Effect of Captopril on $^{99m}$Tc-Diethylenetriaminepentaacetic Acid Renograms in Two-Kidney, One Clip Hypertension

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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 $^{99m}$Tc-diethylenetriaminepentaacetic acid (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 $^{99m}$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 $^{99m}$Tc-DTPA study alone. Captopril induced striking alterations that were most evident in the 15-minute $^{99m}$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 $^{99m}$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 $^{99m}$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 • $^{99m}$Tc-diethylenetriaminepentaacetic acid • 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 $^{99m}$Tc-diethylenetriaminepentaacetic acid (DTPA) renal flow study in a group of patients with angiographically proven RVHT and preserved renal function3 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 $^{99m}$Tc-DTPA renal flow studies.

The purpose of the present study was to evaluate the effect of angiotensin converting enzyme inhibition (CEI) on the $^{99m}$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
decrease in GFR with CEI support the theory that maintenance of intrarenal resistance and GFR are mediated by angiotensin II–dependent, efferent arteriolar constriction when renal perfusion pressure is diminished, as seen with preglomerular stenosis. However, the exact mechanism of this deterioration in GFR during CEI has yet to be elucidated. The second reason for this provocative captopril challenge with our radionuclide studies is that renal vein renin determinations after captopril stimulation have been reported to enhance the diagnostic accuracy of that procedure over conventional renal vein studies. We sought to investigate these renal physiological changes attributed to CEI in an attempt to improve on the noninvasive detection of individual kidney perfusion and function in renal artery stenosis. Thus, the results of \(^{99m}\text{Tc-DTPA}\) renal flow studies coupled with the pharmacological challenge of CEI were compared with the changes in \(^{99m}\text{Tc-DTPA}\) renal clearance. This study was designed to determine the effect of CEI on renal function and to elucidate the mechanism of the deteriorating renal function previously reported in a canine model of renal artery stenosis.

Materials and Methods

Studies were performed in nine female mongrel dogs that were known to have single normal renal arteries from previous angiography. Throughout the studies, the animals were permitted free access to food and water. During the control period, the animals were anesthetized with pentobarbital (30 mg/kg) and conventional clearance studies with PAH and inulin as markers of ERPF and GFR, respectively, were performed with a bladder catheter.\(^9\)\(^10\) Blood pressure determinations by means of a femoral artery catheter also were performed (321 recorder, Hewlett Packard, Waltham, MA, USA). On another day, the anesthetized animals were hydrated to ensure a urine output of greater than 2 ml/min and then underwent the \(^{99m}\text{Tc-DTPA}\) renal flow studies.

For the renal artery stenosis phase of the experiment, the animals were anesthetized and the left renal artery was approached anteriorly. An electromagnetic flow probe (Micron Instruments, Los Angeles, CA, USA) was placed, and measurements of unilateral renal flow were taken after a stabilization period. A metallic surgical clip was then positioned proximal to the flow probe to approximate a 50% reduction in renal blood flow, which was observed during a postclip period ranging from 30 to 60 minutes. On the following day, the well-hydrated animals again underwent the \(^{99m}\text{Tc-DTPA}\) scans. On the second postoperative day, the animals were hydrated with normal saline. Captopril (provided by Squibb, Princeton, NJ, USA) was administered at a dose of 1.5 mg/kg i.v. over 5 minutes and followed by a 60-minute infusion of 1.5 mg/min. The \(^{99m}\text{Tc-DTPA}\) scan was performed during the captopril infusion, while recovery \(^{99m}\text{Tc-DTPA}\) scans without captopril were performed on the third postoperative day. Six animals had mean arterial pressure lowered to the same extent as during captopril infusion, using nitroprusside, and were scanned on the fourth postoperative day. Blood pressure determinations and split function clearance studies of PAH and inulin before and during captopril infusion (1.5 mg/kg bolus and 1.5 mg/min for 60 minutes) were performed in sodium-replete animals with urine collected by individual ureteral catheters on the final day of the experiment. A poststudy angiogram was performed in all animals as well.

For the \(^{99m}\text{Tc-DTPA}\) study, 5 mCi of \(^{99m}\text{Tc-DTPA}\) was injected rapidly through the cephalic vein with the animal lying supine and the anatomy viewed posteriorly by a large field of view gamma camera (General Electric Maxicamera II, Milwaukee, WI, USA). Data were acquired by a PDP 11/34 computer using a predefined study routine operating under Gamma 11 and RT-11 software (Digital Equipment Corporation, Maynard, MA, USA). Data acquisition was formulated into a \(64 \times 64\)-pixel matrix. The dynamics of the \(^{99m}\text{Tc-DTPA}\) study were specified by a collection time of 1 second/frame for 90 seconds, then 10 seconds/frame for 13.5 minutes, for a total of 15 minutes.

The regions of interest were selected to include the aorta, left and right kidneys, and corresponding background areas to be subtracted. A separate time–activity curve for the aortic region was plotted to assess the quality of bolus at the main renal arteries. These resultant time–activity curves then served as input for our analysis programs. A poor aortic curve was a potential criterion for rejecting the study. The time–activity curve for the left and right kidneys was plotted on the same set of axes with the activity scale normalized to the kidney with higher activity. This display format facilitates direct bilateral comparison.

The pairs of time–activity curves from the 90-second and 15-minute \(^{99m}\text{Tc-DTPA}\) renal flow studies were analyzed visually for configuration, slope, and symmetry and judged to be either normal or abnormal. The curves were deemed to be normal if their configuration was in agreement with a previously defined normal kidney template and if there was symmetry of the curves of the left and right kidney. The curves were judged to be diagnostic of renal artery stenosis according to previously described criteria that noted decreases in maximal activity, upslope, and differential (stenotic/contralateral) maximum activity ratio. The curve parameters for an individual kidney were compared before and after the creation of renal artery stenosis for both the stenotic kidney and the contralateral kidney. In addition, curve parameters were analyzed for scans performed during captopril infusion, recovery scans, and nitroprusside infusion. These studies were determined to be diagnostic on the basis of visual analysis using the aforementioned criteria.

The results are expressed as means ± SEM. Statistical analysis was accomplished by use of the paired Student’s \(t\) test.

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 ERPF averaged approximately 30% (20, 28, 33, 47 ml/min). Analysis of the previously described parameters of the 90-second 99mTc-DTPA time-activity curves showed decreases in maximum activity, upslope, and differential (stenotic/contralateral) maximum activity ratios. Although the 15-minute curves that were considered diagnostic of renal artery stenosis demonstrated a depressed peak activity value compared with the contralateral kidney curve, all 15-minute curves exhibited an uptake and accumulation of the radionuclide followed by an excretory phase (see Figure 2B).

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 studies. All nine of the 15-minute 99mTc-DTPA renal flow studies during captopril infusion were considered diagnostic of unilateral renal artery stenosis. More specifically, there were dramatic, reversible changes in the 15-minute 99mTc-DTPA time-activity curves such that the accumulation-uptake and excretory phases were severely blunted or absent (see Figure 3B). Six of the nine studies changed dramatically with captopril infusion, while the remaining three were already significantly depressed secondary to renal artery stenosis alone. These changes reversed after captopril was discontinued, as can be seen in the scans during recovery (see Figure 4B). To exclude the possibility that diminished renal perfusion pressure was responsible for these changes in the 99mTc-DTPA studies during captopril infusion, 99mTc-DTPA studies were repeated in six of the animals while mean arterial pressure was lowered by nitroprusside infusion to a level similar to that observed during captopril infusion (110 ± 5 vs 106 ± 4 mm Hg). The dramatic changes in the 15-minute time-activity curves exhibited during captopril infusion were not seen during nitroprusside infusion. All 99mTc-DTPA time-activity curves during nitroprusside showed both accumulation-uptake and excretory phases (see Figure 5B).

The 90-second and 15-minute 99mTc-DTPA time-activity curve changes are exemplified by studies from Dog 6 depicted in Figures 1 through 5. Following normal 90-second and 15-minute 99mTc-DTPA control studies (see Figure 1), creation of a moderately severe left renal artery stenosis resulted in 90-second and 15-minute 99mTc-DTPA curves that were both considered diagnostic of unilateral renal artery stenosis (see Figure 2). However, captopril infusion resulted in significant alterations in the 15-minute 99mTc-DTPA time-activity curves, demonstrating no uptake and excretory phases of the radionuclide by the stenotic left kidney (see Figure 3B). Changes in the 90-second 99mTc-DTPA study during captopril infusion were less consistent overall (see Figure 3A). Changes in the 99mTc-DTPA time-activity curves of the stenotic left kidney reversed during the recovery study (see Figure 4) and were not seen during the nitroprusside study (see Figure 5). An example of a similar effect of CEI on the 99mTc-DTPA renal flow study for Dog 7 with mild (25–30%) left renal artery stenosis can be seen in Figures 6 through 8. Figure 6 depicts the 90-second and 15-minute studies following the creation of mild renal artery stenosis. These studies did not differ from those of control studies and were considered to be nondiagnostic. Nonetheless, there were dramatic, reversible changes during CEI that are best exhibited by the 15-minute time-activity curve (see Figure 7B), which again shows the absence of uptake-accumulation and excretory phases during CEI and then reverses to baseline during the recovery scan (see Figure 8).

### 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>C\textsubscript{in} (ml/min)</th>
<th>FF</th>
<th>C\textsubscript{PAH} (ml/min)</th>
<th>C\textsubscript{in} (ml/min)</th>
<th>FF</th>
<th>C\textsubscript{PAH} (ml/min)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
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</tr>
<tr>
<td>9</td>
<td>132</td>
<td>100</td>
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<td>13</td>
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<tr>
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<td>147</td>
<td>97</td>
<td>6</td>
<td>2</td>
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<tr>
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<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</td>
<td>11</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>± 2.51</td>
<td>± 0.02</td>
<td>± 0.05*</td>
<td>± 8</td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure; C\textsubscript{in} = inulin clearance; FF = filtration fraction; C\textsubscript{PAH} = p-aminohippuric acid clearance; Pre = before captopril; Post = after captopril.

*p < 0.02, tP < 0.03, tP < 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 ($16.0 \pm 3.1$ vs $11.0 \pm 2.5$ ml/min; $p < 0.03$) and an insignificant fall in GFR of the contralateral kidney ($32.4 \pm 2.6$ vs $28.4 \pm 2.8$ ml/min). Total GFR was reduced from $48.4 \pm 4$ to $38.4 \pm 3$ 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 con-
Figure 3. The 90-second (A) and 15-minute (B) ⁹⁹mTc-DTPA renal flow study during captopril infusion.

Figure 4. The 90-second (A) and 15-minute (B) ⁹⁹mTc-DTPA renal flow study without captopril during the recovery phase.

Renal blood flow during captopril infusion was markedly depressed in the affected, left kidney during CEI, and no changes in the time-activity curves of the contralateral kidney were obvious. Hence, the changes in the 15-minute ⁹⁹mTc-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.

⁹⁹mTc-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 ⁹⁹mTc-DTPA and inulin clearances. Consequently, a reduction of GFR caused by various forms of renal parenchymal disease or obstructive uropathy may alter the ⁹⁹mTc-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 ⁹⁹mTc-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
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$^{20}$ 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 $[^{125}]$iodamate and $[^{131}]$iodhippurate, and reports of individual kidney parameters were not available. In a canine model of unilateral renal artery stenosis, these same investigators$^{21}$ 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 99mTc-DTPA renal flow study, we performed split function clearances of inulin and PAH. Captopril administration, in amounts sufficient to reduce mean arterial 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 infusion. 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 pronounced reduction in mean arterial pressure with captopril 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, whereas changes in GFR of the contralateral kidney following 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 suggests 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-
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 Rosival."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 model of hypertension — presumably a low renin, volume-mediated hypertension) deterioration of single-kidney GFR and impaired sodium [131I]iodohippurate (Hippuran) excretion with captopril in patients with functionally significant unilateral renal artery stenosis has been reported. 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. 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 99mTc-DTPA, coupled with the pharmacological challenge of CEI, in patients with various forms of RVHT deserves further study.

Acknowledgments

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