by glomerular filtration. This radionuclide may be used in nonimaging techniques as a marker of GFR since good correlations have been established with \(^{99m}\)Tc-DTPA and inulin clearances. Consequently, a reduction of GFR caused by various forms of renal parenchymal disease or obstructive uropathy may alter the \(^{99m}\)Tc-DTPA renogram.

Given the reports of the effects of CEI on renal vein renins and renal function in RVHT, pharmacological manipulation with CEI on the \(^{99m}\)Tc-DTPA renogram seemed to offer promise in improving the sensitivity and specificity of detecting renovascular abnormalities using this radionuclide technique. We and others have reported the application of noninvasive radionuclide studies of the kidney with CEI in subjects with RVHT. Preliminary radionuclide studies noting changes in single kidney ERPF and GFR following CEI have been reported recently in patients with RVHT either of their native kidneys or a renal allograft. In addition, radionuclide techniques showed that the administration of captopril in a model of 2K1C hypertension significantly lowered both mean arterial pressure and GFR in the clamped kidney. In our canine model of 2K1C hypertension, we further examined the question of whether these observations.

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**Figure 3.** The 90-second (A) and 15-minute (B) \(^{99m}\)Tc-DTPA renal flow study during captopril infusion.

**Figure 4.** The 90-second (A) and 15-minute (B) \(^{99m}\)Tc-DTPA renal flow study without captopril during the recovery phase.
with CEI were a consequence of the reduction of systemic or renal perfusion pressure with CEI or were specific for the effect of CEI on the stenotic kidney. The results of this study in our model of acute RVHT support the latter hypothesis.

In the acute animal model studied, the changes in the $^{99m}$Tc-DTPA time-activity curves with CEI were not seen when mean arterial pressure was reduced with nitroprusside infusion to a similar degree as that seen during the $^{99m}$Tc-DTPA-captopril studies. These observations suggest that the changes within the stenotic kidney were not simply the result of a reduced renal perfusion pressure, which might be considered critical to maintenance of renal function of the stenotic kidney. This finding is in agreement with recent studies that demonstrated no decline in total GFR or ERPF in patients with unilateral renal artery stenosis when hypertensive levels of mean arterial pressure were reduced to normal with nitroprusside infusion. These findings contrasted with the reduction of both total GFR and ERPF in those patients with bilateral renal artery stenosis when pressure was similarly reduced with nitroprusside. Unfortunately, in these studies total GFR and ERPF were measured using nonimaging radionuclide techniques with $[^{125}]$iodohippurate and $[^{131}]$iodohippurate, and reports of individual kidney parameters were not available. In a canine model of unilateral renal artery stenosis, these same investigators recently reported that systemic nitroprusside infusion plus intrarenal infusion of the angiotensin II antagonist saralasin resulted in a significant fall in GFR that was independent of changes in renal blood flow during nitroprusside renal vasodilatation even under sodium-replete conditions, thus suggesting that the efferent arteriolar effects of angiotensin II may act to sustain GFR in the presence of preglomerular stenosis.

To examine the putative effects of captopril on indi-
individual kidney perfusion and function suggested by the 
\( ^{99m} \text{Tc-DTPA} \) renal flow study, we performed split
function clearances of inulin and PAH. Captopril ad-
ministration, in amounts sufficient to reduce mean ar-
terial pressure below prestenosis levels, produced a
significant decrease in the GFR but no change in the
ERPF of the stenotic kidney. Overall, there was a
significant short-term decrease in total GFR that was
generally accounted for by the decrement in the GFR
of the stenotic kidney, as the GFR of the contralateral
kidney was not changed significantly by captopril in-
fusion. This reduction in the GFR and filtration fraction
of the stenotic kidney is consistent with the postulate of
preservation of GFR in preglomerular stenosis through
efferent arteriolar constriction mediated by angiotensin
II. However, the increases in GFR and renal blood
flow in the contralateral kidney described in the rat
model of 2K1C hypertension were not observed in
the present study. Perhaps the upward trend in the
ERPF of the contralateral kidney in our studies did not
reach statistical significance because of the rather pro-
nounced reduction in mean arterial pressure with cap-
topril during the acute phases of renal artery stenosis.
In models of more chronic 2K1C hypertension, CEI
has consistently increased both total renal blood flow
and renal blood flow of the contralateral kidney despite
significant decreases in mean arterial pressure, where-
as changes in GFR of the contralateral kidney follow-
ing CEI have been less consistent. Other studies have
noted similar increases in renal blood flow of both
the clipped and unclipped kidney with CEI if the
clip is removed just before CEI. This observation sug-
gests that CEI elicits renal vasodilatation by blocking
the effects of circulating, rather than local, angiotensin
II. Although the changes in GFR and renal blood flow
following CEI with the resultant decrease in filtration
fraction have been interpreted as suggesting that angio-

**FIGURE 7.** The 90-second (A) and 15-minute (B) 
\( ^{99m} \text{Tc-DTPA} \) renal flow study during captopril infusion with mild left renal artery stenosis. BP = blood pressure.

**FIGURE 8.** The 90-second (A) and 15-minute (B) 
\( ^{99m} \text{Tc-DTPA} \) renal flow study without captopril during the recovery phase in the same dog as in Figures 6 and 7. BP = blood pressure.
tensin II exerts a greater effect on the efferent rather than the afferent arterioles, that view has been eloquently reviewed and questioned by Navar and Rosivall.\textsuperscript{23}

Our findings of deterioration of renal function in the stenotic kidney following CEI in this model may have application to the human form of RVHT. However, the anesthetized dog model of acute 2K1C hypertension may be more renin-dependent and angiotensin II-dependent than are various forms of human RVHT. This consideration is obviously a major limitation in attempting to apply these observations of CEI to the human condition. Whether the analogous model in humans (or that mimicking one-kidney, one clip hypertension as more akin to the one-kidney, one clip model of hypertension — presumably a low renin, volume-mediated hypertension.) Deterioration of single-kidney GFR and impaired sodium \textsuperscript{131}Io-iodohippurate (Hippuran) excretion with captopril in patients with functionally significant unilateral renal artery stenosis has been reported.\textsuperscript{15} The mechanism of development of azotemia with CEI has also been examined by assessing the effect of enalapril on total GFR and ERPF, as measured by radionuclide techniques in patients with RVHT.\textsuperscript{22} In patients with unilateral renal artery stenosis, GFR fell to 40% of control values at 4 hours but returned to 75% of control at 4 days, even though ERPF was reported to exceed control values. In patients with bilateral disease, neither the decrease in GFR nor the decrease in ERPF induced by enalapril showed a tendency to return toward control values at 4 days. Unfortunately, parameters of single-kidney function were not reported, so that it remains in question whether the more transient decreases and subsequent recovery in GFR seen in the patients with unilateral renal artery stenosis occurred in the stenotic kidney alone or whether improvement in GFR resulted from compensatory changes in the contralateral kidney. In patients with RVHT, one may speculate about the possible adverse effects of CEI on the stenotic kidney (or kidneys) as well as the potential complicating effects of chronic hyperfiltration within the contralateral kidney. Application of these radionuclide techniques with \textsuperscript{99}Tc-DTPA, coupled with the pharmacological challenge of CEI, in patients with various forms of RVHT deserves further study.

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