Regulation of the Renal Circulation during Severe Exercise in Normal Dogs and Dogs with Experimental Heart Failure

By Ronald W. Millard, Charles B. Higgins, Dean Franklin, and Stephen F. Varner

ABSTRACT

The role of sympathetic nerves and circulating catecholamines in mediating the renal vascular response to severe exercise was examined in normal dogs and dogs with experimental heart failure, using paired normal and denervated kidneys. In normal dogs, mean arterial blood pressure increased gradually from 97 ± 4 to 137 ± 6 mm Hg, renal blood flow remained at control levels, and renal vascular resistance rose from 0.57 ± 0.04 to 0.84 ± 0.15 mm Hg/ml min⁻¹ during peak steady-state exercise. The increase in resistance was similar in the denervated renal bed and persisted after alpha-receptor blockade. Exercise in dogs with heart failure increased mean arterial blood pressure slightly from 103 ± 4 to 111 ± 5 mm Hg. In the innervated kidney, blood flow dropped precipitously from 148 ± 6 to 46 ± 9 ml/min, and renal resistance increased from 0.73 ± 0.08 to 3.35 ± 0.53 mm Hg/ml min⁻¹. In the denervated kidney, renal blood flow decreased from 174 ± 12 to 120 ± 1 ml/min, and resistance increased from 0.59 ± 0.07 to 0.94 ± 0.09 mm Hg/ml min⁻¹. After alpha-receptor blockade, the decrease in flow and the increase in resistance to the denervated kidney were further attenuated. Thus, in normal, healthy dogs, the contribution of adrenergic mechanisms to renal vascular regulation appears to be minimal; blood flow remains constant in the presence of elevated pressure, suggesting that autoregulation is responsible for the elevated renal resistance during exercise. In dogs with experimental heart failure, intense renal sympathetic vasoconstriction prevails throughout exercise; the major portion of this response is neurally mediated, with an additional contribution by circulating catecholamines.

KEY WORDS: denervation, hypersensitivity, renal blood flow, telemetry, autoregulation, sympathetic nerves, alpha receptors, catecholamines, arterial blood pressure

It is generally held that the normal renal response to severe exercise involves sufficient sympathetic vasoconstriction to reduce blood flow to the kidney and to divert it to active muscle (1-4). However, this hypothesis has not been substantiated by direct measurement of renal blood flow in conscious dogs during exercise (5-8). The normal response to severe exercise in conscious dogs involves an increase in renal resistance (8), but a sustained reduction in renal blood flow does not occur (5-8). Apparently cardiac output increases sufficiently in the normal dog to satisfy the requirements of the exercising musculature without invoking a compensatory reduction and diversion of renal blood flow. However, in the presence of circulatory impairment, much
more intense renal vasoconstriction occurs with substantial reductions in renal blood flow (8–10).

The goal of this investigation was to determine the extent of sympathetic and autoregulatory control of the renal circulation in normal dogs and dogs with circulatory impairment. To determine the extent of neural adrenergic control of the renal circulation during exercise, the renal vascular response was compared, using paired innervated and denervated kidneys, in unrestrained normal dogs and dogs with heart failure running spontaneously at near maximal speeds in a field. The effects of circulating catecholamines were examined by comparing the response to exercise with the response to intravenous administration of norepinephrine and by determining the response of the denervated kidney to exercise after alpha-receptor blockade with phentolamine.

Methods

Thirteen male mongrel dogs (25–34 kg) anesthetized with sodium pentobarbital (30 mg/kg, iv) underwent an operation for the implantation of miniature pressure gauges in the abdominal aorta (five dogs) and the thoracic aorta (eight dogs) and of Doppler ultrasonic flow transducers on both renal arteries. One renal pedicle was surgically denervated by removal of all extravascular tissue for 2 cm proximal to the hilus excluding the ureter. Experimental heart failure was produced in six dogs by a technique modified slightly from the method of Barger et al. (11), which involves tricuspid avulsion and progressive pulmonary stenosis (10, 11). Three of these dogs were studied in the control state prior to the production of heart failure. Right heart failure was characterized by elevated right ventricular systolic (54 mm Hg) and end-diastolic (13 mm Hg) pressures, ascites (1–6 liters), and an increased ratio of right ventricle to left ventricle wall thickness (0.73 compared with 0.46).

The Doppler ultrasonic flowmeter was used to measure renal blood flow (8, 12, 13). The relationship between velocity as measured by the Doppler flowmeter and volume flow is linear as long as the cross-sectional area of the vessel remains constant. At autopsy it was observed that a firm fibrous shell fixed the vessel to the transducer, thereby minimizing in vivo changes in vessel dimensions. Preterminally, under general anesthesia with sodium pentobarbital, renal arteries were dissected free and cannulated distal to the flow transducer for timed volume collection which confirmed the linear relationship between velocity and volume flow (13). Arterial blood pressure was measured by the previously implanted miniature pressure gauges (14), which were calibrated in vivo against a calibrated Statham P23Db strain-gauge manometer. Mean pressure and flow were derived by integrating the respective phasic data with resistance-capacitance filters having a 2-second time constant. Renal vascular resistance was calculated as the quotient of mean arterial blood pressure (mm Hg) and mean renal blood flow (ml/min). Heart rate was computed using the pressure pulse wave as a trigger stimulus for a cardiotachometer. The results were compared using Student’s paired t-test, group t-test, and analysis of variance as described by Snedecor (15). Significance was established at the 5% level (P < 0.05).

The experiments were conducted 2–6 weeks postoperatively when the dogs appeared to have recovered from surgery. At this time the dogs with heart failure appeared to be in a steady state. Measurements of renal blood flow and arterial blood pressure were obtained by FM/FM radiotelemetric techniques described in detail previously (8, 12). Blood flow in the innervated or denervated kidney was recorded along with arterial blood pressure during a control period and while the dogs ran behind a mobile recording van at speeds of 15–30 mph for up to 2 miles. The performance of dogs with congestive heart failure was limited: they ran at speeds of 10–25 mph for up to 1 mile. In four normal dogs and four dogs with heart failure, the renal flow response during exercise was assessed after alpha-receptor blockade with phentolamine (0.75 mg/kg, iv).1 Alpha-receptor blockade was 90% effective in blocking the hypertensive response to norepinephrine bitartrate (1.0 µg/kg, iv). To test renal vasoconstrictor sensitivity, norepinephrine in graded doses from 0.01 to 1.0 µg/kg was injected intravenously while flow and pressure measurements were recorded in dogs resting quietly in the laboratory.

Kidney tissue biopsies were taken terminally for chemical confirmation of the surgical denervation procedure. We used the trihydroxyindole method of von Euler and Lishajko (18) for fluorometric assay of catecholamines. Fluorescence of the trihydroxyindole derivatives was measured on an Amino-Bowman spectrophotofluorometer. Innervated renal cortical and medullary samples averaged 0.19 µg and 0.08 µg of

1Phentolamine (Regitine) was generously supplied by CIBA.
norepinephrine per gram of tissue, respectively, but norepinephrine concentrations in renal cortical and medullary samples from denervated kidneys were below detectable levels (<0.005 µg/g tissue).

**Results**

*Exercise Response in Healthy Dogs.*—Severe exercise caused heart rate to rise abruptly from 92 ± 6 to 277 ± 4 beats/min, and mean arterial blood pressure increased gradually from 97 ± 4 to 137 ± 6 mm Hg. Initially blood flow in the innervated kidney fell transiently from 171 ± 12 to 122 ± 17 ml/min and renal vascular resistance increased from 0.57 ± 0.04 to 1.3 ± 0.43 mm Hg/ml min⁻¹ (Fig. 1), but during the steady-state response blood flow returned to the preexercise control value while renal resistance remained elevated at 0.84 ± 0.15 mm Hg/ml min⁻¹ (Table 1).

Blood flow to the denervated kidney at rest (168 ± 17 ml/min), which was not significantly different from blood flow to the innervated kidney (171 ± 12 ml/min), failed to decrease initially during exercise; during the steady-state response blood flow was also essentially at preexercise control levels, and renal resistance had increased from 0.62 ± 0.06 to 0.89 ± 0.09 mm Hg/ml min⁻¹, a value similar to that observed in the innervated kidney (Table 1). The major difference between the two responses was that flow did not fall and resistance did not increase as much initially in the denervated kidney; the steady-state responses to severe exercise were essentially similar.

After phentolamine (0.75 mg/kg) a similar level of severe exercise produced a similar response in the denervated renal bed. Mean arterial blood pressure increased from 95 ± 6 to 122 ± 5 mm Hg, and calculated renal vascular resistance increased from 0.52 ± 0.05 to 0.75 ± 0.08 mm Hg/ml min⁻¹; renal flow

![Graph](https://example.com/graph.png)

**FIGURE 1**

Renal vascular response to severe exercise in a normal, healthy dog with a denervated kidney. The responses of phasic and mean arterial pressure and of renal blood flow are shown along with calculated mean renal resistance and heart rate. The renal responses to exercise in dogs with innervated kidneys were similar except for transient reductions in renal flow at the onset of exercise.

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TABLE 1

Effects of Severe Exercise

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Severe exercise (steady state)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (10)</td>
<td>92 ± 6</td>
<td>277 ± 4*</td>
</tr>
<tr>
<td>Normal, alpha-receptor blockade (4)</td>
<td>100 ± 11</td>
<td>281 ± 17*</td>
</tr>
<tr>
<td>Heart failure (6)</td>
<td>125 ± 11</td>
<td>275 ± 6†</td>
</tr>
<tr>
<td>Heart failure, alpha-receptor blockade (4)</td>
<td>147 ± 10</td>
<td>282 ± 8†</td>
</tr>
<tr>
<td><strong>Mean arterial blood pressure (mm Hg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (10)</td>
<td>97 ± 4</td>
<td>137 ± 6*</td>
</tr>
<tr>
<td>Normal, alpha-receptor blockade (4)</td>
<td>95 ± 6</td>
<td>122 ± 5*</td>
</tr>
<tr>
<td>Heart failure (6)</td>
<td>103 ± 4</td>
<td>111 ± 5†</td>
</tr>
<tr>
<td>Heart failure, alpha-receptor blockade (4)</td>
<td>96 ± 8</td>
<td>99 ± 5†</td>
</tr>
<tr>
<td><strong>Innervated renal flow (ml/min)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (8)</td>
<td>171 ± 12</td>
<td>166 ± 26</td>
</tr>
<tr>
<td>Heart failure (6)</td>
<td>148 ± 6</td>
<td>46 ± 9†</td>
</tr>
<tr>
<td><strong>Denervated renal flow (ml/min)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (8)</td>
<td>168 ± 17</td>
<td>151 ± 11</td>
</tr>
<tr>
<td>Normal, alpha-receptor blockade (4)</td>
<td>190 ± 12</td>
<td>168 ± 14</td>
</tr>
<tr>
<td>Heart failure (6)</td>
<td>174 ± 12</td>
<td>120 ± 10†</td>
</tr>
<tr>
<td>Heart failure, alpha-receptor blockade (4)</td>
<td>184 ± 21</td>
<td>168 ± 10†</td>
</tr>
<tr>
<td><strong>Innervated renal resistance (mm Hg/ml min⁻¹)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (8)</td>
<td>0.57 ± 0.04</td>
<td>0.84 ± 0.15*</td>
</tr>
<tr>
<td>Heart failure (6)</td>
<td>0.73 ± 0.08</td>
<td>3.35 ± 0.53*</td>
</tr>
<tr>
<td><strong>Denervated renal resistance (mm Hg/ml min⁻¹)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (8)</td>
<td>0.62 ± 0.06</td>
<td>0.89 ± 0.09*</td>
</tr>
<tr>
<td>Normal, alpha-receptor blockade (4)</td>
<td>0.52 ± 0.05</td>
<td>0.75 ± 0.08*</td>
</tr>
<tr>
<td>Heart failure (6)</td>
<td>0.50 ± 0.07</td>
<td>0.94 ± 0.09†</td>
</tr>
<tr>
<td>Heart failure, alpha-receptor blockade (4)</td>
<td>0.50 ± 0.01</td>
<td>0.50 ± 0.04††</td>
</tr>
</tbody>
</table>

Values are means ± se.

*Change from rest to exercise is statistically significant, P < 0.05.
†Change from rest to exercise in dogs with heart failure is significantly different from that in normal dogs, P < 0.05.
‡Change from rest to exercise in dogs with denervated kidneys is significantly different from that in dogs with innervated kidneys, P < 0.05.
§Change from rest to exercise in dogs with alpha-receptor blockade and denervated kidneys is significantly different from that in dogs with denervated kidneys but without alpha-receptor blockade, P < 0.05.

again remained at control levels during the exercise response (Table 1). Thus, the steady-state increase in renal resistance which occurred in normal dogs during exercise was not mediated by either neural or humoral alpha-adrenergic mechanisms.

**Exercise Response in Dogs with Experimental Congestive Heart Failure.**—Exercise in dogs with experimental heart failure resulted in increases in heart rate to levels similar to those observed in normal dogs (275 ± 6 beats/min), although control heart rates were slightly higher than those in normal dogs (125 ± 11 beats/min). The pressor response to severe exercise was much less: mean arterial blood pressure only rose from 103 ± 4 to 111 ± 5 mm Hg. However, in contrast to normal dogs with either innervated or denervated kidneys, the blood flow to the innervated kidneys of dogs with heart failure decreased abruptly and markedly during severe exercise from 148 ± 6 to 46 ± 9 ml/min and remained depressed throughout the exercise period (Fig. 2). The elevation of calculated mean renal resistance also increased from 0.73 ± 0.08 to 3.35 ± 0.53 mm Hg/ml min⁻¹ (Table 1).

At rest, blood flow to the denervated kidney was 174 ± 12 ml/min and resistance was 0.59 ± 0.07 mm Hg/ml min⁻¹. Exercise caused
much less vasoconstriction in the denervated bed, renal flow declining to 120 ± 10 ml/min and renal resistance increasing to 0.94 ± 0.09 mm Hg/ml min⁻¹ during steady-state severe exercise (Fig. 2).

Phentolamine (0.75 mg/kg) largely prevented the rise in renal resistance in the denervated kidney: flow fell from 184 ± 21 to 168 ± 10 ml/min and resistance increased from 0.50 ± 0.01 to 0.59 ± 0.04 mm Hg/ml min⁻¹ during exercise. These decreases in flow and resistance were not significant (P > 0.5). Thus, the major portion of the renal vasoconstrictor response during exercise in heart failure appeared to be due to sympathetic neural stimulation; the much smaller portion that remained after alpha-receptor blockade appeared to be due largely to circulating catecholamines.

Effects of Intravenously Administered Noradrenaline.—The response of the renal vascular bed to bolus injections of norepinephrine (0.01–1.0 μg/kg, iv) was evaluated in both innervated and denervated renal beds. The response of the latter was characterized by rapid renal vasoconstriction accompanied by a significant pressure rise; the reduction in renal blood flow in the denervated kidney was considerably greater than that observed in the innervated renal bed. Norepinephrine at the highest dose tested (1.0 μg/kg) caused renal vascular resistance to reach a level in the denervated kidney four times greater than that in the innervated kidney, i.e., 4.98 ± 0.85 mm Hg/ml min⁻¹ compared with 1.32 ± 0.14 mm Hg/ml min⁻¹ (Fig. 3).

Discussion

The hypothesis that the renal bed responds to exercise with intense vasoconstriction and a reduction in renal blood flow is not only teleologically attractive but also gathers support on anatomical and physiological bases as well. The kidney is richly innervated with adrenergic vasoconstrictor fibers (17, 18) which, when stimulated, produce substantial vasoconstriction. In addition, elevated levels of circulating catecholamines,
Denervation supersensitivity of the denervated renal vasculature (open circles) compared with resistance responses in the innervated kidney (solid circles) of unanesthetized, healthy dogs. Norepinephrine was administered in the dose range shown by intravenous injection as a bolus. The number of experiments averaged for a particular data point is given in parentheses.

Denervation supersensitivity of the denervated renal vasculature, which should produce substantial renal vasoostriction, have been demonstrated in both exercising animals (19) and man (20), thus providing a secondary vasoconstrictor mechanism to increase renal resistance during exercise. Despite the availability of these adrenergic renal vasoconstrictor mechanisms and the considerable evidence from studies using indirect methods of measuring renal flow in man (1-4) and from studies of simulated exercise in anesthetized animal preparations (21), the renal bed responds to severe exercise in normal, healthy dogs with relatively slight vasoostriction (8) that does not significantly reduce renal blood flow (5-8). The discrepancy between the results from studies conducted in conscious humans and those from studies in dogs could be due to the inability of indirect techniques to measure total arterial inflow precisely in man or, on the other hand, could be the result of a species difference in the visceral vascular responses to exercise. Autoregulatory mechanisms may be relatively more powerful or the cardiovascular reserve may be greater in the dog, thus precluding the need for diversion of blood flow from the kidney to the exercising musculature.

We determined the extent of renal sympathetic control during exercise in normal, healthy dogs and found it to be minimal. Although the initial transient fall in renal flow was prevented by renal denervation, the steady-state levels of renal vascular resistance during severe exercise were similar in normal kidneys, denervated kidneys, and denervated kidneys following alpha-receptor blockade, indicating that renal nerves or circulating catecholamines participated little in the normal renal vascular response to severe exercise. Thus, in the normal, conscious healthy dog, the primary mechanism of regulation of renal blood flow during severe exercise does not appear to involve the sympathoadrenal system; the evidence suggests that an autoregulatory process or another nonadrenergic mechanism prevails. Renal autoregulation has been demonstrated to be effective over the blood pressure range encountered in our experiments (22) and could account for the elevated renal vascular resistance observed during severe exercise.

In contrast to the renal vascular response observed during exercise in healthy dogs, our observations of dogs with experimental congestive heart failure during exercise indicated a greater and significant ($P < 0.001$) elevation in renal vascular resistance in the innervated kidney, an elevation sufficient to reduce renal blood flow drastically. Thus, although autoregulatory or other nonadrenergic mechanisms prevail during severe exercise in normal dogs, an increase in cardiovascular stress, as in the presence of heart failure, allows the reserve adrenergic mechanism to reduce and divert renal blood flow. Other studies from our laboratory have demonstrated similar powerful visceral vasoconstriction and blood flow reduction in dogs with limited heart rate (8) or with limited oxygen-carrying capacity (9).
RENAL BLOOD FLOW DURING EXERCISE

During exercise. When renal nerves were removed, the intense vasoconstriction was markedly attenuated in dogs with heart failure, indicating that the major portion of the renal vasoconstriction during exercise in dogs with heart failure is due to activation of renal sympathetic nerves.

Even in the denervated kidneys of dogs with heart failure, renal resistance increased and renal blood flow decreased during severe exercise, indicating that neurally mediated renal vasoconstriction could not solely account for the vasoconstrictor response. Possibly circulating catecholamines could produce the renal vasoconstriction. This hypothesis was substantiated by the studies after alpha-receptor blockade; the exercise-induced renal vasoconstriction tended to be further attenuated but was not abolished. The slight vasoconstriction that remained could have been due to incomplete alpha-receptor blockade.

The denervated kidneys were shown to be supersensitive to intravenous administration of norepinephrine, both in the normal state and in heart failure, a finding in accord with the studies of Berne et al. (23, 24). If circulating catecholamines participated significantly in the vasoconstriction observed in the denervated kidney, then the kidney should have responded with profound increases in resistance, which could be blocked by phentolamine. The drug was found to be 90% effective in blocking the effects of norepinephrine (1.0 μg/kg). However, alpha-receptor blockade failed to prevent the increase in resistance in the denervated bed of the normal dogs, indicating that increases in circulating norepinephrine participated little in the normal renal response to exercise. In heart failure, although the major portion of the renal vasoconstrictor response was prevented by denervation, a small component of this response was prevented by alpha-receptor blockade. Thus, circulating catecholamines appeared to have little if any role in the regulation of renal resistance in normal dogs, but did participate in the regulation of renal resistance during exercise in dogs with heart failure.

Therefore, the renal response to severe exercise in normal, healthy dogs is governed primarily by autoregulation or other nonadrenergic mechanisms, and little contribution is made by either renal sympathetic nerves or adrenal medullary hormones. In dogs with experimentally induced heart failure, adrenergic renal vasoconstriction predominates, reducing renal blood flow appreciably during severe exercise. Renal blood flow is primarily mediated by renal nerves in dogs under abnormal cardiovascular stress since it can be extensively reduced by renal sympathetic denervation and less extensively reduced by circulating catecholamines; a further reduction can be achieved by the addition of an alpha-adrenergic antagonist.

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References


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