The Effect of Captopril on Renal Blood Flow in Renal Artery Stenosis Assessed by Positron Tomography with Rubidium-82

NAGARA TAMAKI, NATHANIEL M. ALPERT, CARLOS A. RABITO, MARTHA BARLAI-KOVACH, JOHN A. CORREIA, AND H. WILLIAM STRAUSS

SUMMARY The sequence and magnitude of acute changes in renal blood flow following administration of captopril were determined in a canine model of acute unilateral renal artery stenosis using rubidium-82 and positron emission tomography. Data were recorded in each of nine dogs under three conditions: 1) during a baseline control interval, 2) during renal artery stenosis, and 3) during stenosis with intravenous injection of captopril (1.2 mg/kg). Mean arterial blood pressure was 108 ± 12 mm Hg at control, increased significantly to 125 ± 13 mm Hg (p<0.01) during stenosis, and decreased to 98 ± 13 mm Hg (p<0.01) after captopril infusion. Mean renal blood flow was calculated using a steady state single compartment model from the images produced by positron emission tomography. The estimated flow to the affected kidney was 3.37 ± 1.48 ml/min/g at control, 0.86 ± 0.62 ml/min/g during stenosis (p<0.01), and 0.64 ± 0.57 ml/min/g after captopril administration (p = NS compared with precaptopril value). The estimated flow to the contralateral kidney was minimally reduced from a baseline of 3.84 ± 0.95 to 3.24 ± 1.13 ml/min/g (p=NS) during stenosis and increased after captopril infusion (4.08 ± 0.94 ml/min/g; p = 0.01). These data suggest that repetitive imaging with positron emission tomography can be used to delineate acute changes in renal perfusion following captopril administration. (Hypertension 11: 217-222, 1988).

KEY WORDS • positron emission tomography • rubidium-82 • renal blood flow • renovascular hypertension • captopril • renin-angiotensin system

RENAL hemodynamics and function are well regulated by the renin-angiotensin system.1-3 In essential hypertension, when vascular tone is increased, captopril, an angiotensin converting enzyme inhibitor, has proved to be an effective treatment.4,5 In renovascular hypertension, however, the effect of angiotensin converting enzyme inhibitor is complex.6-9 The drug will cause a decrease in systemic blood pressure and may alter intrarenal hemodynamics. The intrarenal changes may cause severe impairment of renal function, particularly in patients with bilateral renal artery stenosis or renal artery stenosis in a solitary kidney. Recently, acute failure has been reported following captopril therapy in some of these patients.9,10 To determine if a reduction in renal perfusion following captopril therapy can cause these changes, it would be useful to measure renal perfusion sequentially in vivo before and after administration of the converting enzyme inhibitor.

Rubidium-82, a generator-produced, monovalent, cationic, positron-emitting radionuclide, has been advocated for the serial assessment of myocardial perfusion using positron emission tomography (PET).11-13 Recently, a noninvasive method for the serial measurement of renal blood flow using PET and the continuous infusion of 82Rb was described.14,15 The 82Rb distribution in the kidney correlated well with microsphere-determined renal blood flow under conditions of normal perfusion and flow reduction. In addition, these studies suggested that flow to the contralateral kidney was reduced during unilateral renal artery stenosis. The present study used the 82Rb infusion technique for the serial assessment of renal blood flow in the acute unilateral renal artery stenosis model to measure the changes in renal blood flow caused by captopril.
Materials and Methods

Radionuclide

$^{82}$Rb (physical half-life, 75 seconds) was obtained from the strontium-82/$^{82}$Rb generator (Squibb Diagnostic, Princeton, NJ, USA). Because of the short half-life of $^{82}$Rb, measurements of renal perfusion were made by imaging the animals during the continuous infusion of $^{82}$Rb (see Protocol). The radionuclide was eluted continuously with a saline eluate at a flow rate of 10 ml/min directly into a central venous catheter.

Animal Preparation

Nine adult mongrel dogs (weight, 15-25 kg) were anesthetized with pentobarbital (25 mg/kg i.v.), intubated, and placed in the right lateral decubitus position. The left kidney was exposed through a left retroperitoneal flank incision. If the left kidney was supplied by two renal arteries, the incision was closed and the dog was turned to the left lateral decubitus position, the right flank was incised and the right renal artery exposed for the preparation. An electromagnetic flow probe was placed around the renal artery to measure total renal blood flow. An adjustable balloon occlusion device was placed on the renal artery distal to the flow probe. During the experiment, the flowmeter was used to titrate the approximate reduction of renal perfusion. A venous catheter was placed in the inferior vena cava for administration of drugs and infusion of $^{82}$Rb.

Microspheres

To confirm the renal blood flow results calculated by PET, microspheres were administered through the left atrium at each phase of the experimental protocol. A polyethylene catheter was placed in the left atrium through a left-sided thoracotomy for microsphere administration injection, and a second catheter was placed in the aorta to monitor aortic pressure and permit arterial sampling of microspheres.

Positron Emission Tomography

A positron camera (Model PC-384, Scanditronix, Essex, MA, USA) with 96 bismuth germanium oxide crystals in each of three rings was employed to record five transverse slices at 14-mm intervals. In-plane resolution with $^{82}$Rb was approximately 9 mm (full width at half maximum). The dog was placed in the lateral position in the camera. A transmission image of the abdomen was recorded with a gallium-68 ring source to allow accurate correction of photon attenuation on the emission images. $^{82}$Rb (10-15 mCi/min) was eluted with saline from the $^{82}$Sr/$^{82}$Rb generator into the inferior vena cava at 10 ml/min. Within 5 to 6 minutes of the start of infusion, the count rate in the field of view stabilized. At that time, a positron emission scan containing 0.7 to 1.5 million counts/slice was recorded over 2 to 4 minutes. Emission data were corrected for attenuation, random coincidence, and scatter and then reconstructed with a filtered back projection method into images with a 128 $\times$ 128 matrix.

Protocol

Baseline flow, blood pressure, and positron emission scans were recorded. Three separate arterial blood samples were drawn during the PET scan, and activity in each sample was immediately measured in a scintillation well counter. The exact times of sample collection and counting were used to correct for physical decay. At the conclusion of the scan, 3 to 5 million microspheres (15 $\pm$ 5 $\mu$m) labeled with 14 $\mu$Ci of cesium-141 were injected into the left atrium. Beginning 15 seconds before injection of the microspheres and continuing for at least 1.75 minutes after injection, aortic blood samples were continuously withdrawn at a rate of 10 ml/min.

The occluder was then gradually tightened to reduce blood flow to 20 to 50% of the control flow (estimated from the renal artery flow probe), and the occluder was fixed to maintain the reduced flow. Forty minutes later, arterial blood pressure was recorded followed by a second PET scan, left atrial administration of $^{82}$Sr (15 $\mu$Ci), and arterial blood sampling as described. At the conclusion of the second scan, captopril (1.2 mg/kg) was infused into the inferior vena cava over 30 minutes while blood pressure was continuously monitored. Ten minutes later, the third PET scan was recorded with $^{82}$Rb, followed by left atrial injection of 15 $\mu$Ci of $^{68}$Sc microspheres as described.

At the end of the experiment, each dog was killed and the kidneys excised and sliced transversely at 14-mm intervals to correspond to the PET images. Each slice was divided into cortex and medulla and further subdivided into 1- to 3-g pieces. The samples were weighed and counted in a multichannel analyzer-equipped well counter for microsphere activity. All samples were corrected for crossover and compared with the activity in the arterial reference sample. The renal blood flow was expressed as milliliters per minute per gram for comparison to PET data.

Data Analysis

Renal blood flow was calculated from the PET perfusion images using the steady state single compartment model, as described previously. In brief, when the short-lived $^{82}$Rb is constantly infused, a dynamic equilibrium (steady state) is attained. The arterial input rate of $^{82}$Rb is balanced by its clearance rate and rate of radioactive decay:

$$F_{E_C} = F_{E_C} + (\lambda)C_t$$

Where $F$ is unit flow (ml/min/g), $E$ is unidirectional extraction fraction of the tracer, $C_t$ is arterial concentration, $C_t$ is tissue concentration, $p$ is the kidney/blood partition coefficient, and $\lambda = \frac{\text{physical decay constant}}{0.533}$.

Therefore, the measurable quantity $C_t/C_s$ is described as:

$$C_t/C_s = \frac{F_{E_t}}{(F_{E_t} + \lambda)}$$

$C_t$ was calculated as average activity concentration,
from PET perfusion images by taking regions of interest over the renal region in each slice ($\mu$Ci/ml). To minimize partial volume effects, only the two or three central slices were used to determine the average concentration of $^{82}$Rb in each kidney. $C_i$ was calculated from the mean of the three arterial blood samples. With $E$ equal to 0.44 and $p$ equal to 3.36, Equation 2 was used to estimate renal blood flow ($F$) from the measured ratio ($C/C_0$). (The values for $E$ and $p$ in this article differ somewhat from the values used previously due to improvement in the dead time correction of the tomographic measurement.)

Statistical Analysis

All hypothesis tests were performed with the SAS system of statistical analysis programs (SAS Institute, Cary, NC, USA). A repeated-measures analysis of variance with planned contrasts was used to test the hypotheses that 1) blood flow in each kidney differed from that in the basal state and 2) blood flow in each kidney after captopril infusion differed from that during stenosis alone. The repeated-measures analysis was performed using the general linear model procedure.

Results

Typical PET transverse sections of the steady state distribution of $^{82}$Rb during a control measurement are shown in Figure 1. The tomograms outline both kidneys and great vessels. The changes from control, to renal artery stenosis, and after captopril infusion are shown for a single slice in a typical animal (Figure 2).

Renal cortical perfusion was much greater than that to the medullary region and was similar in both kidneys under baseline conditions. During renal artery stenosis, the perfusion to the left (stenosed) kidney was reduced by 74% and activity in the contralateral kidney was reduced by 17%. Following captopril infusion, perfusion in the contralateral kidney increased slightly while perfusion to the activity in the stenotic kidney remained depressed.

The mean blood pressure was 108 ± 12 mm Hg at control, increased to 125 ± 13 mm Hg during renal artery stenosis ($p<0.01$), and returned to 98 ± 13 mm Hg after captopril infusion (Figure 3).

PET calculated renal blood flows are listed in Table 1. The control $^{82}$Rb flow was 3.37 ± 1.48 ml/min/g in the affected kidney and 3.84 ± 0.89 ml/min/g in the contralateral kidney. During renal artery stenosis, the $^{82}$Rb calculated flow to the stenotic kidney was reduced to 0.86 ± 0.62 ml/min/g (22% of the control value; $p<0.0001$). In addition, flow to the contralateral kidney was mildly reduced (3.24 ± 1.13 ml/min/g; 84% of the baseline; $p=NS$). After captopril infusion, the flow to the stenotic kidney was slightly reduced (0.64 ± 0.57 ml/min/g; $p=NS$ compared with stenosis alone) while the flow to the contralateral kidney was slightly increased (4.08 ± 0.94 ml/min/g; $p=0.01$ compared with stenosis alone; see Table 1). Striking changes in flow to the contralateral kidney were observed in five dogs (see Table 1), but three dogs (Dogs 2, 5, and 6) revealed no substantial changes in flow during stenosis and after captopril infusion. In the remaining dog (Dog 8), flow to the contralateral kidney was reduced during stenosis and further reduced after captopril infusion. The flow to the stenotic kidney was reduced after captopril infusion in six of the nine dogs.

The microsphere determined renal blood flow at control was 3.34 ± 1.25 ml/min/g in the affected kidney and 3.89 ± 0.89 ml/min/g in the contralateral kidney (see Table 1). During stenosis, the microsphere flow to the stenotic kidney and contralateral kidney was significantly reduced compared with baseline, 1.01 ± 0.64 and 2.87 ± 0.78 ml/min/g, respectively.
After captopril infusion, the flow to the contralateral kidney increased to 3.97 ± 0.94 ml/min/g, but the flow to the stenotic kidney was slightly, but not significantly decreased (0.70 ± 0.68 ml/min/g). Thus, similar changes in microsphere and rubidium renal flow were observed.

Analysis of variance was performed with the dog kidney (affected or contralateral) and state as the main effects, taking into account the possible interaction of kidney with state. *F* values for the main effects and interaction of kidney and state were significant at the */p* level of 0.0001. Further analysis of the data for the affected kidney contrasting the results during stenosis with the basal condition showed significant reduction of blood flow (*/p* = 0.0001). Renal blood flow in the affected kidney was also reduced following captopril infusion relative to the basal state, but differences between the stenotic and captopril state were not statisti-

### Table 1. ^42^Rb-Estimated Renal Blood Flow in Nine Dogs

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Microsphere flow (ml/min/g)</th>
<th>Stenotic kidney (ml/min/g)</th>
<th>Contralateral kidney (ml/min/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Stenosis</td>
<td>Captopril</td>
</tr>
<tr>
<td>1</td>
<td>2.09</td>
<td>1.13</td>
<td>0.10</td>
</tr>
<tr>
<td>2</td>
<td>5.50</td>
<td>2.12</td>
<td>1.38</td>
</tr>
<tr>
<td>3</td>
<td>1.03</td>
<td>0.15</td>
<td>0.10</td>
</tr>
<tr>
<td>4</td>
<td>2.91</td>
<td>1.01</td>
<td>0.53</td>
</tr>
<tr>
<td>5</td>
<td>2.98</td>
<td>1.13</td>
<td>1.21</td>
</tr>
<tr>
<td>6</td>
<td>2.84</td>
<td>0.69</td>
<td>0.52</td>
</tr>
<tr>
<td>7</td>
<td>3.28</td>
<td>0.24</td>
<td>0.34</td>
</tr>
<tr>
<td>8</td>
<td>4.64</td>
<td>0.12</td>
<td>0.08</td>
</tr>
<tr>
<td>9</td>
<td>5.05</td>
<td>1.19</td>
<td>1.49</td>
</tr>
</tbody>
</table>

Mean ± SD

<table>
<thead>
<tr>
<th>Microsphere flow (mean ± SD)</th>
<th>Stenotic kidney</th>
<th>Contralateral kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.37 ± 1.48</td>
<td>0.86 ± 0.62*</td>
<td>0.64 ± 0.57</td>
</tr>
<tr>
<td>3.84 ± 0.95</td>
<td>3.24 ± 1.13</td>
<td>4.08 ± 0.94*</td>
</tr>
</tbody>
</table>

* *p* < 0.05, compared with control values;  †*p* < 0.05, compared with values during stenosis.
cally significant (p = 0.59). A slight but significant increase in renal blood flow was observed in the contralateral kidney following captopril administration.

Discussion

In the present study, the technique of continuous intravenous infusion of $^{82}$Rb and PET imaging was applied to measure sequential changes in blood flow to the kidneys. These studies demonstrated a minimal reduction in perfusion to the contralateral kidney during renal artery stenosis with improvement after captopril infusion. On the other hand, flow to the stenotic kidney did not improve after captopril infusion and was often decreased.

Several investigators have described effects of renal artery stenosis on the blood flow to the stenotic and contralateral kidneys. A recent study by Anderson et al. showed that unilateral renal artery stenosis caused vasoconstriction and decreased perfusion to the contralateral kidney (due to angiotensin II), despite the increase in systemic arterial pressure. The reasons for these changes are complex. In the nonstenosed kidney, angiotensin II infusion causes an increase in preglomerular and efferent arteriolar resistance, while in the stenosed kidney, as renal perfusion pressure is reduced by progressive occlusion of a renal artery, renal blood flow and glomerular filtration rate are sustained by an angiotensin II–dependent efferent arteriolar vasodilatation and an increase in systemic blood pressure. When the level of angiotensin II is reduced by captopril, these reactions are reversed. In the present study, captopril infusion resulted in an increase in perfusion to the contralateral kidney (>10%) in five animals. The stenosed kidney, on the other hand, faced with a decrease in perfusion pressure, also loses the angiotensin II–dependent vasoconstriction of the efferent arteriole. Consequently, renal perfusion and glomerular filtration may decrease following administration of the drug. Six of the nine dogs responded to captopril with a decrease in renal perfusion of less than 10%, while increased perfusion was observed in three. The reason for the variation in response is unclear. Although we did not measure the glomerular filtration rate, PET can also be employed to measure this parameter, using generator-produced $^{68}$Ga–pertechnetic acid (DTPA) and sequential imaging to measure clearance. The combination of perfusion and glomerular filtration rate measurements can provide the information required to characterize the influence of captopril on renal function.

These data raise an important clinical caution. In patients with unilateral renal artery stenosis with an intact contralateral kidney, changes in total renal function seem to be minimal during converting enzyme inhibition, possibly due to a compensatory increase in perfusion and filtration in the contralateral kidney. In the absence of a healthy kidney, such as bilateral renal artery stenosis or stenosis involving a solitary kidney, there is often a decrease in renal blood flow and glomerular filtration rate, and consequently, progressive azotemia. Thus, captopril should be administered cautiously to patients with low renal perfusion pressure, since an intact renin-angiotensin system is crucial to autoregulation of glomerular filtration rate and captopril may destroy the integrity of the system.

In our study, both PET and microsphere techniques demonstrated a decrease in renal blood flow to the stenotic kidney after captopril infusion in six of the nine dogs, although changes in renal blood flow for the group of animals were not statistically significant. Thus, it may be important to assess the changes in individual renal perfusion sequentially when captopril is used.

Although the long-lived rubidium-86 (half-life, 19 days) has been used experimentally for the estimation of renal blood flow, the long half-life is not well suited to making serial measurements. The kinetics of $^{82}$Rb are similar to those of $^{85}$Rb, but the half-life of 75 seconds makes this tracer suitable for repetitive in vivo imaging with the positron camera. PET with $^{82}$Rb has several advantages for serial assessment of renal perfusion. This tracer can be eluted from the generator every 10 minutes. In addition, the short half-life of $^{82}$Rb permits repetitive studies of renal perfusion during various physiological and pharmacological interventions. Previous studies demonstrated a good correlation of $^{82}$Rb estimated flow with microsphere-determined renal blood flow. Moreover, high resolution tomographic images provide a direct visual means for assessing regional perfusion in the kidneys. The technique is straightforward to perform, requiring only an intravenous infusion and PET images if relative renal perfusion is desired. Absolute quantitation of renal perfusion, however, requires arterial blood samples. The PET imaging technique does not have adequate resolution to provide accurate measurements of cortical and medullary flow, however, because the cortical thickness and camera resolution are similar, causing an underestimation of cortical perfusion. As a result, only overall renal perfusion was computed. We applied continuous infusion of the tracer and a steady state model for assessment of renal perfusion because the equilibrium method provides high quality images and is technically less demanding than the bolus technique, which requires rapid tomographic imaging and blood sampling.

Our previous work with $^{82}$Rb in this model of renal artery stenosis demonstrated that the relationship between the measured ratio $C/C_0$ and renal blood flow can be described by Equation 2, with two constant parameters. A literal association of $E$ and $p$ with the unidirectional extraction fraction and equilibrium partition coefficient of $^{82}$Rb should be made with caution, however. It is well known from the work of Crone that the unidirectional extraction fraction depends on capillary bed geometry, permeability, and blood flow, with $E$ tending to fall as flow increases. To measure this extraction fraction, rapid dynamic sampling either by probe or a fast PET camera may be needed. Mullani et al. and Budinger et al. have observed the expected fall in extraction fraction at high flow values in the myocardium. Renal blood
flow, however, is well controlled by autoregulation and does not increase remarkably above baseline. Therefore, the decrease in extraction fraction at high flows is less likely to be a problem.

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