Hemodynamics of Early Experimental Renal Hypertension in Dogs
NORMAL LIMB BLOOD FLOW, ELEVATED LIMB VASCULAR RESISTANCE, AND DECREASED VENOUS COMPLIANCE

By Henry W. Overbeck

ABSTRACT
To investigate the hemodynamics of early experimental renal hypertension, skin and muscle blood flows and intravascular pressures were measured in the isolated, innervated, naturally perfused forelimbs of 44 male mongrel dogs under pentobarbital (35 mg/kg) anesthesia. In addition, venous pressure-volume relationships were studied in temporarily isolated segments of femoral and jugular veins. In 10 dogs (group H-1) one kidney was wrapped in silk 8 days before study; in 12 (H-2) one kidney was wrapped 4 weeks, and a contralateral nephrectomy was done 2 weeks, before study; 22 were prepared as appropriate normotensive controls. A significant rise in mean arterial pressure occurred in groups H-1 and H-2. Compared to corresponding control groups, (1) muscle and skin blood flows in both hypertensive groups were unchanged (P>0.1); (2) muscle and skin resistances/100 g limb weight were increased in group H-2 (P<0.05); and (3) femoral venous pressure-volume curves were shifted toward the pressure axis (P<0.02). These data suggest that in the early stages of experimental renal hypertension in dogs: (1) blood flow in skin and skeletal muscle is not increased; (2) arteriolar resistance is elevated in skin and skeletal muscle; and (3) reduced venous compliance may be present.

KEY WORDS arterial resistance perinephritic hypertension venous resistance small vessel resistance skeletal muscle skin guanethidine propranolol diazoxide

Several investigations indicate that the cardiac output may be elevated in the early stages of experimental renal hypertension (1, 2). Ferrario et al. (2) found increased cardiac output in unanesthetized dogs during the first 4 weeks of perinephritic hypertension. After 4-6 weeks, the cardiac output returned to normal and the hypertension was sustained by increased total peripheral resistance. Because blood volume remains normal (2), it has been suggested that the increased cardiac output in early renal hypertension may be attributable to increased venous tone and venous return (1-3) and that the later peripheral arteriolar constriction may be an autoregulatory response to increased tissue blood flow (1-4).

We have reported hemodynamic studies in dogs in the later stages (> 4 weeks' duration) of perinephritic hypertension (5). In the limb vascular beds of these pentobarbital-anesthetized dogs the blood flow was normal and the resistance increased. Our results were thus compatible with the findings of Ferrario and his co-investigators (2) in the later stages of
hypertension in their dogs. We now report our findings in dogs with perinephritic hypertension of less than 4 weeks' duration, with and without contralateral nephrectomy. We measured blood flows and intravascular pressures in limb skeletal muscle and skin vascular beds. We also investigated volume-pressure relationships in temporarily isolated segments of peripheral veins in situ.

Methods

Healthy male mongrel dogs weighing 18–28 kg were trained to lie quietly during femoral arterial punctures for blood pressure measurements, which were made weekly during an observation period of at least 3 weeks. Animals with mean arterial pressures above 140 mm Hg on two or more occasions were rejected. At the end of this period, 44 dogs were accepted for the experiments. We divided these dogs into four groups, designated H(ypertensive)-1, 10 dogs; H-2, 12 dogs; C(ontrol)-1, 10 dogs; and C-2, 12 dogs. A left flank incision was made under pentobarbital anesthesia and sterile conditions. In dogs of groups H-1 and H-2 we dissected the left kidney free from its fat pad and wrapped it in silk to produce perinephritic hypertension (6). In groups C-1 and C-2 we merely dissected the left kidney free from its fat pad and restored it to its normal position. The flank incision was then closed and procaine penicillin (100,000 units) and streptomycin (0.1 g) were given intramuscularly daily for the first 5 postoperative days. We maintained the dogs on a diet of standard dog chow (Ken-L-Ration meal) pre- and postoperatively. Postoperatively, arterial blood pressure was measured weekly by femoral arterial puncture. Two weeks later, in groups H-2 and C-2 only, we made a right flank incision under pentobarbital anesthesia and sterile conditions and removed the right kidney. Again the incision was closed and antibiotics were administered for 5 days.

We studied limb hemodynamics in dogs of groups H-1 and C-1 8 days after kidney wrapping and sham surgery, respectively (with the opposite kidney untouched). We studied hemodynamics in dogs of groups H-2 and C-2 2 weeks after the nephrectomy.

For the hemodynamic studies, the dogs were anesthetized with sodium pentobarbital, 35 mg/kg, iv (supplemental doses of 50–100 mg were given later as necessary, but no measurements were made during the first 10 minutes following administration). Mechanical ventilation was adjusted so that measured systemic arterial blood pH was maintained at 7.39–7.41. Heparin (10,000–15,000 USP units) was given for systemic anticoagulation. We used the isolated, innervated, naturally perfused forelimb preparation (7) for study of blood flows and pressures. In this preparation, all tissues except the brachial artery, the cephalic and brachial veins, and the forelimb nerves, are severed at the level of the lower humerus. Blood flow through the brachial artery remains intact. Cephalic and brachial veins are cannulated so that venous outflow (designated skin blood flow and muscle blood flow, respectively) may be measured with graduated cylinder and stopwatch; with the median cubital vein ligated, the cephalic vein drains primarily the skin vascular bed, whereas the brachial vein drains primarily skeletal muscle (7). With intravascular catheters we also monitored mean pressures in the aorta (PA), small arteries of the skin (Pssa) and muscle (Pmsa), small veins of the skin (Pssv) and muscle (Pmsv), and the cephalic (Pslv) and brachial (Pmlv) veins. These pressures were detected by a Statham P23Gb pressure transducer and recorded on a Sanborn oscillographic recording machine.

Beginning at least 90 minutes after initial anesthesia, we made repeated measurements of intravascular pressures and of cephalic and brachial venous outflows for 30 minutes. In some dogs, clamps were then tightened on outflow tubing from the cephalic and brachial veins to raise pressure in these veins to approximately 35 mm Hg. We then again made repeated measurements of flows and pressures for 15 minutes to determine the effect of elevated intravenous pressures on venous resistance.

We divided means of intravascular pressure gradients by the appropriate blood flow to calculate steady-state segmental vascular resistances as follows:

\[
\text{Muscle arterial resistance} = \frac{(PA - Pmsa)}{(\text{muscle blood flow}/100 \text{ g forelimb weight})}.
\]

\[
\text{Muscle small vessel resistance} = \frac{(Pmsa - Pmsv)}{(\text{muscle blood flow}/100 \text{ g})}.
\]

\[
\text{Muscle venous resistance} = \frac{(Pmsv - Pmlv)}{(\text{muscle blood flow}/100 \text{ g})}.
\]

\[
\text{Muscle total resistance} = \frac{(PA - Pmlv)}{(\text{muscle blood flow}/100 \text{ g})}.
\]

\[
\text{Skin arterial resistance} = \frac{(PA - Pssa)}{(\text{skin blood flow}/100 \text{ g})}.
\]

\[
\text{Skin small vessel resistance} = \frac{(Pssa - Pssv)}{(\text{skin blood flow}/100 \text{ g})}.
\]

\[
\text{Skin venous resistance} = \frac{(Pssv - Pslv)}{(\text{skin blood flow}/100 \text{ g})}.
\]

\[
\text{Skin total resistance} = \frac{(PA - Pslv)}{(\text{skin blood flow}/100 \text{ g})}.
\]

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Forelimb total resistance = (skin total resistance x muscle total resistance)/(skin total resistance + muscle total resistance).

Forelimb arterial resistance = (skin arterial resistance x muscle arterial resistance)/(skin arterial resistance + muscle arterial resistance).

Forelimb small vessel resistance = (skin small vessel resistance x muscle small vessel resistance)/(skin small vessel resistance + muscle small vessel resistance).

Forelimb venous resistance = (skin venous resistance x muscle venous resistance)/(skin venous resistance + muscle venous resistance).

We calculated mean intravascular skin and muscle venous pressures as (Psvv + Pslv)/2 and (Pmsv + Pmlv)/2, respectively. We compared flows, pressures, and calculated resistances in dogs of the hypertensive groups (H-1 and H-2) with those in dogs of the control groups (C-1 and C-2) by Student's t-test (8).

Additionally, during the initial surgical preparation we isolated 3-cm segments of the femoral and the jugular veins by carefully ligating all side branches. Care was taken not to strip the adventitia from the veins. The same sections of veins were isolated in each dog. A catheter was introduced into each segment through one side branch. Nooses of suture were passed around the ends of each segment but not tightened, so that flow through the segment remained intact.

After the measurements of flows and pressures in the forelimb vascular bed described above, we studied pressure-volume relationships in these venous segments, using techniques similar to those of Greene and coinvestigators (9). The segments were, in turn, temporarily isolated from the circulation by tightening the suture nooses. Blood was then removed from the occluded segment through the indwelling catheter until intrasegmental pressure was at atmospheric level. To produce stepwise increases in intrasegmental pressure we injected 0.05-ml of isosmolar NaCl solution (37°C) tinged with Evans blue dye (0.1 mg/ml) into the segment. Five to 20 such injections were made and intrasegmental pressures of up to 40 mm Hg produced. A 10-second pause after each injection was allowed to establish steady-state pressures. Then the next injection was made. These steady-state intrasegmental pressures were detected with a Statham P23BB pressure transducer and recorded. We then withdrew 0.05-ml samples of saline at similar time intervals, again measuring the resulting pressures. Time required for each volume-pressure study was less than 7 minutes. We then opened the segments to the circulation, repeating the same measurements after a waiting period of at least 25 minutes. Data were accepted if all injected saline was recovered from the segment, indicating that there was no leak, and if the second series of measurements was similar to the first series. Using the means of the two series of measurements, we constructed a volume-pressure curve for each dog. Volumes (injection phase) producing intrasegmental pressures of 10, 20, and 30 mm Hg in hypertensive dogs were compared by Student's t-test with respective volumes in control normotensive dogs.

Finally, in some of the same dogs we studied the effect on femoral venous volume-pressure curves of intravenous injections of propranolol, diazoxide, or guanethidine. We injected only one of these three antihypertensive agents into each dog. Five mg of propranolol HCl was injected intravenously at 1 mg/min into two dogs of each group. In each dog this dose abolished the effect on blood pressure and heart rate of an intravenous infusion of isoproterenol (6 μg/min). In these dogs we performed the final volume-pressure study at least 30 minutes after propranolol was injected. Diazoxide1 (5 mg/kg) was rapidly injected intravenously into two dogs each of groups C-1, C-2, and H-2 25 minutes after the previous volume-pressure study. Approximately 5 minutes after the injection, when a steady-state blood pressure was reestablished, the pressure-volume study was performed. Guanethidine monosulfate2 (13.3 mg) was injected intravenously into two dogs each of groups C-1, C-2, and H-2 25 minutes after the previous volume-pressure study. Approximately 5 minutes after the injection, when a steady-state blood pressure was reestablished, the pressure-volume study was performed. We compared pressure-volume curves in each dog before and after injection of the antihypertensive drug.

At the conclusion of the experiment we killed the dogs, examined the kidney(s), and weighed the amputated forelimb.

Results

From an initial average value of 111.4 mm Hg, mean arterial blood pressure in unanesthetized dogs rose 12.2 mm Hg (P < 0.001, N = 21) during the first 2 weeks after wrapping one kidney in silk. Most of this rise occurred during the first week. When the

1Hyperstat, I.V. provided by the Schering Corporation.

2Ismelin, provided by the CIBA Pharmaceutical Company.
opposite kidney was removed, the arterial pressure rose by an additional 42.4 mm Hg ($P < 0.001$, $N = 12$), on the average. In the control groups, in contrast, from an initial average value of 113.4 mm Hg there was no significant change ($P > 0.5$) in mean arterial blood pressure following sham surgery ($N = 21$) or nephrectomy ($N = 12$). There were no statistically significant differences between hypertensive and control groups in body or forelimb weight (Table 1). The general health of all dogs remained good.

Time required to complete surgical preparations was similar in the groups of dogs, as was the amount, usually slight, of blood loss before and during the hemodynamic observations. Tables 1–3 present group means and standard errors for arterial blood pressure under pentobarbital anesthesia and for measured blood flows, pressures, and calculated resistances in the isolated forelimbs. In the control normotensive dogs and also in hypertensive dogs of group H-1, approximately 90 minutes after induction of anesthesia mean aortic blood pressure had increased about 30 mm Hg over values before anesthesia. In contrast, we observed that pentobarbital anesthesia evoked a lesser rise (approximately 19 mm Hg) in the mean aortic blood pressure of hypertensive dogs of group H-2. In our earlier study (5) we also noted that pentobarbital anesthesia increased arterial pressure to a greater extent in normotensive than in renal hypertensive dogs. As compared to appropriate control groups there were no significant differences in total, muscle, or skin blood flows in the hypertensive dogs at either stage in the development of hypertension. In this regard, mean flows in hypertensives were less, if anything, than flows in normotensives. Following nephrectomy, there appeared the first significant increases in $P_A$, $F_{ms}$, and $F_{ss}$ in anesthetized hypertensive dogs as compared to control dogs. In neither hypertensive group were there significant changes in $P_{msv}$, $F_{mlv}$, $F_{(msv+mlv)/2}$, $P_{ssv}$, $P_{slv}$, or $P_{(ssv+slv)/2}$.

### TABLE 1

**Group Means ($\pm SE$) of Weights, Aortic Pressure, Forelimb Blood Flows, and Resistances**

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<thead>
<tr>
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<tr>
<td>Body wt (kg)</td>
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<tr>
<td>$\pm$</td>
<td>24.0</td>
<td>22.5</td>
<td>23.8</td>
<td>21.7</td>
<td>23.8</td>
<td>22.1</td>
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<tr>
<td>Forelimb wt (kg)</td>
<td>0.8</td>
<td>1.0</td>
<td>0.8*</td>
<td>0.6</td>
<td>0.51</td>
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<tr>
<td>$\pm$</td>
<td>0.612</td>
<td>0.576</td>
<td>0.589</td>
<td>0.508</td>
<td>0.580</td>
<td>0.588</td>
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<tr>
<td>$P_A$ (mm Hg)</td>
<td></td>
<td></td>
<td>149.2</td>
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<td>170.4$^2$</td>
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</tr>
<tr>
<td>$\pm$</td>
<td>150.3</td>
<td>153.0</td>
<td>145.3</td>
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</tr>
<tr>
<td>Forelimb total blood flow (ml/min)</td>
<td>124.0</td>
<td>102.7</td>
<td>118.1</td>
<td>103.6</td>
<td>120.9</td>
<td>103.2</td>
</tr>
<tr>
<td>$\pm$</td>
<td>13.1</td>
<td>12.0</td>
<td>10.2</td>
<td>8.4</td>
<td>8.0</td>
<td>6.9</td>
</tr>
<tr>
<td>(ml/min 100 g$^{-1}$)</td>
<td>20.2</td>
<td>18.0</td>
<td>20.3</td>
<td>17.7</td>
<td>20.2</td>
<td>17.8</td>
</tr>
<tr>
<td>$\pm$</td>
<td>1.8</td>
<td>2.2</td>
<td>1.5</td>
<td>1.5</td>
<td>1.1</td>
<td>1.3</td>
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<tr>
<td>Forelimb resistance (mm Hg/ml min$^{-1}$ 100 g$^{-1}$)</td>
<td>7.12</td>
<td>8.40</td>
<td>6.98</td>
<td>11.12$^3$</td>
<td>7.04</td>
<td>9.96$^4$</td>
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<tr>
<td>$\pm$</td>
<td>0.06</td>
<td>0.97$^2$</td>
<td>0.53</td>
<td>1.40</td>
<td>0.41</td>
<td>0.93$^4$</td>
</tr>
<tr>
<td>Arterial</td>
<td>1.17</td>
<td>1.35</td>
<td>1.09</td>
<td>1.47</td>
<td>1.13</td>
<td>1.41$^2$</td>
</tr>
<tr>
<td>$\pm$</td>
<td>0.08</td>
<td>0.16</td>
<td>0.07</td>
<td>0.17</td>
<td>0.05</td>
<td>0.11</td>
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<tr>
<td>Small vessel</td>
<td>5.71</td>
<td>7.01</td>
<td>5.66</td>
<td>9.36$^2$</td>
<td>5.68</td>
<td>8.29$^2$</td>
</tr>
<tr>
<td>$\pm$</td>
<td>0.64</td>
<td>0.79</td>
<td>0.52</td>
<td>1.26</td>
<td>0.40</td>
<td>0.80</td>
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<tr>
<td>Venous</td>
<td>0.17</td>
<td>0.16</td>
<td>0.16</td>
<td>0.22</td>
<td>0.16</td>
<td>0.20</td>
</tr>
<tr>
<td>$\pm$</td>
<td>0.02</td>
<td>0.03$^2$</td>
<td>0.01</td>
<td>0.03</td>
<td>0.01</td>
<td>0.02$^2$</td>
</tr>
</tbody>
</table>

Number of dogs is given in parentheses with the exceptions noted.

*12 dogs; **22 dogs; ||9 dogs; $^1$21 dogs.

$P < 0.01$; $^2P < 0.05$, for comparison of hypertensive group with appropriate control group.
TABLE 2

<table>
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<tr>
<td>(ml/min)</td>
<td>55.4 ± 5.5</td>
<td>46.8 ± 5.4</td>
<td>55.0 ± 4.6</td>
<td>48.8 ± 4.8</td>
<td>55.2 ± 3.4</td>
<td>47.9 ± 3.4</td>
</tr>
<tr>
<td>(ml/min 100 g⁻¹)</td>
<td>9.00 ± 0.83</td>
<td>8.27 ± 0.89</td>
<td>9.44 ± 0.63</td>
<td>8.34 ± 0.56</td>
<td>9.23 ± 0.47</td>
<td>8.31 ± 0.64</td>
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<tr>
<td>Pressure (mm Hg)</td>
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<tr>
<td>Small artery</td>
<td>122.7 ± 2.3</td>
<td>131.5 ± 1.8</td>
<td>128.8 ± 1.6</td>
<td>161.3* ± 1.7</td>
<td>125.9 ± 1.3</td>
<td>147.8* ± 1.2</td>
</tr>
<tr>
<td>Small vein</td>
<td>16.4 ± 1.6</td>
<td>13.8 ± 1.6</td>
<td>18.1 ± 1.5</td>
<td>14.3 ± 1.4</td>
<td>16.2 ± 1.3</td>
<td>14.1 ± 1.0</td>
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<tr>
<td>Large vein</td>
<td>11.3 ± 1.6</td>
<td>11.2 ± 1.6</td>
<td>12.3 ± 1.5</td>
<td>9.9 ± 1.4</td>
<td>11.8 ± 1.3</td>
<td>10.5 ± 1.0</td>
</tr>
<tr>
<td>Mean intravascular venous</td>
<td>13.9 ± 1.6</td>
<td>12.5 ± 1.7</td>
<td>14.2 ± 1.5</td>
<td>12.1 ± 1.5</td>
<td>14.0 ± 1.2</td>
<td>12.3 ± 1.1</td>
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<tr>
<td>Resistance (mm Hg/ml min⁻¹ 100 g⁻¹)</td>
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<tr>
<td>Total</td>
<td>15.91 ± 1.34</td>
<td>18.58 ± 1.94†</td>
<td>15.02 ± 1.08</td>
<td>24.41† ± 3.31</td>
<td>15.45 ± 0.83</td>
<td>21.91† ± 2.12‡</td>
</tr>
<tr>
<td>Arterial</td>
<td>2.64 ± 0.28</td>
<td>3.01 ± 0.58†</td>
<td>2.12 ± 0.18</td>
<td>3.24 ± 0.47</td>
<td>2.27 ± 0.18</td>
<td>3.14 ± 0.36</td>
</tr>
<tr>
<td>Venous</td>
<td>0.55 ± 0.09</td>
<td>0.39 ± 0.06‡</td>
<td>0.41 ± 0.05</td>
<td>0.58 ± 0.11</td>
<td>0.48 ± 0.05</td>
<td>0.74 ± 0.07§</td>
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Number of dogs is given in parentheses with the exceptions noted.

*P < 0.01; †P < 0.05, for comparison of hypertensive group with appropriate control group.
‡9 dogs; §21 dogs.

As compared to group C-2, total forelimb, total muscle, and total skin resistances were significantly (P<0.05) increased (by +59, +62, and +60%, respectively) in group H-2. Increases in means of these variables also occurred in group H-1, but they were not of statistical significance (0.4 < P < 0.2). In group H-2 the increases in resistance were confined to the small vessel segment of the muscle and skin vascular beds with no statistically significant changes occurring in resistances of the arterial or venous segments. However, if data from groups H-1 and H-2 were combined and compared to combined data from the control groups, not only were the increases in total forelimb, total muscle, total skin, and small vessel resistances of greater statistical significance (P<0.01 in most cases), but, in addition, there was evidence in the hypertensive dogs for significant increases in skin arterial and total limb arterial resistances (P<0.05). In contrast, combining groups H-1 and H-2 did not provide any evidence for differences in venous resistance in hypertensive and normotensive dogs (nor did elevating limb large venous pressures to 35 mm Hg).

Femoral vein pressure-volume curves (injection phase) for individual dogs are presented in Figure 1. Overall, curves in hypertensive dogs are apparently shifted toward the pressure axis, but we detect no differences in curve shape or in the shape of the hysteresis loop (not presented) in hypertensive dogs. The shift toward the pressure axis in the hypertensive groups is clearer in Figure 2, which presents mean values for the four groups of dogs. The shift in group H-1, although not significant by itself, is similar to the significant shift in H-2, suggesting that the
same change occurred in both hypertensive groups. Table 4 presents the statistical treatment of these pressure-volume data: means and standard errors of volumes which produced pressures of 10, 20, and 30 mm Hg during the injection phase. To produce intravenous pressures of 10 mm Hg, volumes were significantly ($P < 0.05$) lower in group H-2 than in C-2. If data from groups H-1 and H-2 were combined and compared to combined data from C-1 and C-2, volumes at all pressures were significantly ($P < 0.02$) lower in hypertensives; this statistical significance was unchanged even if data from the four smallest hypertensive and the four largest normotensive dogs were excluded from the calculations (producing mean body weights of 23.2 and 23.1 kg and mean forelimb weights of 584 and 611 g in normotensives and hypertensives, respectively).

Means of jugular vein pressure-volume curves for the groups are presented in Figure 3. In contrast to the femoral vein, curves in hypertensive dogs were not shifted toward the pressure axis, nor were there significant differences ($P > 0.5$) in volumes producing pressures of 10, 20, and 30 mm Hg in hypertensive and normotensive dogs (Table 4).

To determine if there were any relationships between the changes noted in femoral venous capacitance function and other variables studied, linear correlation coefficients were calculated. There were no significant relationships between femoral venous volumes at pressures of 10 mm Hg and total limb blood flow/100 g, $P_A$, forelimb total resistance, forelimb small vessel resistance, and forelimb venous resistance ($P > 0.05$).

Intravenous injections of propranolol, diazoxide, or guanethidine, although reducing mean arterial pressure, did not significantly

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**Table 3**

*Group Means (± SE) of Skin Flow, Pressures, and Resistances*

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<tr>
<td><strong>Blood flow</strong></td>
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<tr>
<td>(ml/min)</td>
<td>68.6 ± 8.0</td>
<td>55.9 ± 8.0</td>
<td>63.1 ± 5.8</td>
<td>54.8 ± 4.2</td>
<td>55.3 ± 4.8</td>
<td>55.3 ± 4.2</td>
</tr>
<tr>
<td>(ml/min 100 g⁻¹)</td>
<td>11.16 ± 1.15</td>
<td>9.71 ± 1.15</td>
<td>10.85 ± 0.87</td>
<td>9.38 ± 0.83</td>
<td>11.00 ± 0.70</td>
<td>9.53 ± 0.76</td>
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<tr>
<td><strong>Pressure (mm Hg)</strong></td>
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</tr>
<tr>
<td>Small artery</td>
<td>120.7 ± 5.4</td>
<td>128.3 ± 5.3</td>
<td>123.2 ± 4.6</td>
<td>160.1* ± 5.6</td>
<td>122.0 ± 3.4</td>
<td>144.7* ± 5.5</td>
</tr>
<tr>
<td>Small vein</td>
<td>16.8 ± 2.5</td>
<td>15.0 ± 2.0</td>
<td>17.9 ± 2.6</td>
<td>12.1 ± 1.7</td>
<td>11.1 ± 1.5</td>
<td>1.1 ± 1.3</td>
</tr>
<tr>
<td>Large vein</td>
<td>13.7 ± 2.3</td>
<td>-1.7 ± 1.9</td>
<td>14.4 ± 1.9</td>
<td>10.3 ± 1.5</td>
<td>11.1 ± 1.5</td>
<td>1.1 ± 1.3</td>
</tr>
<tr>
<td>Mean intravascular</td>
<td>15.2 ± 2.4</td>
<td>13.6 ± 1.8</td>
<td>16.2 ± 2.3</td>
<td>12.3 ± 1.6</td>
<td>12.9 ± 1.6</td>
<td>12.9 ± 1.2</td>
</tr>
<tr>
<td><strong>Resistance (mm Hg/ml min⁻¹ 100 g⁻¹)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12.97 ± 1.50</td>
<td>16.32 ± 2.34</td>
<td>13.08 ± 1.07</td>
<td>14.03 ± 2.73</td>
<td>18.98* ± 0.82</td>
<td>18.98* ± 1.88</td>
</tr>
<tr>
<td>Arterial</td>
<td>2.21 ± 0.18</td>
<td>2.30 ± 0.35</td>
<td>2.00 ± 0.13</td>
<td>2.00 ± 0.25</td>
<td>2.26 ± 0.11</td>
<td>2.26 ± 0.20</td>
</tr>
<tr>
<td>Small vessel</td>
<td>10.47 ± 0.18</td>
<td>13.66 ± 2.00</td>
<td>10.47 ± 1.11</td>
<td>10.47 ± 2.53</td>
<td>15.86 ± 0.83</td>
<td>15.86 ± 1.70</td>
</tr>
<tr>
<td>Venous</td>
<td>0.28 ± 0.05</td>
<td>0.31 ± 0.08</td>
<td>0.31 ± 0.07</td>
<td>0.31 ± 0.08</td>
<td>0.41 ± 0.04</td>
<td>0.04 ± 0.06</td>
</tr>
</tbody>
</table>

Number of dogs is given in parentheses with the exceptions noted.

$*P < 0.01; †P < 0.05$, for comparison of hypertensive group with appropriate control group.

9 dogs; §21 dogs.
alter pressure-volume relationships in the femoral veins of hypertensive or normotensive dogs.

**Discussion**

In contrast to whole body hemodynamics, regional hemodynamics in experimental renal hypertension have received little investigative attention, with the possible exception of those of the kidney. Studies which have been performed indicate that in chronic renal hypertension the resistances of vascular beds of the limbs (5, 10, 11), heart (12), and probably kidneys (13, 14) are increased, findings reflecting the elevated total peripheral resistance at this stage in the hypertensive process (15).

Similarly, it is generally accepted that the cardiac output is normal in the chronic uncomplicated stages of experimental renal hypertension (15). The normal limb blood flow we found in our previous study in dogs with perinephritic hypertension of more than 4 weeks' duration thus reflects this normal total blood flow.

In contrast to the hemodynamics of chronic stages of experimental renal hypertension, there is now evidence that in the early stages (<4 weeks' duration) the cardiac output in rats and dogs may be significantly elevated (1, 2). In dogs in early stages, the peripheral resistance may be slightly decreased (2). Thus a change in whole body hemodynamics apparently occurs between the early and chronic stages of the hypertensive process. In perinephritic hypertensive dogs, Ferrario and coinvestigators (2) found that this transition took place at about the fourth to sixth week: cardiac output, previously elevated, returned to normal levels and total peripheral resistance, previously decreased, increased and in most dogs became the sole hemodynamic mechanism of the sustained hypertension.

It was of interest, then, for us to restudy the hemodynamic status of the forelimb vascular bed in dogs in the early stages of perinephritic hypertension. We expected that limb hemodynamics would again reflect total body hemodynamics, i.e., elevated limb blood flow and normal or decreased limb vascular resistance. Our present studies were performed at the stage of hypertension when Ferrario and coinvestigators (2) found cardiac output first elevated (group H-1) and
also at the stage when they found cardiac output at its maximum (group H-2). We used experimental techniques and anesthesia similar to those used in our previous study in dogs with chronic hypertension (5), to allow comparison of findings.

The results of the present study, unexpectedly, indicate that the hemodynamic state of the vascular bed of the limb in the early stages of perinephritic hypertension may not reflect that of the whole body. As in the chronic stages, there were significant elevations of limb vascular resistance with no evidence of increases in limb blood flow. Our findings therefore suggest that the limb vascular bed apparently does not participate in the change in whole-body hemodynamics between the early and the chronic stages of the hypertensive process.

Our findings are thus relevant to the hypothesis that arteriolar constriction in chronic stages of hypertension may represent an autoregulatory response to elevated tissue blood flow. In this regard, our data suggest that only 8 days after wrapping one kidney, with the other kidney undisturbed, the arterioles of the limb vascular beds begin to constrict and remain constricted after removal of the opposite kidney and on into development of the chronic stages of hypertension. With no evidence for increased blood flow through these vascular beds at even the very early stage of the development of hypertension, it thus seems most unlikely to us that the arteriolar constriction in the vascular beds of the limb is attributable to an autoregulatory response to increased blood flow.

Our data further indicate that in early experimental renal hypertension in dogs similar hemodynamic states exist in limb skin and

### Table 4

**Venous Pressure-Volume Relationships**

<table>
<thead>
<tr>
<th>Intravenous pressure</th>
<th>C-1 (10)</th>
<th>H-1 (10)</th>
<th>C-2 (12)</th>
<th>H-2 (12)</th>
<th>C-1 + C-2 (22)</th>
<th>H-1 + H-2 (22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mm Hg</td>
<td>0.328 ± 0.039</td>
<td>0.290 ± 0.028</td>
<td>0.196*</td>
<td>0.307 ± 0.023</td>
<td>0.206†</td>
<td></td>
</tr>
<tr>
<td>20 mm Hg</td>
<td>0.507 ± 0.045</td>
<td>0.490 ± 0.046</td>
<td>0.031</td>
<td>0.498 ± 0.030</td>
<td>0.373*</td>
<td></td>
</tr>
<tr>
<td>30 mm Hg</td>
<td>0.592 ± 0.051</td>
<td>0.573 ± 0.046</td>
<td>0.592 ± 0.051</td>
<td>0.582 ± 0.033</td>
<td>0.454*</td>
<td></td>
</tr>
</tbody>
</table>

Values are the group means (±SE) of intravenous volumes (ml). The number of dogs is given in parentheses, with the exceptions noted.

*P < 0.05; † P < 0.01, for comparison of hypertensive group with appropriate control group.

110 dogs; 20 dogs.

![Figure 3](http://circres.ahajournals.org/)

*Jugular vein pressure-volume curves (injection phase), means of groups. Symbols as in Figure 2.*
skeletal muscle vascular beds. It is likely that the skin and skeletal muscle beds of the limb are representative of skin and skeletal muscle beds of other sites in the body. Thus, if cardiac output was elevated in our dogs, our findings indicate that the skeletal muscle and skin vascular beds of the body (which receive approximately 25% of the cardiac output at rest) probably do not share in the increased whole-body blood flow. It would therefore be of great interest to determine which vascular beds do receive the excess blood flow and whether autoregulation is a plausible explanation for arteriolar constriction in those beds.

In contrast to our findings, Brod et al. (16) have reported plethysmographic evidence that resistance in limb skeletal muscle vascular beds is less than that in skin vascular beds in humans with renovascular hypertension. In these patients the muscle fraction of cardiac output was increased (similar limb hemodynamics were produced in normotensive subjects by a 30-minute intravenous infusion of angiotensin II). Differences in results between our study and that of Brod et al. may be attributable to differences in techniques, species, mechanism of hypertension, or stage of hypertension. It should be pointed out that Brod et al. found no evidence for increased cardiac output in their patients with renovascular hypertension.

Many of our conclusions are based on the assumption that cardiac output is, in fact, elevated in dogs in the early stages of perinephritic hypertension. The evidence for this assumption (2), although strong, requires further confirmation. Furthermore, it is possible that pentobarbital lowered the cardiac output in our renal hypertensive dogs to normal levels. We believe that the latter possibility is unlikely because elevated cardiac outputs have been reported in perinephritic hypertensive dogs anesthetized with pentobarbital and urethane (12) and in renal hypertensive rats anesthetized with pentobarbital (17). Furthermore, in normotensive dogs there is evidence that pentobarbital in the doses we used does not alter cardiac output (18), although it does increase total peripheral resistance and arterial blood pressure. In renal hypertensive dogs, pentobarbital in the doses we used reduces arterial blood pressure during the first 60 minutes after administration (19). Thereafter, however, blood pressure returns toward preanesthesia levels; our hemodynamic observations were not begun until at least 90 minutes after administration of initial anesthesia.

As in the chronic stages of perinephritic hypertension (5), the elevated limb resistance in the early stages is primarily confined to the small vessel segment of the limb vascular bed, consisting of small arteries, arterioles, capillaries, and venules. To a degree, the larger arteries of the skin may participate in this vasoconstriction, but there is little evidence of reduction in caliber of veins ranging in diameter from about 0.5 to 5 mm (despite a slightly, but not significantly, lower calculated mean pressure and blood flow in these veins in hypertensive dogs).

Although these smaller limb veins, thus do not appear to be involved in the hypertensive process, the results of our pressure-volume studies suggest that the compliance of larger limb veins (i.e., the femoral vein) may be decreased in the early stages of perinephritic hypertension in dogs. This decrease in femoral venous compliance, which is not shared by the jugular vein, is apparently not attributable to differences in size of the dogs studied nor to any other apparent technical difference, such as the amount of bleeding during the experimental procedure.

We are unable to find reports of previous similar studies of venous pressure-volume relationships in renal hypertensive animals. However, increases in mean circulatory pressure have been reported in dogs with experimental renal hypertension (2, 20) even in the absence of increases in plasma volume (2). It was suggested that these findings may be attributable to decreases in whole-body venous system capacity (2); our finding would support this suggestion. Plethysmographic studies of forearm venous distensibility in humans with essential hypertension have produced conflicting results (21–24).
In contrast to veins, pressure-volume (radius) relationships in arteries have been directly measured in dogs with renal hypertension (25) and in humans with essential hypertension (9). The results of both studies indicate significant decreases of arterial compliance in hypertensives.

The decreased femoral venous compliance we observed in hypertensive dogs is not acutely altered by several antihypertensive agents, including propranolol and guanethidine, which are thought to lower blood pressure at least in part by decreasing cardiac output (26, 27). Thus this study provides no evidence that these agents act acutely via increases in venous compliance, at least in dogs with perinephritic hypertension.

We have no information about the underlying mechanism of the reduced venous compliance we found in hypertensive dogs, but the similar shape of the pressure-volume curves in hypertensives and normotensives suggests that the mechanism may not involve contraction of venous smooth muscle; venoconstriction characteristically changes the pressure-volume curve to a sigmoid configuration (28). Perhaps the decreased venous compliance may be attributable to abnormal vascular wall water and electrolyte metabolism as has been suggested in the case of arteries (25). In this regard it is tempting to speculate that abnormal vascular wall water and electrolyte metabolism may underlie not only the increased arteriolar resistance in hypertension, as has been suggested (29–31), but also the abnormality we observed in venous capacitance function and hence the elevated cardiac output. A generalized decrease in venous compliance would tend to increase "venous return" to the heart and thereby the cardiac output. It is possible that such a mechanism may operate not only in experimental renal hypertension but also in renovascular, borderline, and early essential hypertension in man, in which cardiac outputs have also been reported to be elevated (32–34).

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References
Hemodynamics of Early Experimental Renal Hypertension in Dogs: NORMAL LIMB BLOOD FLOW, ELEVATED LIMB VASCULAR RESISTANCE, AND DECREASED VENOUS COMPLIANCE
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