Angiotensin Converting Enzyme Inhibition Improves Diagnostic Procedures for Renovascular Hypertension in Dogs

GEERT-JAN JONKER, DICK DE ZEEUW, ROEL M. HUISMAN, D. BERT PIERS, HENK BEEKHUIS, AND GJALT K. VAN DER HEM

SUMMARY In renovascular hypertension adaptive mechanisms in the poststenotic kidney are a probable cause of the 20 to 25% false-negative findings during rapid sequence urography or [123I]iodohippurate renography. We blocked the renin-angiotensin system in an effort to increase the yield of these diagnostic procedures. Chronically instrumented, salt-depleted conscious dogs were used in which a light (n = 5), moderate (n = 4), or severe (n = 2) renal artery stenosis was induced. Before stenosis 10 of the dogs showed no left-right differences with either diagnostic procedure, and angiotensin converting enzyme (ACE) inhibition did not change this result. Two to 3 weeks after induction of a renal artery stenosis, all dogs showed signs of renovascular hypertension. However, only 50% of the renograms and 22% of the urograms showed differences between the two kidneys indicative of the presence of stenosis. After ACE inhibition, all previously negative test results became positive (abnormal) and previously existing left-right differences became more evident. Electromagnetically measured renal blood flow on the stenotic side did not change during ACE inhibition (146 ± 13 vs 145 ± 21 ml/min), whereas contralateral blood flow showed a distinct increase (207 ± 18 vs 282 ± 20 ml/min, p < 0.01). In conclusion, ACE inhibition markedly improves the sensitivity of rapid sequence urography and hippurate renography in the diagnosis of renovascular hypertension in the two-kidney, one clip Goldblatt hypertensive dog. The effects of ACE inhibition on the handling of the different tracers do not appear to be related to its effects on renal blood flow or systemic blood pressure. (Hypertension 12: 411-419, 1988)

KEY WORDS • renovascular hypertension • dog • hippurate renography • rapid sequence urography • renal blood flow • renin-angiotensin system • enalaprilat (MK 422)

RENOVASCULAR hypertension is the commonest form of curable hypertension. Identification of patients suffering from renovascular hypertension has become even more important since the introduction of methods for nonsurgical repair of renal artery stenosis. However, commonly used noninvasive screening tests for renovascular hypertension, such as hippurate renography, rapid sequence intravenous urography (IVU), and even renal digital subtraction angiography, fail to detect a substantial part of these patients. A recent review of the literature reported overall sensitivities for renography and IVU of 74% and for renal digital subtraction angiography of 88%. Specificities of these tests were 77, 86, and 89%, respectively. However, the figures for digital subtraction angiography were overestimated because uninterpretable tests were not included.

An asymmetrical (i.e., positive) result in renography and IVU is based on a change in the handling of the tracer by the poststenotic kidney. However, adaptive mechanisms may prevent loss of renal blood flow and glomerular filtration when renal perfusion pressure is decreased. The renin-angiotensin system is believed to play a critical role in these adaptive mechanisms. Therefore, inhibition of this system by angiotensin converting enzyme (ACE) inhibitors could enhance the sensitivity of the diagnostic procedure for renovascular hypertension. This hypothesis was recently supported by animal as well as human experiments. The few animal studies that have been reported were
performed under anesthesia in a canine model with an acute stenosis, which is a quite different situation from that of a conscious patient with chronic renal artery stenosis. The studies in patients involved case histories or small groups; only one larger study has been published. The reason for this limited experience may be that it is difficult to study a homogeneous patient group with respect to degree of renal artery stenosis, duration of the renovascular hypertension, use of antihypertensive drugs, and involvement of other parts of the circulatory system. Moreover, whether the renal artery stenosis is causing the hypertension can only be ascertained retrospectively. These animal and human data were obtained using renography; no studies using IVU have been reported to date.

Therefore, we performed experiments in the conscious, chronically instrumented, two-kidney, one clip Goldblatt hypertensive dog to answer the following questions: Does short-term ACE inhibition improve the sensitivity of IVU and renography as screening methods for the diagnosis of renal artery stenosis? Are the effects of ACE inhibition on blood pressure and renal hemodynamics related to the outcome of the screening tests?

Materials and Methods

Eleven male mongrel dogs weighing 20 to 30 kg were used in this study. They were preselected by angiography of the renal arteries to exclude preexisting renal artery stenosis, double renal arteries, or short artery stems with insufficient length for instrumentation purposes. Before surgical preparation the dogs were allowed to become accustomed to the experimental situation. They were maintained on a salt-restricted diet of less than 1 g of salt per day (h/d Prescription Diet, Hill’s Pet Products, Topeka, KS, USA).

Instrumentation

The dogs were instrumented in two steps under general anesthesia (induction with thiopentone, maintenance anesthesia with nitrous oxide and halothane [Fluothane]). In the first step Tygon tubing (Norton, Akron, OH, USA) catheters were placed in the descending aorta (outside diameter, 2.4 mm; inside diameter, 0.8 mm) and in the right atrium (outside diameter, 3.2 mm; inside diameter, 1.6 mm) through the omocervical artery and vein, respectively. Two weeks later, the right and left renal arteries were exposed retroperitoneally through flank incisions. The arteries were dissected free from surrounding tissue, and electromagnetic blood flow probes (Skalar Medical), and blood pressure was measured by connecting the arterial catheter to a Statham P231D pressure transducer (Gould-Statham Instruments, Hato Rey, Puerto Rico). The RBF and mean blood pressure signals were recorded on paper. At the end of each experiment the RBF zero reference value was obtained by injection of 10 mg of angiotensin II through the arterial catheter in the aorta. With this pharmacological method a reliable zero blood flow can be assessed, as previously reported.

The following experimental protocol was accomplished both before and 2 to 3 weeks after induction of renal artery stenosis of various degrees: IVU and renography were performed before and during short-term ACE inhibition, which was obtained by intravenous injection of 10 μg of angiotensin II through the arterial catheter in the aorta. With this pharmacological method a reliable zero blood flow can be assessed, as previously reported.

Induction of Renal Artery Stenosis

After completion of the first series of tests, renal artery stenosis was induced. The degree of stenosis was determined by the acute reduction of ipsilateral RBF to either approximately 25 (light), 50 (moderate), or 75% (severe) of the prestenosis value. If 1 day later ipsilateral RBF appeared to be substantially higher, the constriction was increased. Therefore, the constritor remained untouched. In this way long-term, stable RBF reductions were obtained. Thus, three subgroups of dogs were

Experimental Design

Experiments were performed before and after induction of renal artery stenosis. During the experiments, the dog was hanging quietly in a hammock and both left and right renal blood flow (RBF) and mean arterial pressure were recorded. The electromagnetic blood flow probes were connected to flowmeters (Skalar Medical), and blood pressure was measured by connecting the arterial catheter to a Statham P231D pressure transducer (Gould-Statham Instruments, Hato Rey, Puerto Rico). The RBF and mean blood pressure signals were recorded on paper. At the end of each experiment the RBF zero reference value was obtained by injection of 10 μg of angiotensin II through the arterial catheter in the aorta. With this pharmacological method a reliable zero blood flow can be assessed, as previously reported.

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formed according to degree of stenosis: light \( n = 5 \), moderate \( n = 4 \), and severe \( n = 2 \).

**Rapid Sequence Urography**

The IVU studies without and during ACE inhibition were performed on 2 consecutive days. Food but not water was withdrawn for at least 16 hours before the test. Thirty milliliters of iohexol, 300 mg I/ml, was injected through the venous catheter. Films were obtained using a Siemens Siremobil 2 x-ray apparatus (Amsterdam, The Netherlands) before and 1, 2, 3, 4, 5, and 10 minutes after the contrast injection. The appearance time of contrast material in the pyeloureteral system was determined for the left and right kidney. IVU results were considered abnormal (i.e., indicative of the presence of unilateral renal artery stenosis) if the difference in appearance time between the two kidneys was 1 minute or longer.

**Hippurate Renography**

At least 3 days was allowed between IVU and renographic studies to avoid carryover effects of the ACE inhibition. Before the renography studies, the dogs had free access to water but food was withheld for at least 8 hours. The renographic studies without and during ACE inhibition were performed on the same day: enalaprilat was injected after completion of the first renographic study, and the next study was performed 20 minutes later. A large-field-of-view gamma camera (Siemens Gammasonics LFOV) with a parallel hole collimator was placed above the back of the animal. Following i.v. injection of approximately 2 MBq of \( ^{123}I \)-iiodohippurate (Cygne, Eindhoven, The Netherlands), the data were recorded in 30-second frames with a 64 x 64 resolution during a 20-minute period, using on-line computer data acquisition (Gamma 11, Digital Equipment Corporation, Maynard, MA, USA). Kidney regions of interest were generated on the sum image of the first nine frames. Time-activity curves of both kidneys were plotted after correction for background activity. The outcome of the renographic study was evaluated using the following criteria (Figure 1): 1) the time to peak of the renograms of both kidneys; 2) the time elapsed between peak and decrease to 75% of peak value, in order to assess the excretory function; and 3) the ratio \( R \), as used by McNeil et al.,17 in order to determine asymmetry between the two kidneys. At least 3 days was allowed between IVU and renographic studies. The study outcome was evaluated using the following criteria: 1) the difference in time to peak between right and left kidney \( (\Delta \tau) \), 2) the difference in time elapsed between peak and decrease to 75% of maximum value between left and right kidney \( (\Delta \tau_2) \), 3) the ratio \( R \). To determine \( R \), the first peak was determined \( (A) \), and the ratio between the two kidneys at that time was calculated \( (A/A') \). Then, the point at which the curve with the first peak had returned to 50% was determined \( (B) \), and the ratio between the two kidneys at that time was calculated \( (B/B') \). Finally, \( R \) was calculated as \( (B/B')(A/A') \) or as \( (A/A')(B/B') \), such that \( 0 < R < 1 \).

**Statistical Analysis**

Data are presented as means ± SEM for the total group and as means (ranges) for the three subgroups. The Wilcoxon test for paired data was used to compare the measurements before and after induction of the renal artery constriction and to evaluate the effect of ACE inhibition. The effect of ACE inhibition on the sensitivity of the diagnostic tests was analyzed with Fisher's exact test. Statistical significance was assumed at a 5% level.

**Results**

**Prestenosis Experiments**

The experiments prior to induction of renal artery stenosis were performed for two reasons: 1) to exclude influences of the surgical procedures on the outcome of renographic and IVU studies and 2) to test the specificity of these tests. Moreover, blood pressure and RBF were measured to establish a baseline value before induction of unilateral renal artery stenosis.

In this phase of the study mean arterial pressure was 119 ± 4 mm Hg. Plasma renin activity averaged 1.2 ± 0.1 nmol angiotensin I (Ang I)/L/hr, which was approximately six times as high as the values before the salt-restricted diet was started, indicating the stimulating effect of the salt depletion on the renin-angiotensin system. As expected,18 left RBF appeared to be consistently greater than right RBF in each dog: The mean values were 247 ± 18 and 200 ± 15 ml/min \( (p < 0.01) \), respectively. The IVU studies did not reveal differences between the left and right kidneys. Although nine out of 10
renograms did not show left-right differences (typical example shown in Figure 2), one of the renograms was abnormal according to our criteria (Dog 9). However, this dog did not show any signs of renal artery stenosis (mean arterial pressure, 118 mm Hg; RBF, 270 ml/min; plasma renin activity, 0.9 nmol Ang I/L/hr). Besides, the IVU of this dog was quite normal.

ACE inhibition decreased mean arterial pressure from 119 ± 4 to 110 ± 3 mm Hg \( (p < 0.001) \), whereas plasma renin activity rose from 1.2 ± 0.1 to 2.3 ± 0.6 nmol Ang I/L/hr (NS). The effect of ACE inhibition was similar on left and right RBF: Left RBF rose 30 ± 5% to 321 ± 33 ml/min \( (p < 0.02) \), and right RBF rose 27 ± 3% to 253 ± 22 ml/min \( (p < 0.02) \). Despite the alterations in blood pressure and RBF, ACE inhibition had no effect on renography (see Figure 2) or IVU. What is more important, ACE inhibition did not induce differences between the left and right kidneys on these tests in any of the dogs. Interestingly, the asymmetry of the previously mentioned abnormal renogram disappeared under ACE inhibition.

Experiments During Unilateral Renal Artery Constriction

The effects of induction of unilateral renal artery stenosis on ipsilateral and contralateral RBF can be seen in Table 1. Ipsilateral RBF decreased in all three groups: In the light stenosis group there was a 20% reduction in RBF, in the moderate stenosis group the reduction was 42%, and in the severe stenosis group, the reduction was 73%. Contralateral blood flow did not change.

Unilateral renal artery constriction led to an increase in mean arterial pressure from 119 ± 4 to 138 ± 5 mm Hg \( (p < 0.001) \) in the total group. Thus, in this model renal artery stenosis caused a significant rise in blood pressure despite the salt-restricted diet. A rise in blood pressure was found consistently in each dog. Moreover, the rise in mean arterial pressure was related to the degree of stenosis: Blood pressure increased by 13 (4-27) mm Hg in the light stenosis group, by 17 (9-22) mm Hg in the moderate stenosis group, and by 27 (15-38) mm Hg in the severe stenosis group.

**Table 1. Effects of ACE Inhibition on Blood Pressure, Renal Blood Flow, and Plasma Renin Activity in Dogs with Unilateral Renal Artery Stenosis**

<table>
<thead>
<tr>
<th>Degree of stenosis</th>
<th>Before stenosis - ACEI</th>
<th>Stenosis + ACEI</th>
<th>Before stenosis - ACEI</th>
<th>Stenosis + ACEI</th>
<th>Before stenosis - ACEI</th>
<th>Stenosis + ACEI</th>
<th>Before stenosis - ACEI</th>
<th>Stenosis + ACEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light (n = 5)</td>
<td>126 ± 143</td>
<td>123</td>
<td>212 ± 170</td>
<td>203</td>
<td>168 ± 180</td>
<td>251</td>
<td>1.0 ± 1.3</td>
<td>2.6 ± 13.2</td>
</tr>
<tr>
<td>Moderate (n = 4)</td>
<td>111 ± 138</td>
<td>125 ± 165</td>
<td>105 ± 140</td>
<td>170 ± 245</td>
<td>166 ± 235</td>
<td>200 ± 300</td>
<td>0.8 ± 1.0</td>
<td>1.0 ± 5.5</td>
</tr>
<tr>
<td>Severe (n = 2)</td>
<td>97 ± 118</td>
<td>115 ± 140</td>
<td>85 ± 125</td>
<td>63 ± 180</td>
<td>170 ± 300</td>
<td>290 ± 400</td>
<td>0.9 ± 2.0</td>
<td>2.4 ± 5.3</td>
</tr>
<tr>
<td>Total group</td>
<td>119 ± 4</td>
<td>138 ± 5</td>
<td>119 ± 62</td>
<td>145 ± 21</td>
<td>206 ± 15</td>
<td>282 ± 204</td>
<td>1.3 ± 0.1</td>
<td>19.2 ± 2.0</td>
</tr>
</tbody>
</table>

Values for the subgroups are means (with ranges shown below) and for the total group are means ± SEM. MAP = mean arterial pressure; iRBF = ipsilateral renal blood flow; cRBF = contralateral renal blood flow; PRA = plasma renin activity; ACEI = ACE inhibition.

\*n = 3 and \( t_n = 1 \) because two contralateral blood flow probes failed.

\( t_p < 0.01 \), compared with stenosis - ACEI values.
TABLE 2. Effects of ACE Inhibition on Characteristics of Renography in 10 Dogs Before and After Induction of Unilateral Renal Artery Stenosis

<table>
<thead>
<tr>
<th>Dog no</th>
<th>−ACEI</th>
<th>+ACEI</th>
<th>Outcome</th>
<th>−ACEI</th>
<th>+ACEI</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔT&lt;sub&gt;p&lt;/sub&gt; (min)</td>
<td>ΔT&lt;sub&gt;75&lt;/sub&gt; (min)</td>
<td>R</td>
<td></td>
<td>ΔT&lt;sub&gt;p&lt;/sub&gt; (min)</td>
<td>ΔT&lt;sub&gt;75&lt;/sub&gt; (min)</td>
</tr>
<tr>
<td>Prestenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
<td>0.98</td>
<td>−</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0.82</td>
<td>−</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0.93</td>
<td>−</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.97</td>
<td>−</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0.95</td>
<td>−</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0.83</td>
<td>−</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0.88</td>
<td>−</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>1.5</td>
<td>4</td>
<td>0.49</td>
<td>+</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0.99</td>
<td>−</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>0.5</td>
<td>0</td>
<td>0.81</td>
<td>−</td>
<td>0</td>
<td>0.5</td>
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<tr>
<td>Poststenosis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Light stenosis</td>
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<tr>
<td>1</td>
<td>0</td>
<td>0.5</td>
<td>0.85</td>
<td>−</td>
<td>&gt;17</td>
<td>&gt;16</td>
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<tr>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0.57</td>
<td>+</td>
<td>&gt;17</td>
<td>&gt;16</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>1.5</td>
<td>0.74</td>
<td>−</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0.93</td>
<td>−</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0.94</td>
<td>−</td>
<td>7</td>
<td>13.5</td>
</tr>
<tr>
<td>Moderate stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0.76</td>
<td>−</td>
<td>&gt;12</td>
<td>&gt;16</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>2</td>
<td>0.96</td>
<td>+</td>
<td>&gt;12</td>
<td>&gt;8</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>3</td>
<td>0.75</td>
<td>+</td>
<td>&gt;15</td>
<td>&gt;13</td>
</tr>
<tr>
<td>Severe stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>5.5</td>
<td>12.5</td>
<td>0.26</td>
<td>+</td>
<td>&gt;17</td>
<td>&gt;15</td>
</tr>
<tr>
<td>11</td>
<td>2.5</td>
<td>2</td>
<td>0.62</td>
<td>+</td>
<td>&gt;17</td>
<td>&gt;16</td>
</tr>
</tbody>
</table>

ACEI = ACE inhibition; ΔT<sub>p</sub> = difference in time to peak between left and right kidneys; ΔT<sub>75</sub> = difference in time elapsed between peak and return to 75% of peak value between both kidneys; R = ratio (see Materials and Methods). Outcome of renographic study was considered normal (−) or abnormal (+).

After stenosis induction plasma renin activity rose from 1.3 ± 0.1 to 3.4 ± 0.5 nmol Ang I/L/hr (p < 0.001) in the total group. The rise was 1.6 (0.2–4.2) in the light stenosis group, 2.1 (0.5–3.8) in the moderate group, and 3.8 (2.1–5.5) nmol Ang I/L/hr in the severe stenosis group. There was a significant relation between the increase in plasma renin activity and the increase in mean arterial pressure (r = 0.74, p < 0.05).

The presence of the renal artery stenosis led to differences between the ipsilateral and contralateral kidney in only 50% of the renographic studies (Table 2) and in only 22% of the IVU studies (Table 3). The more severe the degree of renal artery stenosis the more often the tests were abnormal.

The effects of ACE inhibition on hemodynamics and plasma renin activity for the total group and for the three subgroups are presented in Table 1. As can be seen, ACE inhibition caused a significant decrease of mean arterial pressure and a significant increase of contralateral RBF, whereas ipsilateral RBF showed no significant alteration. However, the data of the individual animals showed a remarkable variation in the reaction of the ipsilateral RBF during ACE inhibition (ranging from decreases of 43% to increases of 40%).

ACE inhibition had remarkable effects on the outcome of renography and rapid sequence IVU in all dogs. Tables 2 and 3 show that all tests that were normal before ACE inhibition now became abnormal, but also that the differences between the two kidneys on the previously abnormal tests became much larger. The effect of ACE inhibition on the presence of differences between the two kidneys was significant (p < 0.002).

In four dogs the studies were repeated 6 weeks after constriction. In the other seven dogs the later studies could not be done because of technical failures, such as clogging of catheters, failure of the RBF probes, and occlusion of the renal artery in one of the dogs with severe stenosis. The values of mean arterial pressure and ipsilateral and contralateral RBF were similar compared with the measurements at 2 to 3 weeks. The effects of ACE inhibition on these variables 6 weeks after constriction were comparable to those seen 2 to 3 weeks after constriction. Similarly, the sensitivity of both IVU and renography was identical at 2 to 3 and at 6 weeks, before as well as during ACE inhibition.

Some typical examples of the effect of ACE inhibition on renography and IVU are given in Figures 3 and 4. Figure 3 depicts the time-activity curves of a dog with light renal artery stenosis. Before the ACE inhibition both kidneys show the same configuration of the time-activity curves with respect to time to peak and excretion of the tracer material. However, during ACE inhibition striking differences between the poststenotic and contralateral kidney appear. The configuration of the time-activity curve of the contralateral kidney is similar.
TABLE 3. Effect of ACE Inhibition on Rapid Sequence Urography in Nine Dogs with Unilateral Renal Artery Stenosis

<table>
<thead>
<tr>
<th>Dog no</th>
<th>Light stenosis</th>
<th>Moderate stenosis</th>
<th>Severe stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔTm (min)</td>
<td>Outcome</td>
<td>ΔTm (min)</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>—</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>—</td>
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</tr>
<tr>
<td>3</td>
<td>0</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>+</td>
<td>&gt;8</td>
</tr>
<tr>
<td>5</td>
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<td>—</td>
<td>1</td>
</tr>
<tr>
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<td>—</td>
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ACEI = ACE inhibition; ΔTm = difference in appearance time of contrast material between left and right kidneys. Outcome of IVU study was considered normal (−) or abnormal (+).

The observed effects of ACE inhibition on the outcome of the diagnostic tests were not correlated with either the alterations of ipsilateral RBF (r = 0.18 and r = 0.31 for renography and IVU, respectively) or the changes in blood pressure (r = 0.27 and r = 0.33 for renography and IVU, respectively).

Discussion

The present study shows that short-term ACE inhibition markedly improves the sensitivity of hippurate renography and rapid sequence IVU for the detection of renal artery stenosis in the conscious, salt-depleted, two-kidney, one clip Goldblatt hypertensive dog. In fact, a 100% sensitivity of these two tests was obtained during short-term ACE inhibition. In that situation, all the false-negative (i.e., showing no left-right differences) tests became clearly positive (abnormal) and the true-positive tests showed remarkable alterations, indicating further deterioration of the poststenotic kidney function. This improvement of sensitivity appears to be independent of the effects of the ACE inhibition on ipsilateral RBF or systemic blood pressure (or both).

The main emphasis in our study was on a subgroup with light but hemodynamically functional renal artery stenosis, since this group would be most likely to yield false-negative results. A stenosis was judged to be hemodynamically significant if it caused a reduction of RBF plus a rise in blood pressure; this effect occurred in all of our dogs. Moreover, all dogs showed rises in plasma renin activity after stenosis of the renal artery. Yet only 50% of the renographic studies and 20% of the IVU studies were abnormal in the situation without ACE inhibition. These percentages are lower than those reported from large clinical studies in which the sensitivity of renography has been reported to vary from 70 to 91% and that of rapid sequence IVU from 58 to 93%. The main cause of this difference probably is the predominance of patients with severe stenosis in the clinical studies, whereas...
we studied dogs with mostly light and moderate stenoses. For instance, in one large study more than half the patients had luminal diameter reductions of more than 80%. Furthermore, comparison of the present study with clinical studies is rather difficult, since we defined the degree of stenosis by the amount of RBF reduction on the stenosed side, whereas an anatomical classification is generally used in clinical studies.

An objection that might be raised against our study is the fact that the dogs were studied in a sodium-depleted state. We feel that the design of the ultimate test in humans should include a previously instituted moderately sodium-restricted diet. This diet is likely to enhance the systemic and renal effects of ACE inhibition and thereby probably will give optimal results. Chances of systemic hypotension are minimal in this situation with the use of enalaprilat as the ACE inhibitor, as we have previously demonstrated in hypertensive patients. Still, the possibility remains that the addition of an ACE inhibitor could cause an improvement in the diagnostic yield of screening procedures for renovascular hypertension, even if the renin-angiotensin system is less activated. This possibility has to be further investigated.

The presented data concerning renography correspond well with recently published reports about renovascular hypertensive patients studied with radionuclide techniques, which also demonstrated clear improvement of the sensitivity of various tests during ACE inhibition. However, it is difficult to assess the degree of stenosis and the duration of the renovascular hypertension in patients. In addition, use of drugs and other (cardiovascular) diseases may interfere with the tests when patients are studied. The mentioned studies provide little information about these points. In two studies medications were withdrawn only 24 hours before the tests. In the largest series of patients the sensitivity of the renograms during ACE inhibition did not reach 100%, partly because of the chosen criteria, but also because of a small kidney in one patient and stenosis in a segmental renal artery in another. In the present study using a canine model these problems were avoided. Similar experiments to ours in a canine model have been reported before, and the results of those studies are comparable with our data. However, in those studies anesthetized dogs with acute renal artery stenosis were used. The anesthesia and the model (acute stenosis) that were used may have made the renal function more dependent on the renin-angiotensin system than may be the case in many renovascular hypertensive patients. To more closely mimic the study design that could be used in hyper-
tensive patients, we performed experiments in conscious dogs with a more long-term renal artery stenosis (2–3 and 6 weeks), but they were maintained on a salt-restricted diet to stress the renin-angiotensin system.

The observed marked effect of ACE inhibition on the outcome of the IVU studies (i.e., a delay in the appearance time of contrast medium on the affected side) has, as far as we know, not been described before. Unfortunately, respiration and other movements of the conscious dog forced us to use short exposure times, which caused low contrast on the x-ray films. Therefore, the other main signs of renal artery stenosis on urography, such as differences in kidney length and late hyperconcentration on the involved side, could not be determined. However, the difference in the appearance time of contrast medium in the pyeloureteral system between the left and right kidney, which we used as a criterion, was the most sensitive feature of IVU in renovascular hypertensive patients. Moreover, this very feature reached 100% sensitivity during ACE inhibition in our model. Therefore, our data suggest that this test may be used as a highly sensitive screening method for renal artery stenosis during ACE inhibition.

The mechanism by which ACE inhibition causes the changes in the diagnostic tests for unilateral renal artery stenosis is still uncertain. The present study shows that changes in neither RBF nor systemic blood pressure play a critical role. A possible causative role for the decrease in blood pressure caused by ACE inhibition was made unlikely by a former study in which a blood pressure decrease obtained with nitroprusside did not cause changes in radionuclide studies, whereas a similar decrease with captopril did. The well-known decrease in poststenotic glomerular filtration rate may be responsible for the decreased excretion of the different trace materials. Alternatively, a fall in urine flow on the affected side may play a role. Unfortunately, the present model did not allow separate measurement of the glomerular filtration rate and the urine flow of the ipsilateral and contralateral kidney. Indeed, further studies to investigate these effects are being initiated at our laboratory.

The present and other studies offer promise for improvement of the diagnostic procedure for renal artery stenosis because of the simplicity of the noninvasive techniques. From our results we cannot conclude that any one of these methods is the best. Each method has its own advantages. Radioisotope studies during ACE inhibition are highly sensitive, cause low radiation exposures, and are easily performed in an outpatient setting with little discomfort for the patient. Such a test may be preferable to rapid sequence urography or digital subtraction angiography as a screening method for renovascular hypertension, but it may also be useful for follow-up of patients treated by operation or percutaneous transluminal renal angioplasty and in the diagnosis of hypertension in renal transplantation patients. On the other hand, radiographic studies supply valuable additional anatomical information about the kidney and urinary tract that may be relevant in differentiating between the causes of secondary forms of hypertension. The present study indicates that ACE inhibition makes these radiographic studies as sensitive as radioisotope studies.

This study showed a clear effect of ACE inhibition on the sensitivity of renography and IVU in this animal model. However, the effect on specificity is much less clear. Despite the relatively small number of experiments, we found one abnormal renogram in a dog in which there were no indications of the presence of renal artery stenosis. We considered this renogram false-positive. Remarkably, the asymmetry of this false-positive renogram disappeared under ACE inhibition. This observation may be of importance, since the specificity is reported to be approximately 77% for renography and 86% for IVU. Therefore, further research in humans is necessary to evaluate these tests, especially with regard to their specificity.

Acknowledgments

We are indebted to Peter Veldkamp, Arnold Schnmer, and Klaas Bel for their technical assistance. We thank Wiebe Zemstra for his skillful construction of the constrictor.

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_Hypertension_. 1988;12:411-419
doi: 10.1161/01.HYP.12.4.411

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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