Hemodynamic and Afferent Renal Nerve Responses to Intrarenal Adenosine in the Dog

RICHARD E. KATHOLI, M.D., GILBERT R. HAGEMAN, PH.D., PATRICK L. WHITLOW, M.D., AND W. THOMAS WOODS, PH.D.

SUMMARY We have found that renal artery adenosine infusion produces hypertension associated with increased activity of the sympathetic nervous system in a uninephrectomized conscious dog with intact renal nerves. The objectives of this study were to: 1) compare the hemodynamic responses to renal artery adenosine infusion in the conscious and α-chloralose-anesthetized dog with both kidneys intact; and 2) to correlate the hemodynamic and afferent renal nerve responses to renal artery and renal pelvic adenosine administration. Infusion of adenosine into the renal artery in the conscious animal produced a significant 22 mm Hg rise in mean arterial pressure, while infusion of adenosine into the renal artery in the α-chloralose-anesthetized dog produced a significant 11 mm Hg rise. Nerve traffic studies revealed that an increase in afferent renal nerve activity occurred 80 to 150 seconds after initiation of renal artery adenosine infusion. In contrast, an increase in afferent renal nerve activity was observed within 15 to 20 seconds after initiation of renal pelvic adenosine administration. Despite the difference in onset of afferent renal nerve activity, the degree of hemodynamic responses with renal pelvic or renal artery adenosine administration were the same. The data indicate that: 1) the response to renal artery infusion of adenosine is attenuated by α-chloralose anesthesia; 2) intrarenal adenosine produces increased afferent renal nerve activity; and 3) renal pelvic adenosine infusion produces an earlier but identical hemodynamic response as renal artery adenosine infusion. These observations extend our previous work, suggesting that intrarenal adenosine produces hypertension by activating the sympathetic nervous system via the afferent renal nerves. These observations also suggest that adenosine-sensitive nerve endings are located within or near the renal pelvis.

KEY WORDS • sympathetic nervous system • α-chloralose • hypertension • renal artery adenosine administration • renal pelvic adenosine administration

Evidence from many laboratories indicates that the afferent renal nerves participate in renorenal and cardiovascular regulation. We have reported studies that suggest that the afferent renal nerves from the clipped kidney enhance sympathetic nervous system activity in the one-kidney, one clip, and the two-kidney, one clip Goldblatt hypertensive rat. Because adenosine is released during renal ischemia and adenosine has been shown to increase the frequency of afferent renal nerve signals in the rat, we hypothesized that intrarenal adenosine might produce hypertension by activating the sympathetic nervous system via the afferent renal nerves. We have found that renal artery adenosine infusion in the chronically instrumented uninephrectomized sodium-replete conscious dog produced a 20 mm Hg mean arterial pressure rise. The elevation in mean arterial pressure during renal artery adenosine infusion was associated with increased heart rate, pulse pressure, cardiac output, and plasma norepinephrine. Ganglionic blockade during renal artery adenosine infusion resulted in a significantly greater decrease in arterial pressure compared to control response. After renal denervation, renal artery adenosine infusion resulted in no change in arterial pressure or plasma norepinephrine. These data thus suggested that intrarenal adenosine produces hypertension associated with increased activity of the sympathetic nervous system in a conscious one-kidney dog with intact renal nerves.

Our next major aim has been to study the afferent limb of the neural response to intrarenal adenosine using neurophysiologic techniques. Since an acute unilateral nephrectomy per se alters hemodynamics, the neurophysiologic studies were planned using the dog with both kidneys intact. This approach introduced two factors that differed from our previous experiments: the effect of anesthesia and study of the
response to intrarenal adenosine in a two-kidney animal. Thus, the objectives of this study were to: 1) compare the hemodynamic responses to renal artery adenosine infusion in the conscious and α-chloralose-anesthetized dog with both kidneys intact; and 2) study the afferent renal nerve response to intrarenal adenosine administration.

Methods

Conscious Animal Preparation

Five adult mongrel dogs selected for their calm, gentle nature were used for these experiments (body weight, 22.2 ± 0.8 kg). At surgery, the animals were anesthetized with sodium pentobarbital (30 mg/kg i.v.), intubated, and supported with mechanical ventilation. Under sterile conditions, a celiotomy was performed. To avoid damage to the renal nerves, a microline catheter was inserted through the aortic wall by means of a steel guidewire and positioned in the left renal artery. An electromagnetic flow probe (Gould Statham Company, Oxnard, California, 2.5 to 3.5 mm in diameter) was placed on the right renal artery for measurement of renal blood flow. Tygon catheters were inserted into the inferior vena cava via the femoral vein for intravenous infusions and into the aorta via the femoral artery for measurement of arterial pressure and blood sampling. A No. 7 Swan Ganz thermodilution catheter was also inserted through the femoral vein into the pulmonary artery for measurement of cardiac output. The three catheters and the flow probe electrodes were exteriorized, and the celiotomy was closed. A cotton jacket was placed around the dog to protect the catheters. The animals were maintained on a standard diet (Hills Hospital Diet, Topeka, Kansas) of approximately 3 mEq sodium/kg/day. Water was available ad libitum.

Measurements

Blood pressure was measured from the indwelling aortic catheter with a P23 Id Statham pressure transducer connected to a Hewlett Packard polygraph. Arterial pressure, heart rate, and right renal blood flow were measured continuously and analyzed on line using a Digital Equipment Corporation LSI-II computer. Cardiac output was measured by injection of 5 ml of iced 5% dextrose in water into the atrial port of the Swan-Ganz catheter (Thermodilution technique — Edwards Laboratory).

Experimental Protocol of Conscious Animals

During recovery from surgery, the animals were taught to stand quietly in the sling. An animal was not considered trained until it could stand quietly for at least a 2-hour period while receiving a renal artery infusion of normal saline (1 ml/min), with the mean arterial pressure and mean heart rate remaining stable at less than 105 mm Hg and less than 90 bpm respectively.

A dose/response curve for renal artery adenosine and arterial pressure was constructed for each animal. After 30 minutes of renal artery saline infusion (1 ml/min), 15-minute renal artery adenosine infusions of 0.6, 1.0, 2.0, and 3.0 μg/kg/min were given using a Harvard pump. The lowest dose of adenosine that elevated mean arterial pressure by 20 mm Hg was subsequently infused for 60 minutes.

Anesthetized Animal Preparation

Animals were studied under α-chloralose (100 mg/kg i.v.) anesthesia. Adult mongrel dogs maintained on a standard kennel diet of approximately 3 mEq sodium/kg/day were used. Respiration was maintained through a cuffed endotracheal tube and a Harvard positive-pressure ventilator to maintain the arterial pH between 7.35 and 7.45. A standard limb lead II electrocardiogram was recorded. A median sternotomy and celiotomy were performed. Electromagnetic flow probes (Gould Statham, 14–16 and 2.5–3.5 mm diameter) were placed around the aorta 2 cm above the aortic valve for measurement of cardiac output and around the right renal artery for determination of renal blood flow. A catheter was placed above the aortic valve via the internal mammary artery for measurement of central aortic pressure. A perfumed catheter was placed in the left renal artery for adenosine infusion. A branching, double lumen catheter as described by Recordati et al. was placed in the left ureter. This catheter was constructed and placed so that the pelvic pressure could be monitored, the free flow of urine could continue, and the adenosine could be infused into the renal pelvis with minimal change in pelvic pressure. After the animal was prepared, no measurements were made for at least 60 minutes to allow for stabilization. During the experiments, hemodynamic measurements were recorded continuously and analyzed as described under the conscious dog studies. A dose/response curve for renal artery adenosine and arterial pressure was then constructed for each animal, as described above. Based on pilot observations in the anesthetized dog, the dose of adenosine that elevated mean arterial pressure by 10 mm Hg was selected for subsequent 60-minute infusion. Later in the experiment, denervation of the right (contralateral) kidney was carried out to assess the role of the efferent renal nerves during the response to adenosine. Renal denervation was accomplished by stripping the renal artery adventitia and painting the renal artery with 20% phenol (wt/vol) in ethanol.

Afferent Renal Nerve Recordings

Afferent signals were obtained from left renal nerves by placing the peripheral end of severed nerves in a mineral oil bath. After desheathing and splitting, the multifiber nerve preparation was placed across contiguous stainless steel bipolar electrodes. Nerve signals elicited by adenosine administration into the renal artery or renal pelvis were amplified, filtered (200–1,000 Hz bandpass), and recorded as described previously.8
Nerve Traffic Analysis

At the beginning of each experiment, the threshold of the nerve impulse tachometer was adjusted so that "control" afferent activity (impulse frequency detected at control blood pressure) was between 1 and 15 Hz. "Control" afferent renal nerve activity was analyzed for at least 5 minutes before adenosine administration. The value for "control" afferent activity expressed in the Results section represents the mean frequency of "control" spontaneous activity. The value expressed in the Results section for increased afferent activity during adenosine infusion represents the mean frequency from 30 to 60 seconds after onset.

Statistical Analysis

Results are expressed as means ± SE. Hemodynamic data were analyzed by a randomized block design with standard analysis of variance and Duncan's multiple range test. The mean nerve impulse frequency during control was compared to that during intrarenal adenosine administration in the same dog using the paired Student's t test. Latency of onset of increased nerve activity during renal artery adenosine administration was defined as the latency after onset of the 30-second interval before adenosine administration was begun. The "onset" of increased neural activity to adenosine administration was defined as an increase in recorded impulse frequency that exceeded two standard deviations above the mean "control" spontaneous activity. The value expressed in the Results section for increased afferent activity during adenosine infusion was < 0.05.

Results

Renal Artery Adenosine Infusion in the Conscious Dog

After a 30-minute control period during which normal saline was infused (1 ml/min), left renal artery adenosine infusion (0.92 ± 0.08 μg/kg/min) was begun. Within 3 minutes in each animal there was an increase in heart rate followed by an increase in mean arterial pressure. As shown in table 1, after 20 minutes of left renal artery adenosine infusion there was a 27% increase in heart rate, a 25% increase in cardiac output, and a 23% increase in mean arterial pressure. Right renal blood flow (the kidney contralateral to the kidney in which adenosine was being infused) was unchanged, so that the right renal vascular resistance had increased 20%. Total peripheral vascular resistance did not significantly change. The same hemodynamic changes were noted after 60 minutes of infusion (table 1). The hematocrit of these animals remained constant (41% ± 2%) throughout each experiment.

Renal Artery Adenosine Infusion in the Anesthetized Dog

Hemodynamic Response

Left renal artery adenosine infusion (1.75 ± 0.13 μg/kg/min) produced an increase in mean arterial pressure within 5 minutes in each animal. The dose of adenosine used in the α-chloralose anesthetized animals (n = 8) was significantly greater than that used in the conscious animals (n = 5). As shown in table 2, there was a 14% increase in cardiac output and a 9% increase in mean arterial pressure with no change in heart rate after 20 minutes of left renal artery adenosine infusion. The changes in arterial pressure and cardiac output in response to adenosine in the anesthetized dogs were significantly less (p < 0.05) than those seen in the conscious animals. Right renal blood flow was unchanged such that right renal vascular resistance increased 16%. Total peripheral vascular resistance did not significantly change. Similar hemodynamic changes were noted after 60 minutes of infusion (table 2). The hematocrit of these animals remained constant (40% ± 2%) throughout each experiment. After discontinuing renal artery adenosine infusion (change back to saline infusion), all hemodynamic measurements returned to control values within 8 ± 3 minutes.

### Table 1. Systemic and Right Renal Hemodynamic Changes Before and During Left Renal Artery Adenosine (0.92 ± 0.08 μg/kg/min) Infusion in Five Conscious Dogs

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>MAP</td>
<td>115 ± 6</td>
<td>125 ± 8*</td>
<td>126 ± 8*</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>150 ± 8</td>
<td>149 ± 10</td>
<td>150 ± 9</td>
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<tr>
<td>CO (l/min)</td>
<td>2.73 ± 0.31</td>
<td>3.10 ± 0.32*</td>
<td>3.15 ± 0.30*</td>
</tr>
<tr>
<td>TPR (RU)</td>
<td>42.1 ± 2.4</td>
<td>40.3 ± 2.3</td>
<td>40.0 ± 2.4</td>
</tr>
<tr>
<td>RBF (ml/min)</td>
<td>280 ± 25</td>
<td>274 ± 25</td>
<td>276 ± 25</td>
</tr>
<tr>
<td>RVR (RU)</td>
<td>0.41 ± 0.03t</td>
<td>0.46 ± 0.03*</td>
<td>0.46 ± 0.03*</td>
</tr>
</tbody>
</table>

Values are means ± SE. MAP = mean arterial pressure; HR = heart rate; CO = cardiac output; TPR = total peripheral vascular resistance expressed in Resistance Units (RU); RBF = renal blood flow; RVR = renal vascular resistance expressed in units (ru). TPR was calculated from MAP/CO; RVR was calculated from MAP/RBF.

* *tp < 0.01 compared to preinfusion values.

### Table 2. Systemic and Right Renal Hemodynamic Changes Before and During Left Renal Artery Adenosine (1.75 ± 0.13 μg/kg/min) Infusion in Eight α-Chloralose-Anesthetized Dogs

<table>
<thead>
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<tbody>
<tr>
<td>MAP</td>
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<tr>
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<tr>
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<td>274 ± 25</td>
<td>276 ± 25</td>
</tr>
<tr>
<td>RVR (RU)</td>
<td>0.41 ± 0.03t</td>
<td>0.46 ± 0.03*</td>
<td>0.46 ± 0.03*</td>
</tr>
</tbody>
</table>

Values are means ± SE. For abbreviations see table 1.

* *tp < 0.01 compared to preinfusion values.
To determine whether the increase in renal vascular resistance seen in the right kidney was mediated by the renal nerves, renal denervation of the right kidney was performed subsequently in four of the animals. Renal denervation did not significantly change control right renal blood flow. Repeat left renal artery adenosine infusion produced the same increase in arterial pressure (10%) and cardiac output (15%) but now right renal blood flow increased 14% \( (p < 0.01) \) with no change seen in renal vascular resistance.

**Afferent Renal Nerve Response**

After characterizing the hemodynamic responses to left renal artery adenosine infusion (table 2), the left renal nerve was isolated, severed, and prepared for afferent nerve traffic recording. As shown in figure 1, there was a latency in the onset of increased afferent renal nerve activity to renal artery adenosine infusion. In all eight animals, a significant increase in afferent renal nerve activity (control, \( 5.0 \pm 0.5 \) Hz vs adenosine, \( 23.0 \pm 4.9 \) Hz; \( p < 0.01 \)) occurred in 80 to 150 (mean 120 \( \pm 12 \)) seconds. The increased afferent renal nerve activity continued as long as the renal artery adenosine infusion continued. After discontinuing the renal artery adenosine infusion, afferent renal nerve activity returned to control levels within 6 \( \pm 3 \) minutes. Repeat renal artery adenosine infusion at twofold and fivefold higher doses did not change the latency in onset of afferent renal nerve activity.

**Renal Pelvic Adenosine Infusion in the Anesthetized Dog**

The latency in onset of afferent renal nerve activity observed with renal artery adenosine infusion might be due to the location of adenosine sensitive nerve endings. Chemoreceptive nerve endings have been described in the submucosal layers of the renal pelvis. A latency in onset during renal artery adenosine administration could be explained by the time required for adenosine to be filtered and reach sufficient concentration in the renal pelvic urine for threshold to be reached. Pilot studies revealed that renal pelvic adenosine infusion resulted in a much earlier onset of afferent renal nerve activity compared to renal artery adenosine administration. Accordingly, the hemodynamic and afferent renal nerve responses were measured during renal pelvic adenosine infusion and compared with the responses to renal artery adenosine administration in four of the animals. The mean dose of adenosine used for renal pelvic administration was two times the renal artery infusion dose since this was determined in pilot studies to be a suprathreshold concentration without systemic effects.

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**Figure 1.** Neurogram (above) and the computer-generated histogram (below) illustrating the latency in onset and the increased afferent renal nerve activity during infusion of adenosine into the renal artery of an \( \alpha \)-chloralose-anesthetized dog. The neurogram at 150 seconds demonstrates that increased afferent renal nerve activity precedes the elevation in arterial pressure.
Hemodynamic Response

Left renal pelvic adenosine infusion (4 μg/kg/min) in four animals produced an increase in mean arterial pressure within four minutes in each animal. Renal pelvic infusion did not significantly alter renal pelvic pressure during the course of the experiments. As shown in table 3, there was a 15% increase in cardiac output and a 10% increase in mean arterial pressure with no change in heart rate. Right renal blood flow was unchanged such that right renal vascular resistance increased 13%. Total peripheral vascular resistance did not significantly change. The only significant difference in the hemodynamic response between renal artery and renal pelvic adenosine infusion in the four animals was that arterial pressure rise occurred 1 minute earlier with renal pelvic administration. After discontinuing renal pelvic adenosine administration, all hemodynamic parameters returned to control values within 4 ± 1 minutes. In three of the animals, the catheter was then pulled back such that infusion would occur into the ureter rather than the renal pelvis. Adenosine infusion with the catheter at this position never elicited hemodynamic changes. At completion of each experiment, catheter position was confirmed visually.

Afferent Renal Nerve Response

A significant increase in afferent renal nerve activity (control, 5.1 ± 1.1 Hz vs adenosine, 19.1 ± 5.5 Hz; p < 0.01) occurred in 15 to 20 (mean 18 ± 1) seconds after beginning renal pelvic adenosine administration. The increased afferent renal nerve activity continued as long as the renal pelvic adenosine infusion continued. After discontinuing the renal pelvic adenosine infusion, afferent renal nerve activity returned to control levels within 3 ± 1 minutes. In these four animals renal artery adenosine administration produced a significant increase in afferent renal nerve activity (control, 4.9 ± 0.6 Hz vs adenosine, 20.0 ± 4.5 Hz; p < 0.01) in 105 ± 8 seconds. In these four animals, the latency of onset of increased afferent renal nerve activity occurred significantly (p < 0.01) sooner with renal pelvic adenosine administration.

Discussion

Our study has demonstrated that: 1) infusion of adenosine into the renal artery produces hypertension in both the conscious and α-chloralose-anesthetized dog with intact renal nerves; 2) infusion of adenosine into the renal pelvis produces hypertension similar to that seen when adenosine is administered into the renal artery of the α-chloralose-anesthetized dog; 3) the onset of increased afferent renal nerve activity occurs earlier with renal pelvic adenosine administration than it does with renal artery infusion. These observations extend our previous work suggesting that intrarenal adenosine produces hypertension by activating the sympathetic nervous system via the afferent renal nerves and suggest that adenosine sensitive nerve endings may be located within or near the renal pelvis.

The hemodynamic responses to renal artery adenosine infusion observed in this study in the conscious dog with both kidneys intact were similar to those we previously reported in conscious uninephrectomized animals. Since we planned to perform our anesthetized experiments in a two-kidney animal, we thought proper comparison of the effects of anesthesia on the hemodynamic response required renal artery adenosine infusion in a two-kidney conscious animal. This also allowed study of the response of the contralateral kidney during renal artery adenosine infusion. We observed no change in renal blood flow in the contralateral kidney during adenosine administration despite an increase in cardiac output. The resultant increased renal vascular resistance in the contralateral kidney could be a manifestation of the efferent sympathetic response. This was later confirmed in the anesthetized animal for renal denervation abolished the contralateral kidney’s increase in renal vascular resistance during intrarenal adenosine administration. A disproportionately greater increase in renal vascular resistance compared to other vascular beds (total peripheral resistance was unchanged) has been observed in other settings such as the sympathetic response to exercise in the conscious dog with complete heart block. A disproportionate increase in renal vascular resistance would facilitate a hypertensive process by shifting the arterial pressure-sodium excretion curve for the kidney to the right.

A number of other investigators have infused adenosine into the renal artery for 10 to 20 minutes when studying the effects of adenosine on renal blood flow, glomerular filtration rate, and renin secretion. In contrast to these previous reports, we observed a significant increase in mean arterial pressure during a 60 minute renal artery adenosine infusion in both the conscious and α-chloralose-anesthetized dog. A factor that may explain these differences is that the previous experiments were performed in the sodium pentobarbital-anesthetized dog. Whereas sodium pentobarbital anesthesia depresses chemoreceptor reflexes the most, even α-chloralose anesthesia attenuates these re-

### Table 3. Systemic and Right Renal Hemodynamic Changes Before and During Left Renal Pelvic Adenosine (4 μg/kg/min) Infusion in Four α-Chloralose-Anesthetized Dogs

<table>
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<tr>
<th>Parameter</th>
<th>Pre-infusion</th>
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</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>113 ± 5</td>
<td>124 ± 7*</td>
<td>124 ± 7*</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>148 ± 8</td>
<td>151 ± 9</td>
<td>151 ± 9</td>
</tr>
<tr>
<td>CO (liter/min)</td>
<td>2.84 ± 0.28</td>
<td>3.27 ± 0.34*</td>
<td>3.21 ± 0.36*</td>
</tr>
<tr>
<td>TPR (RU)</td>
<td>39.8 ± 1.9</td>
<td>37.9 ± 2.2</td>
<td>38.6 ± 2.3</td>
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<tr>
<td>RBF (ml/min)</td>
<td>270 ± 18</td>
<td>266 ± 22</td>
<td>261 ± 21</td>
</tr>
<tr>
<td>RVR (ru)</td>
<td>0.42 ± 0.02</td>
<td>0.47 ± 0.02*</td>
<td>0.48 ± 0.02*</td>
</tr>
</tbody>
</table>

Values are means ± SE. For abbreviations see table 1. *p < 0.01 compared to preinfusion values.
sponses compared to the conscious state. Support for this possibility was our observation that the response to intrarenal adenosine in the α-chloralose-anesthetized dog was less marked and somewhat different than that seen in the conscious animal. We observed smaller increases in arterial pressure and cardiac output in the anesthetized animal while heart rate which was elevated during the control period did not change.

We previously reported that denervation of the kidney into which adenosine was infused prevented the rise in arterial pressure and the increase in sympathetic nervous system activity observed in animals with intact renal nerves during renal artery adenosine infusion. These observations were consistent with the hypothesis that infusion of adenosine into the kidney stimulates a receptor for adenosine which enhances afferent renal nerve signals and therefore increases sympathetic nervous system activity: In support of such a role for adenosine in the kidney was the report that intrarenal adenosine enhances afferent renal nerve activity in the rat. We found a similar increase in afferent renal nerve traffic with intrarenal adenosine administration in the dog.

The observation that there was a 80- to 150-second latency in onset of increased afferent renal nerve activity with renal artery adenosine infusion raised the possibility that adenosine sensitive nerve endings might be located in the renal pelvis where chemoreceptors have been described. Consistent with this possibility was the finding that increased afferent renal nerve activity in response to renal pelvic adenosine administration occurred much sooner than with renal artery infusion. While we cannot be certain that the increased afferent renal nerve activity elicited by renal pelvic adenosine administration was due to stimulation of the same receptors (since we were recording from a multifiber nerve preparation), the hemodynamic responses were identical. We do not think that the enhanced afferent renal nerve activity was due to stimulation of mechanoreceptors because the double lumen catheter system held renal pelvic pressure constant.

Increased renal adenosine release due to reduced blood flow caused by renal artery stenosis might be a mechanism for activation of the sympathetic nervous system via the afferent renal nerves in one-kidney, one clip, and two-kidney, one clip Goldblatt hypertension. The relationship of intrarenal adenosine-induced sympathetic nervous system activity in the pathogenesis of renovascular hypertension merits further study.

Acknowledgments

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