Systemic and Coronary Hemodynamic Effects of Pinacidil in Awake Normotensive and Hypertensive Dogs

SEINOSUKE KAWASHIMA AND CHANG-SENG LIANG

SUMMARY We studied the systemic and coronary hemodynamic effects of a new antihypertensive agent, pinacidil, in nine morphine-sedated chronically instrumented dogs with one-kidney renal hypertension and eight similarly treated sham-operated normotensive dogs. The renal hypertensive dogs exhibited higher mean aortic blood pressure, total peripheral vascular resistance, and plasma renin activity before pinacidil administration than the sham-operated animals. The renal hypertensive dogs also had a lower left ventricular norepinephrine content, but the two groups did not differ significantly in plasma norepinephrine levels, cardiac output, or heart rate. Pinacidil decreased mean aortic pressure and total peripheral vascular resistance and increased cardiac output and heart rate in both groups. The changes in aortic pressure, total peripheral vascular resistance, and cardiac output were similar between the two groups, but the increase in heart rate was attenuated in renal hypertension. The peak rate of rise of left ventricular pressure (dP/dt), the ratio of left ventricular dP/dt and the developed pressure during isovolumic contraction (dP/dt/P), myocardial oxygen consumption, and plasma norepinephrine levels increased after pinacidil administration in the sham-operated dogs, but did not change in the renal hypertension group. The two groups did not differ in their responses of left ventricular dP/dt to intravenous isoproterenol. Pinacidil also caused coronary vasodilation in both groups, as evidenced by an increase in coronary blood flow and decreases in coronary vascular resistance and myocardial oxygen extraction. The decrease in myocardial oxygen extraction was similar in the two groups, but the increase in coronary blood flow was significantly less ($p < 0.05$), probably because of the absence of an increase in myocardial oxygen consumption in the renal hypertensive dogs. Our results indicate that the systemic and coronary vasodilator effects of pinacidil are unaffected by renal hypertension, but its chronotropic and inotropic responses are greatly attenuated or abolished. The reduced cardiac effects of pinacidil in renal hypertension probably are related to a diminished reflex sympathetic response to systemic vasodilation. (Hypertension 7:525-532, 1985)

KEY WORDS • vasodilator • pinacidil • renal hypertension • myocardial blood flow • vasodilation • cardiac $\beta$-adrenergic receptor responsiveness

PINACIDIL, a cyanoguanidine derivative, is a new antihypertensive agent$^1$ $^2$ currently under clinical investigation. We have shown recently that, in addition to decreasing aortic pressure, pinacidil exerts a potent coronary vasodilator effect in normotensive dogs.$^1$ Also, compared with hydralazine, pinacidil has less chronotropic and inotropic effects, which can be reduced or abolished by propranolol.$^3$ These cardiac actions of pinacidil in normotensive dogs probably are caused, at least in part, by the baroreceptor-mediated reflex sympathetic stimulation. A variety of neurohormonal and vascular structural changes occur in hypertension, which invalidate attempts to extrapolate the findings in normotensive dogs directly to hypertensive conditions. Although blood vessels with high initial resistances have been shown to be more susceptible to vasomotor stimuli,$^4$ structural and functional alterations may have occurred in the vascular beds during hypertension to reduce the vascular reactivity.$^5$ $^6$ Furthermore, hypertension has been shown to be associated with reduced baroreceptor sensitivity and elevated plasma catecholamine lev-
els. Thus, pinacidil may exert discordant effects in normotensive and hypertensive animals.

The purpose of the present study was to investigate the systemic and coronary hemodynamic effects of pinacidil in awake dogs with one-kidney renal hypertension. The results were compared with those in sham-operated normotensive dogs. In addition, to determine whether the sympathetic nervous system plays a role in modulating the effects of pinacidil, we measured plasma and myocardial norepinephrine contents and cardiac β-adrenergic receptor responsiveness to isoproterenol in both experimental groups.

Methods

Adult beagles weighing 8.8 to 13.6 kg were anesthetized with sodium pentobarbital (25 mg/kg i.v.) and mechanically ventilated with a Harvard respirator (Harvard Apparatus Co., Inc., S. Natick, MA, USA). A sterile left thoracotomy was performed through the fifth intercostal space for placement of Tygon catheters (Norton Co., Plastics & Synthetics Div., Akron, OH, USA) in the main pulmonary artery, left atrium, and descending thoracic aorta. The chest was closed, and catheters were exteriorized at the back of the neck. A left flank incision was then made to expose the left renal artery. In a group of 13 dogs, the renal artery waslicated to reduce renal blood flow by approximately 60% as measured by an electromagnetic flowmeter (Carolina Medical Electronics, Inc., King, NC, USA). In another eight dogs, the kidneys were exposed but no renal artery constriction was made. All dogs were allowed to recover for 2 weeks, during which time they were trained to lie quietly on a table. Two weeks later, the dogs were reanesthetized for right nephrectomy through a flank incision. In two dogs of each group, the order of renal surgery was reversed (i.e., right nephrectomy was done with thoracotomy followed by either left renal artery constriction or sham operation 2 weeks later). Dogs with severe uremia, manifested by weakness, refusal to eat, and serum creatinine levels greater than 5 mg/dl or hematocrit less than 28%, were excluded.

Measurements and Calculations

Hemodynamic studies were performed 5 to 7 days after the second operation. On the day of the experiment, animals were pretreated with morphine sulfate (0.5 mg/kg) and placed in the right decubitus position on a table. With local anesthesia with 0.5% lidocaine and fluoroscopic guidance, a Coumard catheter was introduced into the coronary sinus through an external jugular vein, and a Millar transducer-tip catheter (Millar Instruments Inc., Houston, TX, USA) was inserted into the left ventricle through a femoral artery. Both the Coumard and previously implanted Tygon catheters were connected to Statham P23Db transducers (Statham Instruments Inc., Oxnard, CA, USA) and a multichannel Brush 480 recorder (Gould Inc., Instruments Division, Cleveland, OH, USA) for measuring blood pressures and taking blood samples. The Millar catheter was connected to the Brush recorder for measuring left ventricular end-diastolic pressure and peak rate of pressure rise of left ventricular pressure (dP/dt). The ratio of left ventricular dP/dt at a developed pressure of 50 mm Hg and the developed pressure during isovolumic contraction (dP/dt/P) was measured. Left ventricular dP/dt/P was used as an index of myocardial contractility relatively independent of changes in afterload.

Cardiac output was measured by an indocyanine green (Cardio-Green, Hynson, Westcott and Dunning Inc., Baltimore, MD, USA) dye dilution technique with a Gilford model 140 cardiac output system (Gilford Instrument Laboratories Inc., Oberlin, OH, USA). Heart rate was determined from the electrocardiogram. Coronary and renal blood flows were measured by a radioactive microsphere technique. One million microspheres, 15 ± 3 μm in diameter and labeled with cerium-141, tin-113, ruthenium-103, scandium-46, or niobium-95 (New England Nuclear, Boston, MA, USA) were injected into the left atrium, followed by a flush of 10 ml of normal saline. Arterial reference blood was withdrawn with a Harvard pump (Harvard Apparatus Co., Inc.) at a rate of 7.75 ml/minute, beginning 10 seconds before the injection of microspheres and continuing for 80 seconds thereafter.

After the experiment the dogs were killed with a lethal dose of pentobarbital, and the heart and kidneys were removed. The heart was subsequently divided into the left ventricle including the septum and the right ventricular free wall. Counts of radioactivity in the organs and reference blood samples were measured in a Packard gamma spectrometer and Model 9012 multichannel analyzer (Packard Instrument Co., Inc., Downer’s Grove, IL, USA) at appropriate window settings corresponding to each of the radionuclides. The radioactivity of each isotope was corrected for background, and crossover activity from other isotopes was subtracted, with the use of five simultaneous equations that were solved using the technique of Gaussian elimination. Coefficients from these equations were obtained by using the response to a given isotope on each of the channels associated with the other isotopes. Absolute blood flow was calculated on a PDP-11/23 minicomputer (Digital Equipment Co., Maynard, MA, USA) with the formula: organ flow (ml/100 g/min) = [arterial reference flow (ml/min) × organ nuclide activity × organ weight (g)]/[arterial reference nuclide activity × organ weight (g)]. Total peripheral vascular resistance (dyne·sec·cm⁻²) was obtained by dividing mean aortic pressure (mm Hg) by cardiac output (L/min) times 79.92. Right atrial pressure was assumed to be negligible compared with aortic pressure. Coronary vascular resistance (dyne·sec·cm⁻²) was calculated by dividing left ventricular blood flow (ml/min/100 g) into the difference between mean aortic pressure and mean coronary sinus pressure (mm Hg) times 79,920.

Arterial and coronary sinus blood samples were taken simultaneously for measuring arteriovenous oxygen difference across the heart with a Lex-O₂-Con analyzer.
(Lexington Instruments Corp., Waltham, MA, USA). Myocardial oxygen extraction and myocardial oxygen consumption were calculated by conventional formulas. Arterial blood also was taken to measure plasma norepinephrine levels with a modified high-performance liquid chromatographic method with electrochemical detection and plasma renin activity by radioimmunoassay. In addition, a 1-g to 2-g sample of left ventricular muscle was taken from each dog immediately after death for determining myocardial norepinephrine content. The tissue was minced and homogenized in ice-cold 0.4 M perchloric acid and 5 mM glutathione with a Brinkmann Polytron PT-20 homogenizer (Brinkmann Instruments, Westbury, NY, USA). The homogenate was then centrifuged, and the supernatant was stored in a -70°C freezer to await extraction. To extract catecholamines, both the plasma samples and tissue homogenates were mixed with acid-washed aluminum oxide in a 1.5 M Tris buffer-Na2EDTA solution containing 3,4-dihydrobenzylamine as an internal standard. The alumina was washed three times and aspirated near dryness during the first two times. After the second wash, the alumina slurry was transferred to a Microfilter loaded with RC 58 membranes and spin-dried at 1000 g for 30 seconds. Next, 200 μL of 0.1 M perchloric acid was added to the Microfilter sample compartment, and the acidic filtered extract collected; 50 to 200 μL of the extract was injected onto a Bioanalytical Systems C18 analytic column (Bioanalytic Systems, Inc., West Lafayette, IN, USA), and the output of the electrochemical detector was recorded on a Hewlett-Packard strip chart recorder (Hewlett-Packard Co., Waltham, MA, USA). Catecholamine concentrations were determined by comparing the curves of the unknown samples to those of comparable standards. The coefficient of variation of duplicate samples is 4.8%.

Experimental Protocol
Baseline hemodynamic measurements were taken at least 2 hours after morphine administration and 45 minutes after the catheterization. Neither mean aortic pressure nor heart rate changed significantly from precatheterization values. After the third wash, the perchloric acid extraction was injected onto a Bioanalytical Systems C18 analytic column (Bioanalytic Systems, Inc., West Lafayette, IN, USA), and the output of the electrochemical detector was recorded on a Hewlett-Packard strip chart recorder (Hewlett-Packard Co., Waltham, MA, USA). Catecholamine concentrations were determined by comparing the curves of the unknown samples to those of comparable standards. The coefficient of variation of duplicate samples is 4.8%.

TABLE I. Effects of Renal Artery Constriction on Renal Blood Flow, Arterial Blood Pressure, Plasma Renin Activity, and Myocardial and Plasma Norepinephrine Levels

<table>
<thead>
<tr>
<th>Group</th>
<th>Renal blood flow (ml/100 g/min)</th>
<th>MAP (mm Hg)</th>
<th>Total PVR (10⁻²)</th>
<th>PRA (ng/hr/ml)</th>
<th>Norepinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal hypertension (n = 9)</td>
<td>428 ± 20</td>
<td>122 ± 1</td>
<td>5.9 ± 0.4</td>
<td>0.7 ± 0.2</td>
<td>1.41 ± 0.13</td>
</tr>
<tr>
<td>Sham operation (n = 8)</td>
<td>171 ± 27*</td>
<td>154 ± 4*</td>
<td>7.9 ± 0.6*</td>
<td>3.0 ± 0.3*</td>
<td>0.92 ± 0.13*</td>
</tr>
</tbody>
</table>

Values are means ± se.
MAP = mean arterial pressure; PRA = plasma renin activity; PVR = peripheral vascular resistance; n = number of experiments per group.
*p < 0.05, compared with sham-operated group (Student's t test for unpaired data).
sure, total peripheral vascular resistance, and plasma renin activity than the sham-operated animals. Left ventricular weight did not differ between the sham (57 ± 6 g) and hypertensive dogs (58 ± 3 g), but myocardial norepinephrine content was lower in the latter group. Plasma norepinephrine concentration did not differ between the two groups. Moreover, there were no differences in baseline heart rate and cardiac output between the two groups (Table 2). On the other hand, the baseline values of left ventricular dP/dt and dP/dt/P were higher in the hypertensive dogs than in the sham-operated dogs.

Systemic Hemodynamic Responses to Pinacidil

As we have shown previously, pinacidil produced its peak hemodynamic effects shortly after administration; these lessened gradually and reached a steady state within 15 minutes. Therefore, the four hemodynamic measurements obtained between 15 and 30 minutes after each dose were averaged, and the averages were used for statistical analysis. Pinacidil decreased mean aortic pressure and peripheral vascular resistance in both groups (see Table 2). Heart rate and cardiac output increased significantly (p < 0.05) after the third dose of pinacidil in the sham-operated dogs, but not until the highest dose had been administered in the hypertensive dogs. Left ventricular dP/dt and dP/dt/P increased after pinacidil administration in the sham-operated dogs but not in dogs with renal hypertension. Mean left atrial pressure decreased from 2.9 ± 1.1 to 0.4 ± 0.9 mm Hg after the largest dose of pinacidil in the sham operation group and from 6.1 ± 1.2 to 2.3 ± 0.8 mm Hg in the renal hypertension group. The difference in baseline left atrial pressure between the two groups was not statistically significant (t = 1.96, df = 15).

Figure 1 depicts the systemic hemodynamic effects produced by the largest dose of pinacidil in the two groups. Because baseline values differed between the groups, percent changes were used for statistical com-

![Figure 1. Effects of pinacidil at a cumulative dose of 0.4 mg/kg on mean aortic blood pressure, heart rate, cardiac output, and total peripheral vascular resistance in normotensive sham-operated dogs (n = 8) and renal hypertensive dogs (n = 9). Bars = se; * = value that differs significantly from the corresponding value in the sham operation group (p < 0.05).](http://hyper.ahajournals.org/)

**Table 2. Effects of Pinacidil on Systemic Hemodynamics in Sham-Operated and Renal Hypertensive Dogs**

<table>
<thead>
<tr>
<th>Group</th>
<th>Pinacidil dose (mg/kg)</th>
<th>Mean aortic pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Cardiac output (L/min)</th>
<th>Total PVR (dyne·sec·cm⁻³, × 10⁻²)</th>
<th>dP/dt (mm Hg/sec, × 10⁻³)</th>
<th>dP/dt/P (sec⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham operation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 8)</td>
<td>0</td>
<td>122 ± 1</td>
<td>87 ± 9</td>
<td>1.75 ± 0.12</td>
<td>5.9 ± 0.4</td>
<td>3.2 ± 0.2</td>
<td>57 ± 3</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>120 ± 2</td>
<td>95 ± 10</td>
<td>1.84 ± 0.16</td>
<td>5.4 ± 0.5</td>
<td>3.4 ± 0.3</td>
<td>58 ± 3</td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td>123 ± 3</td>
<td>109 ± 10</td>
<td>1.90 ± 0.18</td>
<td>5.5 ± 0.6</td>
<td>3.2 ± 0.3</td>
<td>61 ± 4</td>
</tr>
<tr>
<td></td>
<td>0.20</td>
<td>119 ± 3</td>
<td>139 ± 15*</td>
<td>2.08 ± 0.17*</td>
<td>4.8 ± 0.5*</td>
<td>4.3 ± 0.3*</td>
<td>64 ± 3</td>
</tr>
<tr>
<td></td>
<td>0.40</td>
<td>95 ± 4*</td>
<td>190 ± 12*</td>
<td>2.31 ± 0.18*</td>
<td>3.5 ± 0.3*</td>
<td>4.9 ± 0.4*</td>
<td>71 ± 6*</td>
</tr>
<tr>
<td>Renal hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 9)</td>
<td>0</td>
<td>154 ± 4</td>
<td>76 ± 5</td>
<td>1.60 ± 0.10</td>
<td>7.9 ± 0.6</td>
<td>4.8 ± 0.4</td>
<td>66 ± 3</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>153 ± 3</td>
<td>80 ± 5</td>
<td>1.69 ± 0.12</td>
<td>7.6 ± 0.6</td>
<td>5.2 ± 0.6</td>
<td>66 ± 4</td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td>153 ± 4</td>
<td>83 ± 8</td>
<td>1.74 ± 0.13</td>
<td>7.4 ± 0.6</td>
<td>5.4 ± 0.7</td>
<td>67 ± 4</td>
</tr>
<tr>
<td></td>
<td>0.20</td>
<td>145 ± 5</td>
<td>96 ± 9</td>
<td>1.71 ± 0.08</td>
<td>6.9 ± 0.4</td>
<td>5.0 ± 0.6</td>
<td>65 ± 3</td>
</tr>
<tr>
<td></td>
<td>0.40</td>
<td>126 ± 6*</td>
<td>131 ± 13*</td>
<td>2.04 ± 0.12*</td>
<td>5.1 ± 0.4*</td>
<td>5.2 ± 0.5</td>
<td>67 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± se.
PVR = peripheral vascular resistance; dP/dt = rate of change in pressure; dP/dt/P = ratio of dP/dt to developed pressure during isovolumic contraction; n = number of experiments per group.

*p < 0.05, compared with baseline value (analysis of variance and Dunnet's test).
parisons. Pinacidil produced comparable percent reductions in mean aortic pressure and peripheral vascular resistance in the two groups. The two groups also did not differ when the effects were expressed as absolute changes from baseline values; mean aortic pressure decreased by 27 ± 4 and 28 ± 6 mm Hg, and total peripheral vascular resistance decreased by 2429 ± 326 and 2829 ± 752 dyne·sec·cm⁻¹ in the sham operation and renal hypertension groups respectively. Pinacidil also produced similar increases in cardiac output in the two groups, as determined by either percent (see Figure 1) or absolute (0.60 ± 0.13 versus 0.43 ± 0.11 L/min) changes. The increase in heart rate produced by pinacidil was significantly attenuated in the renal hypertension group (p < 0.05). Stroke volume, on the other hand, was decreased by pinacidil from 22 ± 2 to 17 ± 2 ml in the renal hypertension group and from 21 ± 3 and 13 ± 1 ml in the sham operation group. Although the mean percent reduction in stroke volume appeared to be greater in the latter group (38 ± 5% versus 20 ± 8%), the difference was not statistically significant (t = 1.90, df = 15).

Plasma norepinephrine levels increased from 0.48 ± 0.10 to 0.86 ± 0.20 ng/ml (p < 0.05) after the highest dose of pinacidil in the sham operation group, but did not change significantly in the renal hypertension group (0.65 ± 0.20 to 0.60 ± 0.11 ng/ml).

The effects on left ventricular dP/dt of isoproterenol in the renal hypertension and sham groups are shown in Figure 2. In these subgroups of dogs, the baseline values of left ventricular dP/dt also were higher in the renal hypertensive dogs (5331 ± 327 mm Hg/sec) than in the normotensive dogs (3973 ± 269 mm Hg/sec). Figure 2 shows that the maximum effects of each dose of isoproterenol, expressed as percent changes of the baseline, did not differ between the two groups. Neither was the absolute increase produced by the largest dose of isoproterenol different between the two groups (2896 ± 532 versus 2481 ± 366 mm Hg/sec).

Coronary Hemodynamic Responses to Pinacidil

Baseline values of left ventricular blood flow, coronary vascular resistance, myocardial oxygen consumption, and myocardial oxygen extraction did not differ significantly between the sham operation and renal hypertension groups (Table 3). Baseline right ventricular blood flow also did not differ between the two groups (62 ± 7 versus 63 ± 7 ml/100 g/min), but the baseline coronary sinus pressure was lower in the former group (0.8 ± 0.3 versus 3.5 ± 1.0 mm Hg; t = 2.54, df = 15, p < 0.05). Table 3 further shows that pinacidil caused a dose-dependent increase in left ventricular blood flow and a corresponding decrease in coronary vascular resistance in both groups. These changes became significant with the second dose of pinacidil in the sham-operated dogs, but were not significant until the highest dose was administered in the hypertensive dogs (p < 0.05). In addition, the percent changes of left ventricular blood flow after the largest dose of pinacidil were greater in the sham operation group than in the renal hypertension group (Figure 3). The increase in right ventricular blood flow produced by pinacidil also was less in the renal hypertension (148 ± 32%) than in the sham operation group (368 ± 66%). Myocardial oxygen consumption increased after pinacidil in the sham operation group only. In contrast, pinacidil administration produced a similar reduction in myocardial oxygen extraction in both groups. Coronary sinus oxygen saturation increased from 22 ± 2 to 65 ± 3% after the largest dose of pinacidil in the sham operation group and from 15 ± 2 to 52 ± 6% in the renal hypertension group.

Discussion

The present experiments were performed at an early stage of renovascular hypertension, associated with increased plasma renin activity and total peripheral vascular resistance. As cardiac output did not differ significantly between the renal hypertension and sham groups, the elevation of arterial pressure during early renal hypertension was caused chiefly by the vasoconstrictor action of angiotensin II. Angiotensin II also may increase blood pressure indirectly by its action on the central and peripheral sympathetic pathways. The sympathetic nervous system has been shown to play an important role in the development and maintenance of an elevated arterial pressure in experimental renal hypertension; however, plasma catecholamine levels have not been found to be consistently increased in renovascular hypertension. Likewise, plasma norepinephrine levels did not increase significantly during hypertension in our experiments. In contrast, left ventricular norepinephrine concentration was decreased.
### Table 3. Effects of Pinacidil on Coronary Hemodynamics in Sham-Operated and Renal Hypertensive Dogs

<table>
<thead>
<tr>
<th>Group</th>
<th>Pinacidil dose (mg/kg)</th>
<th>Left ventricular blood flow (ml/100 g/min)</th>
<th>Coronary vascular resistance (dyne·sec·cm⁻²·10⁻⁶ g·x·10⁻³)</th>
<th>Myocardial oxygen Consumption (ml/100 g/min)</th>
<th>Extraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham operation (n = 8)</td>
<td>0</td>
<td>103 ± 11</td>
<td>122 ± 18</td>
<td>9.6 ± 1.3</td>
<td>77 ± 2</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>127 ± 12</td>
<td>103 ± 20</td>
<td>10.3 ± 1.4</td>
<td>71 ± 3</td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td>138 ± 13</td>
<td>87 ± 14*</td>
<td>11.2 ± 1.4</td>
<td>68 ± 5</td>
</tr>
<tr>
<td></td>
<td>0.20</td>
<td>185 ± 18*</td>
<td>61 ± 9*</td>
<td>10.5 ± 1.2</td>
<td>49 ± 3*</td>
</tr>
<tr>
<td></td>
<td>0.40</td>
<td>441 ± 65*</td>
<td>26 ± 5*</td>
<td>13.3 ± 2.1*</td>
<td>31 ± 4*</td>
</tr>
<tr>
<td>Renal hypertension (n = 9)</td>
<td>0</td>
<td>97 ± 9</td>
<td>131 ± 11</td>
<td>11.2 ± 1.3</td>
<td>83 ± 3</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>122 ± 12</td>
<td>109 ± 10</td>
<td>12.7 ± 1.4</td>
<td>81 ± 3</td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td>117 ± 11</td>
<td>110 ± 11</td>
<td>11.5 ± 1.2</td>
<td>75 ± 3</td>
</tr>
<tr>
<td></td>
<td>0.20</td>
<td>113 ± 12</td>
<td>113 ± 17</td>
<td>10.0 ± 1.4</td>
<td>68 ± 6*</td>
</tr>
<tr>
<td></td>
<td>0.40</td>
<td>225 ± 29*</td>
<td>46 ± 5*</td>
<td>11.8 ± 1.4</td>
<td>43 ± 6*</td>
</tr>
</tbody>
</table>

Values are means ± SE.  

n = number of experiments per group.  

*p < 0.05, compared with baseline value (analysis of variance and Dunnett’s test).

As left ventricular weight did not change, the reduced norepinephrine content could not be attributed to dilution by increased ventricular mass. A decrease in myocardial norepinephrine content has been found previously in several types of experimental hypertension.21-23 The reason for this reduction in myocardial norepinephrine content is not entirely clear. An increased norepinephrine turnover rate has been found in the heart of renal hypertensive animals.25-27 Furthermore, it has been postulated that the decreased capacity of storage granules in sympathetic terminals is responsible for the reduced myocardial norepinephrine content in rats made hypertensive with deoxycorticosterone and sodium.28 Whether such a mechanism also operates in renal hypertension remains to be determined.

Our results indicate that pinacidil is an effective antihypertensive agent. It produced similar reductions in aortic pressure and total peripheral vascular resistance, expressed as either absolute or percent changes of baseline values, in both normotensive and hypertensive dogs. Unlike the normotensive animals, however, the hypertensive dogs exhibited no increases in left ventricular dp/dt and dp/dt/P after pinacidil administration. Baseline values of left ventricular dp/dt and dp/dt/P were elevated in the renal hypertensive group. These changes are similar to those reported by Hawthorne et al.23 and probably were related to the elevated aortic pressure and heightened sympathetic and renin-angiotensin activities. Nevertheless, the increased basal values of left ventricular dp/dt and dp/dt/P probably were not responsible for the diminished responses of the hypertensive dogs to pinacidil because the normotensive and hypertensive animals had similar inotropic responses to isoproterenol during the early stage of renal hypertension (see Figure 2).

We have shown previously that the cardiac inotropic action of pinacidil is indirect, resulting from reflex sympathetic activation as arterial pressure decreases.3 Reduced baroreceptor sensitivity has been shown to occur in renovascular hypertension.1,8,9 Our results...
showing that plasma norepinephrine levels did not increase after pinacidil administration in renal hypertension are consistent with the impaired baroreceptor reflex. The primary defect probably lies in either the carotid baroreceptors or the efferent pathways to the heart, or both. The reduced myocardial store of norepinephrine could also be responsible in part for the diminished inotropic responses to pinacidil in hypertension. In addition, myocardial $\beta$-adrenergic receptor number has been shown to be reduced in chronically hypertensive animals with left ventricular hypertrophy. This change in myocardial $\beta$-adrenergic receptors may contribute to the diminished inotropic responsiveness to sympathetic stimulation in animals with left ventricular hypertrophy. This mechanism probably was relatively unimportant in our animals without left ventricular hypertrophy because there was no difference in the inotropic responsiveness to isoproterenol between the normotensive and hypertensive dogs.

The chronotropic response to pinacidil also was attenuated in renal hypertension, but it was relatively preserved compared with the inotropic response. Similarly, renal hypertension does not abolish the positive chronotropic response to nitroglycerin. Unlike the inotropic response, which is primarily sympathetically mediated, the reflex increase in heart rate is mediated by both sympathetic stimulation and parasympathetic withdrawal. As there was no positive inotropic effect of pinacidil in renal hypertensive dogs, the increase in heart rate produced by pinacidil in hypertension probably was caused by parasympathetic withdrawal.

The present study confirms our earlier report that the increase in coronary blood flow produced by pinacidil is accompanied by an increase in myocardial oxygen consumption and a marked reduction in myocardial oxygen extraction in normotensive dogs. The increase in myocardial oxygen consumption was caused, at least in part, by the increases in heart rate and myocardial contractility. The findings suggest that coronary vasodilator effects of pinacidil are mediated by both primary coronary vasodilation and secondary metabolic vasodilation resulting from the increased myocardial oxygen demand. Our results further show that the increase in left ventricular blood flow was smaller in the renal hypertension than in the sham operation group. The increase in right ventricular blood flow was also attenuated, which suggests that the increase in left ventricular wall tension was not responsible for the reduced coronary vasodilation in the left ventricle during arterial hypertension. Furthermore, because pinacidil caused comparable reductions in myocardial oxygen extraction in both groups, the primary vasodilator action probably was unaffected by renal hypertension. On the other hand, unlike the response produced in normotensive dogs, pinacidil did not increase myocardial oxygen consumption in renal hypertension. Thus, it appears that the attenuation of the coronary vasodilative effect of pinacidil in renal hypertension probably is related to the reduction of metabolically linked coronary vasodilation.

Acknowledgment
The authors thank Lisa Guthinger, Alexander Tsui, Catherine Mesner, Jayne Bouldry-Whitin, and Carol Waytovich for their expert assistance.

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S Kawashima and C S Liang

_Hypertension_. 1985;7:525-532
doi: 10.1161/01.HYP.7.4.525

_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

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