Regional and Systemic Hemodynamic Patterns in Rabbits with Neurogenic Hypertension

By Natalie Alexander and Vincent DeQuattro

ABSTRACT
The hemodynamic basis of neurogenic hypertension was studied in unanesthetized rabbits 10 minutes to 30 days after sinoaortic denervation (SAD). The fractional distribution of $^{85}$Rb to body tissues was determined and used to calculate regional blood flow from the value of cardiac output obtained from an arterial dilution curve of the indicator. Sham-operated rabbits served as controls. Increased cardiac output was a major hemodynamic component of SAD hypertension in 69% of the rabbits studied 1–40 hours postoperatively (acutely) but in only 25% of those studied 3–30 days after surgery (chronically). In the majority of the chronic SAD rabbits, increased total peripheral resistance (TPR) was the basis of the hypertension. All SAD rabbits had increased heart rates. Acutely, most high-cardiac output hypertensive rabbits had increased splanchnic resistance with normal blood flow, whereas all of them had low or normal renal resistance with high blood flow. Flows were increased in other major regions. Acutely, in the few high-TPR hypertensive rabbits, resistance was significantly increased in splanchnic tissue, liver, and carcass but not in the kidneys. Chronically, renal resistance was elevated in both types of hypertension. Chronic high-TPR rabbits had increased resistance in all major regions, but, unlike the acute high-TPR group, increased carcass resistance was located in bone rather than skeletal muscle. In the few chronic high-cardiac output hypertensive rabbits, TPR was reduced and regional blood flows were high with the exception of that to the kidneys and liver. Skin received a larger percent of cardiac output in chronic hypertensive rabbits than it did in acute hypertensive rabbits regardless of the hemodynamic basis of the hypertension.

KEY WORDS: regional blood flow in hypertension, $^{85}$Rb, regional vascular resistance in hypertension, sinoaortic denervation, cardiac output and hypertension, total peripheral resistance, sympathetic nervous system and hypertension.

- Sinoaortic denervation (SAD) eliminates a major source of neural inhibition to the sympathetic nervous system and produces hypertension. Characteristically, blood pressure is labile: in some cases, arterial blood pressure fluctuates from hypertensive to normotensive and even hypotensive levels (1–3). SAD hypertensive rabbits have tachycardia resulting from reduced vagal and increased sympathetic neural tone (4), and the biosynthesis of catecholamines is enhanced in the left ventricle and the adrenal glands (5). These findings are similar to those characteristic of early essential hypertension in man, i.e., labile arterial blood pressure, tachycardia, and, in some patients, enhanced catecholamine biosynthesis and involvement of the sympathetic nervous system (6, 7). Increased cardiac output constitutes the early basis of hypertension in some humans with essential hypertension (8, 9) and in some neurogenic hypertensive dogs (2).

In the present investigation, regional and systemic hemodynamic patterns were determined in SAD rabbits at postoperative times ranging from 10 minutes to 30 days. From these data, we attempted to answer the following questions. Was the hemodynamic basis of SAD hypertension an increase in total peripheral vascular resistance (TPR)? If so, was this increase uniform throughout the vascular tree or was resistance increased only in certain regions? Alternatively, was the hemodynamic basis of hypertension an elevated cardiac output with or without concomitant regional resistance changes? Finally, were the changes present in rabbits studied early in the postoperative period the same as those present in rabbits studied later?

Some of the same rabbits were used in a recent study of the relationship between catecholamine metabolism of splanchnic blood vessels and splanchnic vascular resistance (10).
Methods

Female New Zealand rabbits weighing 2.5-3.5 kg were studied. The procedures used for sinoaortic denervation and sham operations have been precisely described previously (5). No general anesthesia was used; local nerve block of cervical skin and muscle tissue was maintained with 2% procaine.

One or 2 days before cardiovascular measurements were made, the neck skin was anesthetized, a sealed polyvinyl tube filled with a heparin solution (5,000 units/ml) was passed from the right jugular vein until its tip lay near the right atrium, and the excess tubing was curled below the skin at the back of the neck. For the experiment, the rabbit was placed in a small cage, the jugular vein tubing was exposed, the ear artery was cannulated (5), and both cannulas were led outside the cage. The rabbit was not handled further and sat quietly while the remaining procedures were carried out. Arterial blood pressure was recorded continuously for 30 minutes, and then 20-50 μl of RbCl (20-50 μc) was placed in the end of the exteriorized jugular vein tubing. The isotope was used to determine cardiac output and its regional distribution by the indicator fractionation method first described by Sapirstein (11). At zero time, the ear artery cannula was cut so that blood dripped into a small collector rotating at a rate of about 90 samples/min. At 1 second, the isotope was washed rapidly into the heart with 1 ml of warm saline, and blood samples were collected for 15 seconds. At 60 seconds, the rabbit was killed by intravenously administering an overdose of sodium pentobarbital. A sham-operated rabbit and a SAD rabbit were studied on the same day under the same conditions; tissues from both rabbits were processed together.

After death, tissues were dissected, weighed, placed in containers with 6N HCl, and cooked at 20 lb pressure for 40 minutes. For determination of radioactivity, tissue and blood samples were placed in a well scintillation counter with a 3-inch sodium iodide crystal. Duplicate 2-ml samples of each tissue digest and duplicate 10 μl samples of blood diluted with water to 2 ml were counted. Calculations were based on total counts found in the rabbit. Cardiac output was calculated by the Stewart principle of radioisotope dilution. Regional blood flow was calculated as the fraction of total counts in the tissue—the flow fraction—multiplied by cardiac output; regional peripheral resistance and TPR were calculated as the quotients of mean arterial blood pressure divided by regional blood flow and cardiac output.
output, respectively (11). Stroke volume was the quotient of cardiac output divided by heart rate, which was counted from the recorded arterial blood pressure pulses. Student's t-test for unpaired samples was used to analyze the statistical significance of differences between data from SAD and sham-operated rabbits obtained during the same postoperative interval.

**Results**

Figure 1 is a plot of cardiac output vs. TPR for 33 SAD hypertensive rabbits and 32 sham-operated rabbits studied between 1 hour and 30 days postoperatively. The hemodynamic basis of the hypertension in the majority of the SAD rabbits beginning at 3 days was increased TPR as indicated by the shift of the SAD data into the lower right quadrants of the middle and right sections of the figure. The average TPR for all of the SAD hypertensive rabbits studied after 3 days was 23% higher than that for rabbits studied 1-40 hours after surgery (0.43 ± 0.1 (sd) vs. 0.35 ± 0.1 mm Hg/[ml/min kg⁻¹], P = < 0.05). The average TPR for sham-operated rabbits after 3 days was 9% higher than it was in the earlier group (0.35 ± 0.05 vs. 0.32 ± 0.04 mm Hg/[ml/min kg⁻¹], P = NS). The highest value for cardiac output among 23 of 24 sham-operated rabbits studied 3-30 days postoperatively was 250 ml/min kg⁻¹ (horizontal line, Fig. 1); 69% of the SAD hypertensive rabbits, studied 1-40 hours postoperatively had cardiac output values above 250 ml/min kg⁻¹ compared with only 25% of those studied later. Thus, increased cardiac output was a major hemodynamic component of the hypertension in the majority of the hypertensive rabbits studied in the early period. The average cardiac output for all SAD rabbits at 1-40 hours was 28% higher than that for those studied later (309 ± 146 vs. 241 ± 56 ml/min kg⁻¹, P < 0.1). The average cardiac output for sham-operated rabbits was the same at both intervals (229 ± 40 vs. 228 ± 30 ml/min kg⁻¹).

Preliminary results revealed regional hemodynamic differences between hypertensive rabbits with increased cardiac output and those with increased TPR. Therefore, the data were analyzed in the following way. All SAD hypertensive rabbits with cardiac output values above 250 ml/min kg⁻¹ were classed as high-cardiac output hypertensives and the others were classed as high-TPR hypertensives. Both groups were separated into acute—1-40 hours—and chronic—3-30 days—subgroups, and the data were compared with those from sham-operated rabbits studied during the same time intervals. Table 1 lists the average postoperative times of study and the number of rabbits in the SAD hypertensive groups and in both sham-operated groups. The relatively long chronic period, 3-30 days, was used for comparison of group mean values, since no significant differences were found between 3-8- and 10-30-day SAD rabbits with the same type of hypertension.

**MEAN SYSTEMIC AND REGIONAL VALUES FOR SHAM-OPERATED RABBITS**

Absolute systemic and regional hemodynamic mean values for 23 chronic sham-operated rabbits appear in Tables 2 and 3. These values are similar to those obtained by other workers who used the labeled microsphere method in unanesthetized normal rabbits (12).

**SYSTEMIC EFFECTS OF SAD**

Table 4 shows that mean arterial blood pressure and heart rate were increased early and late in the postoperative course regardless of the hemodynamic basis of the hypertension. Stroke volume was significantly reduced in hypertensive rabbits with increased TPR. Chronic, but not acute, high-

**TABLE 1**

Average Postoperative Times of Study and Number of Rabbits in Each Group

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High cardiac</td>
<td>Sham-operated</td>
</tr>
<tr>
<td></td>
<td>output</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>14 hr</td>
<td>10 hr</td>
</tr>
<tr>
<td>postoperative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>time of study</td>
<td>14 hr</td>
<td>14 hr</td>
</tr>
<tr>
<td>No. of rabbits</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>

Although experiments were carried out on an equal number of sham-operated and SAD rabbits, data were not calculated when a poor isotope dilution curve was obtained or for some other technical reason. Data from each acute and each chronic sham-operated rabbit appear in Figures 1 and 2, but for purposes of comparison with SAD mean data the three sham-operated rabbits, two acute and one chronic (see Fig. 1, left and right), with cardiac outputs above 250 ml/min kg⁻¹ were not used for calculation of results shown in subsequent tables.
HEMODYNAMICS OF SAD HYPERTENSION

TABLE 2

Systemic Hemodynamic Measurements in the Chronic Sham-Operated Rabbits

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>78 ± 1</td>
<td>23</td>
</tr>
<tr>
<td>Cardiac output (ml/min kg⁻¹)</td>
<td>223 ± 4</td>
<td>23</td>
</tr>
<tr>
<td>Total peripheral resistance (mm Hg/ml/min kg⁻¹)</td>
<td>0.35 ± 0.008</td>
<td>23</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>226 ± 5</td>
<td>23</td>
</tr>
<tr>
<td>Stroke volume (ml/min kg⁻¹ beat⁻¹)</td>
<td>1.02 ± 0.04</td>
<td>23</td>
</tr>
</tbody>
</table>

The mean values for the acute sham-operated group were 1-10% lower.

cardiac output hypertensive rabbits had an associated significant reduction in TPR (14%, P < 0.01).

REGIONAL EFFECTS OF SAD

The shift to the right of the TPR data shown in Figure 1 reflected the effect of SAD on separate vascular regions with certain exceptions and modifications that are pointed out in the following sections. Figure 2 displays flow-resistance plots for the kidneys, splanchnic tissue, liver (arterial circulation), and carcass of each SAD hypertensive and sham-operated rabbit considered in Figure 1. Mean blood flow and resistance values for these and additional regions appear in Figures 3 and 4; the former shows acute and latter shows chronic hypertensive group data expressed as a percent of the mean values for sham-operated rabbits. Mean values for a subgroup (1-4 hours) of the acute high-cardiac output group appearing separately in Figure 3 showed a significant increase in splanchnic resistance not exhibited by the group as a whole. Any significant change in the flow fraction, i.e., percent of cardiac output, will be described for each region.

Kidney.—Renal blood flow increased during the first 2 postoperative days for most hypertensive rabbits (Fig. 2), and the mean increase reached a statistically significant level for high-cardiac output hypertensive rabbits (Fig. 3). Renal resistance in 12 of 13 acute SAD rabbits was within or below the range for sham-operated rabbits (Fig. 2).

From 3 days on, most SAD rabbits had a normal renal blood flow with a high renal resistance (Fig. 2); mean renal resistance was increased in both chronic groups (P < 0.05 and P < 0.01, Fig. 4). An increase in the chronic high-cardiac output group was unexpected, since mean TPR was reduced in this group (Table 4 and Fig. 4).

Splanchnic Tissue and Liver (Arterial Circulation).—Splanchnic resistance, in contrast to renal resistance, was increased in most acute hypertensive rabbits (Fig. 2). Splanchnic tissue was the only region in acute high-cardiac output hypertensive rabbits that received a reduced percent of the cardiac output. Compared with sham-operated rabbits, the reduction was 16% (P < 0.05) for the entire group and 24% (P < 0.01) for the 1-4-hour subgroup. Thus, splanchnic flow in the acute group as a whole was increased less than cardiac output and in the subgroup was normal as the result of the 35% increase (P < 0.02) in splanchnic resistance.

TABLE 3

Regional Hemodynamic Measurements in the Chronic Sham-Operated Rabbits

<table>
<thead>
<tr>
<th>Region</th>
<th>Flow Fraction* (% of cardiac output)</th>
<th>Flow (ml/min 100g⁻¹)</th>
<th>Resistance (mm Hg/ml/min 100 g⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidneys</td>
<td>19 ± 0.8</td>
<td>526 ± 17</td>
<td>0.15 ± 0.004</td>
</tr>
<tr>
<td>Splanchnic tissue</td>
<td>22 ± 0.48</td>
<td>82 ± 2</td>
<td>0.96 ± 0.03</td>
</tr>
<tr>
<td>Liver, arterial circulation</td>
<td>7.7 ± 0.25</td>
<td>44 ± 2</td>
<td>1.9 ± 0.08</td>
</tr>
<tr>
<td>Heart</td>
<td>1.5 ± 0.045</td>
<td>161 ± 4</td>
<td>0.49 ± 0.01</td>
</tr>
<tr>
<td>Skin</td>
<td>11.2 ± 0.75</td>
<td>16 ± 1</td>
<td>5.4 ± 0.4</td>
</tr>
<tr>
<td>Carcass</td>
<td>33.6 ± 0.65</td>
<td>14 ± 0.4</td>
<td>5.7 ± 0.24</td>
</tr>
<tr>
<td>Hindlegs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>1.8 ± 0.11</td>
<td>20.7 ± 0.5</td>
<td>3.8 ± 0.13</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>4.4 ± 0.24</td>
<td>8.9 ± 0.5</td>
<td>9.0 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SE for 23 rabbits. The mean values for the acute sham-operated group were 1-10% lower. Splanchnic tissue includes stomach, large and small intestines, mesentery, spleen, and pancreas, skin includes total body skin, ears, and tail, and carcass includes head, neck, thoracic wall, abdominal wall, and limbs.

* Fraction of the total body count multiplied by 100; it represents the percent of cardiac output.
TABLE 4
Systemic Hemodynamics in SAD Hypertension: Percent Difference from Mean Values for Sham-Operated Rabbits

<table>
<thead>
<tr>
<th></th>
<th>High-cardiac output hypertension</th>
<th>High-TPR hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute (% difference)</td>
<td>Chronic (% difference)</td>
</tr>
<tr>
<td>Mean arterial blood pressure</td>
<td>+37*</td>
<td>+23*</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>-7</td>
<td>-14†</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>+63*</td>
<td>+46*</td>
</tr>
<tr>
<td>Heart rate</td>
<td>+40*</td>
<td>+25*</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>+15</td>
<td>+17</td>
</tr>
</tbody>
</table>

Chronic systemic values for sham-operated rabbits appear in Table 2; acute values for sham-operated rabbits were up to 10% lower. The average postoperative time and the number of rabbits in all groups are given in Table 1.

* P < 0.001.
† P < 0.01.
‡ P < 0.05.
§ P < 0.02.

(Fig. 3). The acute high-cardiac output subgroup also had some increase (17%, P < 0.1) in liver arterial resistance. This increase and the splanchnic increase were less than the increases in both regions of the acute high-TPR hypertensive rabbits (Fig. 3).

As in the acute group, vascular resistance was increased significantly in both these regions in chronic high-TPR hypertensive rabbits (Figs. 2 and 4). The hepatic arterial flow fraction was reduced to 79% of the value for sham-operated rabbits (P < 0.01) in chronic high-cardiac output hypertensive rabbits. This reduction minimized the arterial flow increase (16%, NS) in contrast to the large portal increase represented by splanchnic flow (37%, P < 0.001).

Heart.—Cardiac flow fractions were increased in both types of acute hypertensive rabbits (high-cardiac output group: 33%, P < 0.01; high-TPR group: 27%, P < 0.02), but flow was increased significantly in only the high-cardiac output group (Fig. 3).

The cardiac hemodynamic patterns of each

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**FIGURE 2**
Blood flow vs. vascular resistance in kidney, splanchnic tissue, liver, and carcass for each SAD and sham-operated rabbit studied between 1 hour and 30 days postoperatively. Solid circles = high-TPR hypertensive rabbits, open circles = high-cardiac output hypertensive rabbits, and triangles = sham-operated rabbits. Time ranges for each section for each region are the same as they are in Figure 1.

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Acute regional hemodynamic changes in SAD hypertensive rabbits. Top: Blood flow changes. Bottom: Resistance changes. For statistical purposes, SAD hindleg values of both the acute and the chronic groups (see Fig. 4) were compared to 15 sham-operated values, 13 chronic and 2 acute. P values: * = < 0.05, ** = < 0.02, *** = < 0.01, **** = < 0.001, and • = < 0.1.

Carcass, Hindleg Muscle, and Hindleg Bone.—In all three regions, mean blood flow was high in the acute high-cardiac output group (Fig. 3) and normal to low in the acute high-TPR group. The latter showed a 50% (P < 0.01) increase in mean carcass resistance which appeared to be located primarily in muscle (Fig. 3), assuming that the changes in hindleg muscle reflected the effect of SAD on carcass muscle in general. (A separate unpublished study has shown that hindleg muscle and psoas muscle have the same direction and magnitude of change in SAD rabbits.)

High carcass resistance appeared to be located in bone rather than in muscle in the chronic high-TPR group. This fact was suggested by the large increase in hindleg bone resistance (56%, P < 0.001). Hindleg muscle, on the other hand, showed no significant increase in resistance, and, although muscle mean blood flow was only 15% higher than the value for the sham-operated group, 70% of the high-TPR hypertensive rabbits had flows greater than 9.9 ml/min kg^-1, a value attained by only 2 of 15 sham-operated rabbits. The pattern was reversed in the high-cardiac output group, i.e., carcass resistance was reduced (29%, P < 0.01). Resistance was significantly reduced in hindleg muscle, and both muscle and bone had elevated blood flows. Thus, skeletal muscle resistance was either normal or low in chronic hypertensive rabbits.

Skin.—This tissue showed the most variability as indicated by the large SE in Table 3; the only significant change occurred in the chronic high-cardiac output group, for which skin flow was 70% higher than that in sham-operated rabbits (Fig. 4). Skin was the only region in addition to heart and skeletal muscle that did not show a large rise in...
vascular resistance in the chronic high-TPR hypertensive rabbits.

Skin was the only region to receive a percent of the cardiac output in chronic hypertension of both types greater than that which it received in acute hypertension (4%, $P < 0.02$) (Table 5). Moreover, kidney was the only region to show a significant inverse change of similar magnitude (4-5%, $P < 0.05$) (Table 5). This fact suggests that skin received blood diverted from the kidney in chronic SAD hypertension.

**IMMEDIATE POSTSURGICAL HYPERTENSION**

Two SAD and two sham-operated rabbits were studied 10 minutes after surgery, since preliminary studies showed that arterial blood pressure reached

**TABLE 5**

| Flow Fraction (% of Cardiac Output) Increase to Skin and Decrease to Kidney in Chronic Neurogenic Hypertension |
|---|---|---|---|---|---|---|---|---|---|
|  |     |   |     |     |     |     |     |     |     |
| Acute | Chronic | Difference | $P$ | Acute | Chronic | Difference | $P$ |
| Skin  | Kidney  |      |      |      |      |      |      |
| High-cardiac output hypertension | 9 | 13 | +4 | < 0.02 | 20 | 15 | -5 | < 0.05 |
| High-TPR hypertension | 9 | 13 | +4 | < 0.02 | 22 | 18 | -4 | < 0.05 |
| Sham-operated rabbits | 10 | 11 | +1 | NS | 19 | 19 | 0 | NS |

*FIGURE 4*

Chronic regional hemodynamic changes in SAD hypertensive rabbits. See Figure 3 for explanation.
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a maximum 10 minutes after SAD and declined at variable rates during the next hour. High TPR was the hemodynamic basis for hypertension in each SAD rabbit, and the mean increases in TPR and arterial blood pressure were 80% and 59%, respectively (P < 0.01 for both). Resistance increased significantly in kidney, splanchnic, carcass, and skin regions, respectively, 43%, 49%, 106%, and 125%; liver arterial circulation had the least increase, namely, 26%.

ACUTE CHANGES IN NORMOTENSIVE SAD RABBITS

It was possible to study nine SAD rabbits when their arterial blood pressure was normal sometime during the first 40 hours after denervation. Arterial blood pressure was more labile during this period than it was at later times. Heart rate was increased 26% above values for sham-operated rabbits, but cardiac output was normal. Splanchnic vascular resistance was increased (27%, P < 0.02), although TPR was normal. No other regional changes were significantly different from those for the 1-40-hour sham-operated rabbits.

Discussion

It appears that the hemodynamic basis of neurogenic hypertension shifts, just as does arterial blood pressure (1), subject to variations in the degree of sympathoadrenal control. Sharp pressure increases due to increases in cardiac output or TPR have been seen in two different studies of SAD dogs (2, 13). In the present study, high cardiac output in most hypertensive rabbits, but normal cardiac output in some, and a high frequency of normal arterial blood pressure during the first 40 hours may reflect a shifting hemodynamic basis of hypertension as well as the variable magnitude of sympathoadrenal activity occurring in a single animal. Some preliminary evidence for this phenomenon is shown in Table 6. The hemodynamic basis of arterial blood pressure in the same resting SAD rabbit could shift from increased TPR to increased cardiac output or vice versa on the same or different days, whereas sham-operated rabbits had relatively consistent values. This variability in cardiac output and TPR found in resting SAD rabbits is noticeable in SAD dogs during postural changes or brief periods of excitement (13). Mean arterial blood pressure is the most variable of the hemodynamic parameters in both SAD rabbits and dogs.

Raised cardiac output was found in 69% of the SAD rabbits studied during the first 2 days and in only 25% of those studied thereafter. Studies of other forms of hypertension support the concept that increased cardiac output is the most frequently occurring basis of hypertension in the early postoperative course. Monkeys with hypertension induced by operant conditioning have elevated cardiac outputs at 20 minutes and 4 hours, but by 24 hours and 72 hours hypertension is associated with increased TPR and normal cardiac output (14). Hawthorne and co-workers (15) have found that cardiac contractility and cardiac output are increased in conscious dogs for the first 72 hours of renal hypertension; thereafter, cardiac output returns to normal and TPR is elevated. In studies of SAD hypertensive dogs with implanted flow probes, the initial hemodynamic basis of hypertension is evenly divided between high cardiac output and high TPR (2).

We know of two other regional hemodynamic studies of hypertensive animals: a study of SAD rabbits by Chalmers et al. (16), in which portal, renal, muscle, and skin flows were measured by the thermal dilution technique and found to be normal during the first week after SAD, and a study of regional changes with labeled microspheres in five monkeys with hypertension induced by operant conditioning and continued for 72 hours. The results of the latter study differ in several respects from those of the present study (14). In the

![Table 6](http://circres.ahajournals.org/lookup/suppl/doi:10.1161/01.RES.35.4.643/-/DC1/Tab6.png)

"MABP = mean arterial blood pressure. Cardiac output was measured by the cardiogreen dye dilution method. The rabbits sat quietly in a small cage while mean arterial blood pressure was recorded continuously; the value listed was recorded just before the cardiac output determination.

* Cardiac output tests 1, 2, and 3 were done 0.5 hours apart.

† Cardiac output tests 1 and 2 were done 1 hour apart and alternately between SAD and Sham-operated rabbits on both days.

![Circulation Research](http://circres.ahajournals.org/lookup/suppl/doi:10.1161/01.RES.35.4.643/-/DC1/Fig1.png)

"Acute changes in normotensive SAD rabbits.

![Graph 1](http://circres.ahajournals.org/lookup/suppl/doi:10.1161/01.RES.35.4.643/-/DC1/Graph1.png)

"Graph 1: Acute changes in normotensive SAD rabbits.

![Graph 2](http://circres.ahajournals.org/lookup/suppl/doi:10.1161/01.RES.35.4.643/-/DC1/Graph2.png)

"Graph 2: Hemodynamic variability of individual SAD rabbits.

![Graph 3](http://circres.ahajournals.org/lookup/suppl/doi:10.1161/01.RES.35.4.643/-/DC1/Graph3.png)

"Graph 3: Hemodynamic variability of individual SAD rabbits.
monkeys, renal blood flow was always reduced; liver and bone flows were increased throughout the period of hypertension, but at 72 hours flow was reduced to skeletal muscle and gastrointestinal tract organs. In SAD rabbits, flow to any region was never reduced severely at any time. Regional flows in high-TPR rabbits were close to flows in sham-operated rabbits with an occasional rabbit having reduced flow to the visceral beds (Fig. 2). The effect of SAD on regional hemodynamics was much less extreme than that produced in the monkeys with operant conditioning hypertension even though the magnitude of the mean arterial blood pressure increase was similar in both groups. Resting mean arterial blood pressure averaged 78 mm Hg in the sham-operated rabbits compared with the base-line pressure of 102 mm Hg in the monkeys. This difference probably reflects a morphological or functional difference in resistance vessels between the two species; therefore, the effectiveness of vasoactive stimuli could be quite different in the two species.

Within 1 hour of SAD, renal vasoconstriction, observed at 10 minutes, had subsided and renal blood flow was elevated for the next 2 days in most SAD hypertensive rabbits. This rise was probably associated with an increase in intrarenal arterial blood pressure and diuresis, as suggested by the plasma volume and body weight changes that we have found in a separate group of SAD rabbits. This unpublished study showed that plasma volume was reduced below preoperative values 4 hours and 24 hours after SAD in six of nine rabbits; body weights changed in the same direction, indicating a net loss of body fluid. The need to eliminate excess waste products as a result of enhanced metabolism may contribute to high renal flows. Evidence (unpublished) of an acute metabolic response to SAD was a large rise in blood glucose levels for the first 2 days only.

Renal blood flow was normal and associated with increased resistance in both chronic SAD groups. This finding confirms the finding of normal flow and elevated resistance in rabbits 3–8 days after SAD by Korner’s group (16, 17). Korner has suggested that this fact supports Guyton’s concept (18) that the basis of sustained hypertension is the elevated renal resistance required for the maintenance of body fluids and electrolytes. Our plasma volume study supports this concept also, since plasma volumes and body weights return to normal by 7 or 21 days; neither exceeds normal values.

Hepatic arterial and splanchnic resistances were increased in all high-TPR hypertensive rabbits. Moreover, both 1-4-hour high-cardiac output rabbits and acute normotensive SAD rabbits had increased splanchnic resistance; neither group had increased resistance in any other region. Thus, the splanchnic circulation seems to be very sensitive acutely to vasoconstrictor effects of SAD. We have shown elsewhere that the catecholamine synthesis of splanchnic blood vessels is increased in both acute and chronic SAD rabbits (10).

Carcass resistance, like splanchnic and hepatic resistances, was increased in acute and chronic high-TPR rabbits, but in chronic rabbits the source of resistance was bone, not primarily skeletal muscle as it was acutely. Bone could account for the increased carcass resistance; it represents about 24% of the total carcass weight (average value obtained from complete dissection of three carcasses) but receives more than twice the blood flow of skeletal muscle. Hindleg muscle flow was increased in chronic high-cardiac output rabbits because of elevated arterial blood pressure and a significant reduction in vascular resistance. Furthermore, muscle flow was somewhat increased in high-TPR hypertensive rabbits. Thus, the chronic SAD rabbit showed increased skeletal muscle flow, a finding similar to that in humans with essential hypertension (19).

We have reported previously that adrenal epinephrine biosynthesis is increased in rabbits 3 weeks after SAD (5). A 15-minute infusion of nonpressor amounts of epinephrine into unanesthetized rabbits reduces bone blood flow 30% below that of saline-infused controls (unpublished observations). Circulating epinephrine tends to oppose neural constriction of skeletal muscle vessels and to add to it in bone vessels. Circulating epinephrine is thus an important factor in the determination of the hemodynamic basis of SAD hypertension at any given time.

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