Renal hemodynamic responses to dynamic exercise in rabbits


Renal hemodynamic responses to dynamic exercise in rabbits. J. Appl. Physiol. 85(5): 1605–1614, 1998.—Cardiovascular hemodynamics, including renal blood flow, were measured in rabbits with one intact and one denervated kidney during various intensities of treadmill exercise. Within the first 10 s of exercise, there was rapid vasoconstriction in the innervated kidney associated with decreases in renal blood flow (range −10 to −17%). The vasoconstriction in the innervated kidney was evident at all workloads and was intensity dependent. There was no significant vasoconstriction or change in renal blood flow (range 0.5 to −3.1%) in the denervated kidney at the onset of exercise. However, a slowly developing vasoconstriction occurred in the denervated kidney as exercise progressed to 2 min at all workloads. Examination of responses to exercise performed under α-adrenergic blockade with phentolamine (5 mg/kg iv) revealed that the vasoconstriction in the innervated kidney at the onset of exercise and the delayed vasoconstriction in the denervated kidney were due primarily to activation of α-adrenergic receptors. In addition, a residual vasoconstriction was also present in the innervated kidney after α-adrenergic blockade, suggesting that, during exercise, activation of other renal vasoconstrictor mechanisms occurs which is dependent on the presence of renal nerves.

renal blood flow; renal nerves; renal denervation; α-adrenergic receptors; phentolamine

METHODS

All experimental procedures were approved by the Institutional Animal Care and Use Committee and were conducted in accordance with the American Physiological Society’s Guiding Principles in the Care and Use of Animals. Female New Zealand White rabbits (weight 3–4.5 kg, n = 9) were selected for their willingness to run on a motor-driven treadmill. After selection, rabbits were acclimated to the treadmill by running one to two times per week. These sessions consisted of one to two short (2- to 5-min) bouts of exercise at 15 m/min and 17% grade (10°). These nine rabbits were included in another study that examined renal hemodynamic responses to activation of the nasopharyngeal reflex with formaldehyde vapor (21). Surgical Preparation

Rabbits were anesthetized initially with tiletamine-zolazepam (15 mg/kg Telazol im, Elkins-Sinn, Cherry Hill, NJ) and xylazine hydrochloride (5 mg/kg im, Butler, Columbus, OH) and then were intubated with a cuffed endotracheal tube. To maintain a surgical level of anesthesia, the rabbits were mechanically ventilated with 2% halothane in room air. Animals were given enrofloxacin (5 mg/kg im; Baytril, Bayer Animal Health, Shawnee Mission, KS) to reduce the chance of postsurgical infection. Buprenorphine hydrochloride (0.03 mg/kg im; Buprenex, Reckitt & Colman, Kingston-upon-Hull, UK) was given postoperatively for pain management.
In each animal, ultrasonic transit-time flow probes (Transonic Systems, Ithaca, NY) were implanted around each renal artery according to previously published methods (2). Briefly, each kidney was exposed via a retroperitoneal approach, and a 1 × 2-cm piece of silicone rubber medical-grade sheeting (0.007-in. thickness, Technical Products, Decatur, GA) was placed under the renal artery and in some cases the renal vein. The flow probe was then placed delicately around the renal artery to avoid damaging the renal nerves. The ends of the silicone sheeting were brought together around the probe and sutured together for probe stabilization. The connector ends of the probes were wrapped in sterile parafilm and tunneled to subcutaneous pockets for later retrieval. In each animal, one kidney was surgically denervated before probe implantation by stripping the renal artery and vein near the hilus of the kidney and painting the vessels with 5% phenol. Probe implantation on the contralateral kidney served as a sham surgery for the renal denervation. Rabbits were allowed 2–5 wk to recover before being studied.

Experimental Procedures

Instrumentation. On the day of experimentation, arterial blood pressure was obtained from a small Teflon catheter (24 gauge, Angiocath, Deseret, Sandy, UT) placed into the central ear artery via a percutaneous insertion. In some cases, a cutdown under a local 4% lidocaine block was used. A short pressure line was connected to the animal's back. Venous access was obtained by placing a 24-gauge Teflon catheter percutaneously into the contralateral ear vein. The connector ends of the flow probes were retrieved from their subcutaneous pockets and connected to the flowmeter (model T206, Transonic, Ithaca, NY).

Nasopharyngeal reflex. The nasopharyngeal reflex was activated by placing a cotton swab, soaked in 37% formaldehyde (JT Baker Chemical, Philipsburg, NJ), in front of the animal’s nose for 5–10 s. The cotton swab was presented until a substantial bradycardia and a decrease in renal blood flow in the innervated kidney were observed. Because the nasopharyngeal reflex has been shown to produce a large decrease in renal blood flow (6, 36) mediated by renal nerves (6), only those animals with decreases in renal blood flow in the sham-operated kidney and little or no change in renal blood flow in the surgically denervated kidney were selected for this study. Tissue catecholamines were also used to verify renal innervation status (see Tissue catecholamine analysis).

Exercise protocol. Three exercise intensities were used in this study, and the animals were given a minimum of 45 min of rest between exercise bouts. At one intensity, the treadmill was set at 7 m/min (0% grade), and the rabbits ran for 5 min. Rabbits exercising at this intensity and duration utilize ~84% of their aerobic capacity and plasma lactate levels remain <4 mM (10). At the second exercise intensity, the treadmill was set at 12 m/min (0% grade), and the rabbits ran for 2 min. At this intensity rabbits are exercising at ~92% of estimated aerobic capacity (10). These two exercise intensities have been used in a previous study examining renal sympathetic nerve activity during treadmill exercise in rabbits (22).

At the third exercise intensity, the rabbits ran at a treadmill speed of 15 m/min (17% grade) until they were unwilling to run any longer. This same intensity was repeated in animals pretreated with the α1-adrenergic-receptor antagonist phentolamine mesylate (5 mg/kg iv; Sigma Chemical, St. Louis, MO). The α1-adrenergic agonist phenylephrine hydrochloride (10 µg/kg iv; Sigma Chemical) was used to test the adequacy of α1-adrenergic blockade by phentolamine.

Tissue catecholamine analysis. On completion of the experiments, rabbits were overdosed with a commercial euthanasia solution (Succomb, Butler, Columbus, OH), and each kidney was removed, blotted dry on gauze, weighed, and flash frozen in liquid nitrogen. Samples were kept at −70°C until assayed for norepinephrine content.

Norepinephrine content was determined by reverse-phase HPLC with electrochemical detection. Briefly, the frozen samples were homogenized in a Tris-EDTA buffer with sodium metabisulfite and alumina. The liquid homogenate was spun at 2,300 rpm for 3 min. The pellet was washed, resuspended in 0.1 M HClO4, and spun at 2,300 rpm for 3 min. The supernatant was filtered, and norepinephrine content was determined after reverse-phase HPLC by using an amperometric detector (BAS LC-4B, West Lafayette, IN).

Data analysis. Phasic arterial pressure and blood flows were stored simultaneously on magnetic tape with a video cassette data recorder (Vetter, Rebersburg, PA) and written to paper on a polygraph (Grass, West Warwick, RI). Data were analyzed off line by using a computer (Apple 850 Power Personal Computer) and MacLab System at 100 Hz (ADI Instruments, Castle Hill, Australia) to calculate mean arterial pressure, heart rate (HR), mean renal blood flow, and mean renal vascular conductance (mean renal blood flow/mean arterial pressure). Renal vascular conductance was used instead of renal vascular resistance because it has been argued that conductance better reflects changes in vascular tone in vivo, especially when the experimental manipulation causes larger changes in organ blood flow than in systemic arterial blood pressure (15, 23).

RESULTS

Responses to Formaldehyde

Activation of the nasopharyngeal reflex by using formaldehyde vapor dramatically decreased renal blood flow in sham-operated kidneys (~30 ± 3 ml/min) and in
innervated and the surgically denervated kidneys were

some cases reduced renal blood flow to zero (n = 4). In

sharp contrast, formaldehyde vapor had only a small
effect on renal blood flow in surgically denervated

kidneys (−3.9 ± 0.9 ml/min). We have suggested that

the nasopharyngeal reflex is a simple and convenient in

vivo method for assessing functional innervation of the

kidney after surgical denervation (21).

Renal Norepinephrine Content

Kidney weights were similar in the surgically dener-
vated kidneys compared with sham-operated kidneys
(12.2 ± 1.1 g vs. 11.7 ± 1.1 g; P = 0.71). Renal norepineph-
rine content was significantly higher in sham-operated kidneys
(95.7 ± 19.8 pg/mg tissue) compared with surgically denervated kidneys
(4.4 ± 1.6 pg/mg tissue; P < 0.01). On the basis of results of the functional test (formalde-
hyde) and the biochemical test (tissue catecholamine content), the sham-operated kidneys were considered innervated and the surgically denervated kidneys were considered denervated.

Responses to Phenylephrine Before α-Adrenergic Blockade (Table 1)

Arterial pressure increased and HR reflexively decreased in response to phenylephrine infusion. At rest, renal blood flow and renal vascular conductance were significantly lower in the denervated kidney. The absolute changes in renal blood flow and renal vascular conductance were similar in both kidneys in response to phenylephrine infusion. However, the relative changes in renal blood flow and renal vascular conductance were significantly greater in the denervated kidney, which suggests that the denervated kidney was more sensitive to α-adrenergic stimulation.

Effect of Exercise

Table 2 contains the arterial pressure and HR re-
sponses to the three exercise workloads. Baseline mean arterial pressure and HR were not different before each exercise workload was performed. Mean arterial pressure and HR increased in an intensity-related fashion (P < 0.05). HR was elevated significantly within the first 10 s of exercise, and mean arterial pressure was elevated significantly within the first 20 s of exercise at all workloads.

The largest exercise-induced changes in cardiovascu-
lar variables were observed at 15 m/min (17% grade). Figure 1 is a raw-data tracing taken from one rabbit exercising on the treadmill at 15 m/min (17% grade). As expected, HR increased rapidly at the start of exercise and appeared to reach a steady state by 2 min. Because arterial pressure increased and renal blood flow in the denervated kidney remained essentially unchanged, there was a slight reduction in renal vascular conductance in the denervated kidney. In sharp contrast, renal blood flow and renal vascular conductance in the inner-

Table 1. Peak hemodynamic responses to phenylephrine (10 μg/kg)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>PE</th>
<th>Absolute Change</th>
<th>% Change</th>
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<tbody>
<tr>
<td>MAP, mmHg</td>
<td>87 ± 3</td>
<td>115 ± 5*</td>
<td>29 ± 3</td>
<td>33 ± 4</td>
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<tr>
<td>HR, beats/min</td>
<td>240 ± 11</td>
<td>201 ± 8*</td>
<td>-40 ± 7</td>
<td>-16 ± 2</td>
</tr>
<tr>
<td>IRBF, ml/min</td>
<td>39 ± 5</td>
<td>28 ± 5*</td>
<td>-11 ± 4</td>
<td>-28 ± 8</td>
</tr>
<tr>
<td>DRBF, ml/min</td>
<td>28 ± 5†</td>
<td>14 ± 5*</td>
<td>-14 ± 3</td>
<td>-51 ± 7†</td>
</tr>
<tr>
<td>IRVC, ml·min⁻¹·mmHg⁻¹</td>
<td>0.46 ± 0.06</td>
<td>0.26 ± 0.05*</td>
<td>-0.20 ± 0.04</td>
<td>-44 ± 7</td>
</tr>
<tr>
<td>DRVC, ml·min⁻¹·mmHg⁻¹</td>
<td>0.33 ± 0.06†</td>
<td>0.13 ± 0.03*</td>
<td>-0.21 ± 0.04</td>
<td>-63 ± 6†</td>
</tr>
</tbody>
</table>

Values are means ± SE for 9 rabbits. PE, phenylephrine; MAP, mean arterial pressure; HR, heart rate; IRBF, innervated renal blood flow; DRBF, denervated renal blood flow; IRVC, innervated renal vascular conductance; DRVC, denervated renal vascular conductance. *P < 0.05, PE vs. baseline. †P < 0.01, denervated vs. innervated kidney.

Table 2. Hemodynamic responses taken at rest and after onset of various intensities of treadmill exercise in rabbits

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>10 s</th>
<th>20 s</th>
<th>30 s</th>
<th>1 min</th>
<th>2 min</th>
<th>Exhaustion</th>
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<tr>
<td>MAP, mmHg</td>
<td>85 ± 3</td>
<td>89 ± 4</td>
<td>92 ± 3*</td>
<td>92 ± 3*</td>
<td>94 ± 3*</td>
<td>93 ± 3*</td>
<td></td>
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<tr>
<td>HR, beats/min</td>
<td>258 ± 11</td>
<td>294 ± 7*</td>
<td>295 ± 8*</td>
<td>304 ± 7*</td>
<td>320 ± 7*</td>
<td>331 ± 6*</td>
<td></td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>82 ± 1</td>
<td>87 ± 2</td>
<td>91 ± 2*</td>
<td>94 ± 2*</td>
<td>95 ± 2*</td>
<td>96 ± 2*</td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>246 ± 10</td>
<td>303 ± 10*</td>
<td>309 ± 9*</td>
<td>319 ± 8*</td>
<td>332 ± 7</td>
<td>346 ± 7*</td>
<td></td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>81 ± 2</td>
<td>87 ± 4</td>
<td>96 ± 3*</td>
<td>96 ± 3*</td>
<td>97 ± 2*</td>
<td>99 ± 3*</td>
<td>99 ± 4*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>248 ± 11</td>
<td>306 ± 7*</td>
<td>315 ± 8*</td>
<td>330 ± 6*</td>
<td>348 ± 6*</td>
<td>365 ± 5*</td>
<td>388 ± 4*</td>
</tr>
</tbody>
</table>

Phentolamine + 15 m/min, 17% grade

| MAP, mmHg  | 77 ± 3 | 64 ± 2† | 60 ± 3† | 64 ± 3† | 66 ± 3† | 69 ± 3† | 70 ± 3† |
| HR, beats/min | 239 ± 21 | 301 ± 19* | 337 ± 17* | 355 ± 10* | 373 ± 8* | 385 ± 7* | 393 ± 6* |

Values are means ± SE for 9 rabbits. *Significant change from rest, P < 0.01. †Significant change compared with 15 m/min, 17% grade, without phentolamine, P < 0.01.
vated kidney decreased dramatically at the onset of exercise, reached a steady state after 2 min, and remained depressed until the animal refused to run any longer.

Figure 2 illustrates the blood flow responses at each exercise intensity in denervated and innervated kidneys. Resting blood flow was higher in the innervated vs. denervated kidney before each exercise bout. During exercise at all three workloads, renal blood flow decreased in the innervated kidney within the first 10 s of exercise (range \(-10\%\) to \(-17\%\)) and remained depressed throughout each exercise bout, and the response was intensity dependent (\(P < 0.01\)). In contrast, renal blood flow in the denervated kidney remained essentially unchanged at the onset of exercise at each workload (range \(-1\%\) to \(+3\%\)) and remained stable throughout each exercise bout, and this response was not related to intensity (\(P > 0.05\)). At 7 m/min, blood flow in the innervated kidney decreased but was still significantly higher than blood flow in the denervated kidney. At the two higher exercise workloads, blood flow in the innervated kidney decreased to levels similar to those observed in the denervated kidney.

Figure 3 shows the changes in vascular conductance in the denervated and innervated kidneys at each exercise intensity. Resting vascular conductance was significantly lower in the denervated kidney. Renal vascular conductance decreased significantly in the innervated kidney within 10 s of the onset of exercise (\(-17.7\%\) to \(-22.7\%\)) and remained depressed over the entire time course of exercise, and the response was intensity dependent (\(P < 0.01\)). In the denervated kidney, renal vascular conductance was not altered during the first 30 s of exercise at any workload. However, renal vascular conductance significantly decreased by 2 min of exercise at 7 m/min (\(-17 \pm 3\%\)) and 12 m/min (\(-27 \pm 3\%\)). At 15 m/min (17% grade), the decrease in renal vascular conductance in the denervated kidney occurred earlier, at 1 min after the onset of exercise (\(-31 \pm 4\%\)). During exercise at all three workloads, the values for renal vascular conductance were similar between the innervated and denervated kidneys (Fig. 3).

Effect of \(\alpha\)-Adrenergic Blockade on the Responses to Exercise

Adequacy of \(\alpha\)-adrenergic blockade by phentolamine was tested by examining renal vascular responses to
phenylephrine. Phentolamine abolished the decrease in renal blood flow produced by phenylephrine in both the innervated ($-28 \pm 8$ vs. $-2.0 \pm 1\%$) and denervated kidney ($-51 \pm 7$ vs. $-3 \pm 1\%$).

There were no significant differences in baseline mean arterial pressure or HR after phentolamine (Table 2). Unlike exercise in the absence of $\alpha$-adrenergic blockade, arterial pressure decreased significantly at the onset of exercise with phentolamine pretreatment. The depressor response was sustained through 2 min of exercise but was not different from its preexercise value at the time of exhaustion. HR responses to exercise appeared larger after $\alpha$-adrenergic blockade but did not reach statistical significance.

Figure 4 depicts the changes in renal blood flow during exercise at 15 m/min in the presence and absence of $\alpha$-adrenergic blockade. Phentolamine did not alter resting blood flows in the innervated ($40 \pm 6$ vs. $42 \pm 6$ ml/min) or denervated kidney ($29 \pm 5$ vs. $26 \pm 5$ ml/min). Therefore, similar to the other exercise conditions, resting renal blood flow was higher in the innervated kidney compared with the denervated kidney after $\alpha$-adrenergic blockade. During exercise at 15 m/min, the reduction in renal blood flow in the innervated kidney was not affected by $\alpha$-adrenergic blockade. However, in the denervated kidney there was an abrupt decrease in renal blood flow at the onset of exercise with $\alpha$-adrenergic blockade, which was not present in the absence of $\alpha$-adrenergic blockade.

The effects of $\alpha$-adrenergic blockade on renal vascular conductance responses to exercise at 15 m/min are shown in Fig. 5. Resting vascular conductance was not altered by phentolamine in either the innervated $(0.49 \pm 0.07$ vs. $0.54 \pm 0.07$ ml $\cdot$ min$^{-1}$ $\cdot$ mmHg$^{-1}$) or denervated kidney $(0.36 \pm 0.06$ vs. $0.33 \pm 0.05$ ml $\cdot$ min$^{-1}$ $\cdot$ mmHg$^{-1}$). Phentolamine abolished the abrupt decrease in renal vascular conductance in the innervated kidney at the onset of exercise (0–30 s). At the onset of exercise, renal vascular conductance increased slightly in the denervated kidney. Thus the fall in renal blood flow observed in both the innervated and denervated kidney at the onset of exercise with phentolamine treatment was likely a passive response to the abrupt fall in arterial pressure.

As exercise continued past 30 s, a significant, sustained reduction in renal vascular conductance developed in the innervated kidney despite $\alpha$-adrenergic blockade. In contrast, phentolamine abolished the slowly developed reduction in renal vascular conductance observed in the denervated kidney during exercise under the unblocked condition. Thus a combination of renal denervation and $\alpha$-adrenergic blockade eliminated the renal vasoconstriction associated with dynamic exercise in rabbits.
Fig. 3. Renal vascular conductance responses in innervated (●) and denervated kidney (△) at rest and during 3 different exercise intensities (7 m/min, 0% grade (A); 12 m/min, 0% grade (B); and 15 m/min, 17% grade (C)). Values are means ± SE for 9 rabbits. *Significant change from rest in innervated kidney (above lines) or denervated kidney (below lines), P < 0.01. # Significant difference between innervated and denervated kidneys, P < 0.01. Note decrease in renal vascular conductance at onset of exercise (0–30 s) in innervated kidney and a slowly developing vasoconstriction in denervated kidney that is statistically significant (P < 0.01) at 1 min (15 m/min, 17% grade) and 2 min (all workloads) of exercise.

Fig. 4. Renal blood flow responses in innervated (A) and denervated (B) kidney during treadmill exercise at 15 m/min (17% grade) in the presence (▼) and absence (●) of α-adrenergic-receptor blockade with phentolamine mesylate (5 mg/kg iv). Values are means ± SE for 9 rabbits. * Significant change from rest in presence (below lines) and absence (above lines) of phentolamine, P < 0.01. # Significant differences between exercise with and without α-adrenergic blockade, P < 0.01.
Time to Exhaustion

At 15 m/min (17% grade) without \(\alpha\)-adrenergic blockade, the rabbits exercised for an average of 410 ± 67 s. After \(\alpha\)-adrenergic blockade, exercise duration was shortened to 209 ± 55 s (\(P < 0.01\) from unblocked condition).

DISCUSSION

The results of this study demonstrate the importance of renal nerves in control of blood flow to the kidney at the onset of exercise. At all three exercise intensities, a decrease in renal blood flow due to renal vasoconstriction was observed in the innervated kidney within the first 10 s of treadmill exercise and was sustained as long as exercise continued. In contrast, neither a decrease in renal blood flow nor vasoconstriction occurred in the denervated kidney at the onset of exercise. A slowly developing vasoconstriction did occur in the denervated kidney as exercise continued, which was blocked by \(\alpha\)-adrenergic blockade. These results suggest that circulating catecholamines can contribute to the renal vasoconstrictor response during exercise.

At the highest workload, \(\alpha\)-adrenergic blockade abolished the initial renal vasoconstriction in the innervated kidney, supporting a role for neurally released norepinephrine in the vasoconstrictor response. As exercise continued past 30 s, a residual vasoconstrictor response developed in the innervated kidney but not in the denervated kidney. That residual vasoconstriction occurred after \(\alpha\)-adrenergic block in the innervated kidney but not in the denervated kidney suggests that a neurally mediated renal vasoconstriction can occur independently of \(\alpha\)-adrenergic receptors.

Although resting blood flow and vascular conductance were lower in the denervated kidney, the denervated vasculature was capable of responding adequately to \(\alpha\)-adrenergic stimulation. Indeed, the vasoconstrictor response to phenylephrine was potentiated in the denervated kidney, as indicated by the greater relative change in vascular conductance. When significant differences in baseline flow occur, the relative change in conductance is the most appropriate index of blood vessel radius. This is due to the fact that absolute changes in conductance can vary greatly when identical changes in vessel radius are imposed on differing baseline blood flows, whereas a given percent reduction in conductance always reflects a predictable percent reduction in the radius of the vessel despite differing baseline blood flows. In the present study, the percent change in renal vascular conductance to phenylephrine was significantly greater in the denervated kidney, which suggests the possibility of denervation supersensitivity (8, 12).

The minor reductions in renal blood flow and renal vascular conductance in the denervated kidney coupled with the striking vasoconstriction in the innervated kidney resulted in similar levels of absolute flow and conductance during exercise. If renal nerves were not important in mediating the initial vasoconstriction, we would have expected vascular conductance in the denervated kidney to decrease at the onset of exercise; in other words, the denervated kidney would have demonstrated a response similar to the innervated kidney. In contrast, the significant interaction between innervation status and renal hemodynamic responses to exercise demonstrates that the kidneys responded differ-
ently to the stimulus of exercise and that the state of innervation is important in renal vascular responses to exercise.

In humans, dynamic exercise produces an intensity-dependent decrease in renal blood flow (32). Previous studies examining renal blood flow responses during dynamic exercise in rabbits have reported that decreases in renal blood flow occur within the first 20 s of exercise (7) and that renal vasoconstriction continues through at least 2 min of exercise (4). The results of the present study complement and extend these previous findings, in that intensity-dependent renal vasoconstriction was observed within the first 10 s of exercise in the innervated kidney and was sustained throughout each exercise bout. More importantly, our data suggest that the immediate decrease in renal blood flow is due to neurally mediated renal vasoconstriction, because no changes in renal blood flow or vascular conductance were observed in the denervated kidney at the onset of exercise. This study supports a physiological role for the increase in renal sympathetic nerve activity observed at the onset of dynamic exercise in rabbits (5, 22).

To our knowledge, there is only one other report (9) that has examined the effects of renal denervation in an intact-animal model that exhibits sustained decreases in renal blood flow during dynamic exercise. Hohimer and Smith (9) reported that unilateral denervation abolished the initial renal vasoconstriction observed in baboons performing light exercise. Therefore, the evidence to date demonstrates that renal nerves are responsible for the initial renal vasoconstriction during exercise across a wide range of intensities.

There have been a number of studies performed in dogs that have examined the renal blood flow response to dynamic exercise (16, 19, 29, 33, 34). Renal denervation has been shown to block the decrease in renal blood flow in dogs with circulatory compromise such as splenectomy or pacing-induced heart failure (19, 33). Because healthy dogs do not exhibit a sustained decrease in renal blood flow even at exhaustive workloads (16, 19, 34), other investigators have questioned the validity of the dog as an appropriate model for studying renal hemodynamic responses to exercise (9, 29). There is an increase in renal vascular resistance during exercise in dogs, indicating renal vasoconstriction (16, 19, 34). However, the increase in renal vascular resistance is unaffected by renal denervation or \( \alpha \)-adrenergic blockade, suggesting an autoregulatory phenomenon (16, 19, 34). In contrast, in the present study the combination of renal denervation and \( \alpha \)-adrenergic block abolished renal vasoconstriction during exercise. These results argue against a strong role for autoregulation in the renal vasoconstrictor response to short-term exercise in the rabbit.

In the present study, there was significant renal vasoconstriction in the denervated kidney by 2 min of exercise at each workload and by 1 min at the highest workload. These data suggest that compensatory mechanisms exist in the renal vasculature that act independently of direct renal innervation to permit redistribution of blood flow away from the kidneys as exercise duration or intensity increases. Because phentolamine pretreatment abolished the slowly developing vasoconstrictor response, \( \alpha \)-adrenergic receptors appear to produce vasoconstriction in the denervated kidney via circulating catecholamines. Interestingly, the intact kidney is thought to contribute a significant portion of the elevated plasma norepinephrine during dynamic exercise in humans (32). Norepinephrine is the dominant catecholamine released from the kidney (3). Therefore, it is possible that, in the rabbit, norepinephrine spillover from the innervated kidney contributed to circulating catecholamines that were responsible for the vasoconstriction in denervated kidney. It is important to note that the magnitude of the vasoconstriction observed in the denervated kidney could be influenced by an enhanced sensitivity to circulating catecholamines (8, 12). Denervation supersensitivity has been shown to occur in denervated rat kidneys (8, 12, 13) and may be due to an increase in the number of \( \alpha \)-adrenergic receptors in the renal vasculature (37).

The residual vasoconstriction apparent in the innervated kidney during exercise with \( \alpha \)-adrenergic blockade suggests that a nerve-dependent mechanism produced vasoconstriction independent of \( \alpha \)-adrenergic receptors. The classic neurotransmitter at postganglionic sympathetic nerves is norepinephrine, but more recently it has been shown that sympathetic nerve stimulation produces corelease of other vasoconstrictor substances, such as neuropeptide Y (24). There are now several studies that provide evidence for an increase in neuropeptide Y during physical activity in humans (1, 17, 25) that may be related to decreases in renal blood flow (32). Exogenous neuropeptide Y causes renal vasoconstriction in rabbits that is independent of \( \alpha \)-adrenergic receptors (20). Because renal sympathetic nerve activity increases in an intensity-dependent manner in rabbits (22), we speculate that higher intensity exercise will produce greater activation of renal sympathetic nerves, resulting in corelease of norepinephrine and neuropeptide Y.

Alternatively, the \( \alpha \)-adrenergic-independent vasoconstriction in the innervated kidney may be mediated by the renin-angiotensin system. Stimulation of renal nerves results in renal release of renin, which is mediated by \( \beta \)-adrenergic receptors (3). The hypothesis that angiotensin II may be involved in renal vasoconstriction during exercise is supported by studies in which dynamic exercise was associated with increases in renal overflow of renin and angiotensin II (32). In addition, Stebbins and Symons (31) reported that losartan, an angiotensin AT1-receptor antagonist, attenuated decreases in renal blood flow and increases in renal vascular resistance observed in exercising miniature swine.

In the present study, \( \alpha \)-adrenergic blockade abolished the slowly developing vasoconstriction observed in the denervated kidney, which argues against a significant role for circulating angiotensin II in the renal vascular response to exercise in the rabbit. How-
ever, we did not measure plasma levels of renin or angiotensin II and thus cannot evaluate whether chronic unilateral renal denervation or phentolamine pretreatment altered circulating levels of angiotensin II during exercise in the rabbit. Although unilateral denervation should decrease β-adrenergic-mediated renin release from the ipsilateral kidney, the abrupt fall in renal perfusion pressure at the onset of exercise with α-adrenergic block should have been a potent stimulus for renin release from both kidneys (3).

In summary, our study demonstrates that renal nerves, via activation of α-adrenergic receptors, are primarily responsible for the abrupt decreases in renal blood flow and renal vascular conductance at the onset of dynamic exercise in rabbits. In the absence of renal nerves, renal blood flow does not decrease during moderate to heavy dynamic exercise. The renal vasoconstriction observed during steady-state exercise in the innervated kidney appears to have a neurally mediated, α-adrenergic-independent component.

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