Regional Vascular Capacitance in Rabbit One-Kidney, One Clip Hypertension

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SUMMARY One-kidney Goldblatt hypertensive rabbits (New Zealand White) were studied after durations of renal artery clipping that varied from 6 to 17 days. Measurements included arterial pressure (ABP), iliac venous pressure (IVP), left atrial pressure (LAP), cardiac output (CO) (by thermodilution), blood volume (BV), cardiopulmonary volume (CPV), and hindleg thermodilution volume (HLV). These were determined at steady-state as well as during acute blood volume expansion. In sham-clipped animals, ABP was 74 ± 1 mm Hg. This increased to 92 ± 3 mm Hg by 6 to 9 days post-clipping, to 96 ± 3 mm Hg by 10 to 13 days, to 89 ± 4 mm Hg by 14 to 17 days. CO remained near 150 ml/min kg until Day 13 and fell to 127 ± 8 ml/min kg at 14 to 17 days because of a fall in heart rate. Blood volume and stroke volume did not change significantly from 62 ± 1 ml/kg and 0.60 ± 0.04 ml/kg, respectively. The development of hypertension was due entirely to changes in peripheral resistance. CPV was 8.5 ml/kg initially and increased significantly as hypertension developed. HLV did not change significantly from about 10 ml/kg. During acute blood volume expansion, hypertensive animals showed smaller transient increases in CO than did sham-clipped normotensives, but the associated blood pressure rise was greater. This reduced vasodilator capacity was accompanied by reduced distensibility of the cardiopulmonary bed. In sham-clipped animals, the cardiopulmonary pressure/volume slope was between 0.05 and 0.07 mm Hg per ml/kg. This increased to 0.44 mm Hg per ml/kg by 14–17 days of clipping. The corresponding value for the hindleg region did not change significantly from 0.2 mm Hg per ml/kg. Cardiac output and stroke volume were directly correlated with cardiopulmonary volume. The slope of this correlation decreased significantly during hypertension. The data suggest that decreased cardiopulmonary compliance in hypertension minimizes transient changes in cardiac output. This is especially important for arterial blood pressure control in view of the impaired vasodilator capacity of the hypertensive circulation. (Hypertension 5: 712–721, 1983)

KEY WORDS • vascular capacitance • cardiopulmonary volume • Goldblatt hypertension

DECREASED venous distensibility has been found in animal models of renal and genetic hypertension and in human essential hypertension. It would be expected to reduce the volume-storage capacity of veins and thereby cause redistribution of blood within the cardiovascular system. Even a small shift of volume from the venous to the arterial circulation would raise arterial blood pressure greatly, and it has been proposed that established hypertension is in part maintained by an imbalance between a normal circulating blood volume and a decreased volume capacitance of the vasculature.

Although it has been argued that reduced venous distensibility in hypertension is less likely to be an effect of the raised arterial pressure and more likely to be one of its contributing causes, it is not known whether changes in distensibility are progressive; it is not known whether there are differences among tissues with respect to such changes nor what effect these changes have on regional vascular volumes either at steady state or during an acute volume stress.

The purpose of these experiments was to measure, at steady-state and during acute blood volume expansion, the volume in the cardiopulmonary region and in the hindleg region of rabbits with one-kidney Goldblatt hypertension of increasing duration.

Methods Experiments were performed on 36 male New Zealand White rabbits, anesthetized with sodium pentobarbital (25 mg/kg) injected into a marginal ear vein.
The right kidney was removed and after minimal dissection, a stainless steel clip (average size of opening = 0.57 mm)14 was applied to the left renal artery. In every second animal the clip was immediately removed; these were the "sham-clipped." In others the clip was left in place over the left renal artery. All animals were allowed to recover from the surgery for a length of time that varied between 6 days and 17 days. On each of the first 2 recovery days they were given, intramuscularly, 0.5 ml Pen-Di-Strep (composition per milliliter: procaine penicillin G, 200,000 IU; dihydrostreptomycin base, 250 mg; Rogar/STB London, Ontario, Canada).

On the experimental day, the procedures were nonsterile. Following sodium pentobarbital anesthesia, a tracheostomy was performed and the animals were ventilated with 95% O2, 5% CO2 at 35 to 45 breaths per minute and a tidal volume of 100 ml. These were adjusted as required to maintain blood pH near 7.4. The ventilation system operated at a mean pressure of 6 mm Hg with an end-expiratory pressure of 2 mm Hg.

PE-200 tubing was advanced to the right atrium via the right external jugular vein. The left cephalic vein was cannulated with PE-50 tubing, and a maintenance infusion of 4.5% bovine serum albumin in Ringer Locke solution (NaCl = 115 mM; KCl = 5mM; NaHCO3 = 25 mM) was immediately started into this vein at 3 ml/hr.

The right internal iliac artery, the right iliolumbar artery, and all smaller arteries branching from the right common iliac artery were ligated. A polyethylene catheter (PE-90) was introduced into the left external iliac artery, and advanced until its tip lay inside the abdominal aorta just cephalad to the iliac bifurcation. It was held in place with a ligature placed around the abdominal aorta just cephalad to the iliac bifurcation. The left ureter was cannulated with PE-200 tubing. The sternum was split so that Swan Ganz thermodilution catheter (No. 93-132-5F, Edwards Laboratories, Santa Ana, California) from which the balloon tip had been cut, was fed into the inferior vena cava via the left external iliac vein until the thermistor lay about 1 cm cephalad to the iliac bifurcation. The left ureter was cannulated with PE-90 tubing. The sternum was split so that Swan Ganz catheters, similar to that described above, could be placed in the left atrium and in the pulmonary artery. The chest was left open during the remainder of the experiment. Statham transducers were connected to the appropriate catheters in the abdominal aorta, the left atrium, the right atrium, the pulmonary artery, and at the iliac venous bifurcation.

Blood samples were taken from the aortic catheter for the purpose of determining hematocrit (by the micromethod), plasma protein concentration (by refractometer), plasma electrolytes, and blood gases. Plasma volume was calculated as the dilution space of 15 µCi 125I RIHSA (Frosst Radiopharmaceuticals, Dorval, Quebec, Canada).

Flows and volumes were calculated from thermodilution curves produced by rapid injection of 1.5 ml room-temperature saline and recorded in the inferior vena cava, the pulmonary artery, and the left atrium. The points of saline injection were the right common iliac artery for hindleg flow and volume and the right atrium for cardiac output and cardiopulmonary volume.

Following surgical preparation, each animal rested for 30 minutes and was then heparinized (1500 U/kg body weight). All measurements were taken repeatedly during a 1-hour control period. After that the blood volume was expanded by intravenous infusion of 4.5% bovine albumin in Ringer Locke solution. The total volume infused was 33% of the blood volume (estimated to have been 7% of body weight). The rate of infusion was chosen such that the required volume was infused over a 30-minute period. All measurements were continued through the volume expansion period and for 60 minutes thereafter.

The indicator dilution curves were digitized, and both their areas and mean transit times were calculated by a digital computer program that fitted them to a gamma function.15 The exponential decay portion of each curve was taken to extend to a point where the amplitude was 40% of peak deflection. Flow calculations were based on the formula:

\[
\text{Flow} = KV \left( T_b - T_j \right) dS_i \left( dS_0 \times \int T_j \, dt \right)
\]

where K = constant to convert to ml/min; V = volume of indicator saline injected; dS_i = specific gravity of blood, saline (g/cm³); S_0, S_i = specific heat of blood, saline (cal/g°C); and \( \int T_j \, dt \) = area under thermodilution curve.

Specific heat and gravity of blood were calculated from the prevailing hematocrit and the values given by Mendelowitz16 for pure plasma (S = 0.94; d = 1.026) and for pure red cells (S = 0.77; d = 1.108). Values for saline (S = 0.997; d = 1.005) were taken from Ganz and Swan.17

Hindleg volume was calculated as the product of hindleg flow and mean transit time from iliac artery to iliac vein. Two mean transit times entered the calculation of cardiopulmonary volume (CPV) from cardiac output (CO): that from the right atrium to the left atrium (t_LR) and that from the right atrium to the pulmonary artery (t_HP): CPV = CO \times (t_HP - t_LR). Although this volume consisted mostly of pulmonary volume, it did include the left atrium. For that reason we describe it as cardiopulmonary volume.

The thermistors had been previously calibrated against a mercury thermometer over the range 36° to 42°C. In this limited range, the thermistor bridge output voltage was given by a straight line with a correlation coefficient r near −0.999. When temperatures in the range of 39° to 41°C were measured simultaneously with the calibrated thermistor and a mercury thermometer, they differed by no more than 0.1°C. Most of this difference was due to errors introduced by the thickness of the pen recorder line. The difference between body temperature and indicator temperature (T_b − T_j)
was generally in the order of 20°C. Therefore, we estimate that the maximum error introduced by our method was 1%.

Measured blood pH and pCO₂ (mm Hg) were used to derive plasma bicarbonate concentration from the formula:

\[(\text{HCO}_3^-) = 0.0306 \times 10^{-0.9524} \times \text{pCO}_2 \times 10^{(\text{pH} - 6.191)} \text{ (mEq/liter)}\]

The animals were divided into three groups according to the length of time during which the renal arterial clip had been in place before the day of the experiment. The three groups and their respective sham animals were 6 to 9 days, 10 to 13 days, and 14 to 17 days.

Data evaluation included the calculation of instantaneous blood volume from the measured control period plasma volume and the instantaneous hematocrit, both corrected for loss due to blood sampling. It included also a regression analysis on plots of iliac venous pressure against hindleg volume and of "intrapulmonary pressure" against cardiopulmonary volume. "Intrapulmonary pressure" is defined here as one half of the sum of pulmonary arterial pressure and left atrial pressure. The slope of these regression lines will be referred to as effective elasticity (\(E = dp/dv\)) and the inverse slope will be referred to as effective capacitance.

### Results

#### Steady State

Averaged steady-state blood chemistry and hemodynamic values are shown in tables 1 and 2 respectively. As expected, the animals showed slight increases in weight with increasing age (table 1). Although there were no differences in their hematocrits, sham animals tended to have a higher plasma protein concentration than their clipped hypertensive matches. They also tended to have a lower plasma potassium concentration, while differences in plasma sodium concentration were variable. We have no explanation for these differences and attach no importance to them.

The rate of urine flow was significantly lower in clipped animals up to 13 days of clipping (table 1). Beyond that time, it did not differ from sham-clipped animals. There were no significant differences in the acid-base status of the animals (table 1), and all pO₂ values were above the range 90–100 mm Hg normally found in spontaneously breathing animals.

Table 2 shows that the mean arterial blood pressure of clipped animals in all three groups was significantly higher than in the appropriate sham animals. However, the arterial blood pressure did not continue to rise with increasing duration of clipping because cardiac output (CO, table 2) decreased from a mean value of 165 ml/min·kg body weight in 6- to 9-day clipped animals to 142 ml/min·kg in 10- to 13-day animals, and 127 ml/min·kg in 14- to 17-day animals. This decline in cardiac output was due to a progressive fall in heart rate (table 2). Stroke volume showed no significant changes. Hindleg blood flow tended to be lower in hypertensive animals (table 2) and hindleg vascular resistance was higher in them (table 2). The flow differences were statistically significant only during the first 6 to 9 days of renal artery stenosis.

Hypertensive animals in each of the three groups showed a significantly increased cardiopulmonary volume (table 2), but a hindleg volume that was no different from that of the corresponding sham group.

#### Volume Expansion Transients

After volume expansion, all animals showed only a threefold increase in urine flow. This rate of fluid loss

### Table 1. Control Period Values in Goldblatt-Clipped Rabbits and in Sham Controls

<table>
<thead>
<tr>
<th>Duration of renal artery stenosis</th>
<th>6 to 9 days</th>
<th>10 to 13 days</th>
<th>14 to 17 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of animals</td>
<td>Clip</td>
<td>Sham</td>
<td>Clip</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>2.56 ± 0.06</td>
<td>2.55 ± 0.09</td>
<td>NS</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>34 ± 0</td>
<td>34 ± 0</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma protein (g/100 ml)</td>
<td>5.3 ± 0.4</td>
<td>5.6 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma sodium (mEq/liter)</td>
<td>150 ± 3</td>
<td>154 ± 0</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>Plasma potassium (mEq/liter)</td>
<td>3.7 ± 0.1</td>
<td>3.2 ± 0.1</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Plasma bicarbonate (mEq/liter)</td>
<td>19 ± 2</td>
<td>17 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>pO₂ (mm Hg)</td>
<td>182 ± 18</td>
<td>204 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>pCO₂ (mm Hg)</td>
<td>28 ± 2</td>
<td>27 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 ± 0.02</td>
<td>7.44 ± 0.02</td>
<td>NS</td>
</tr>
<tr>
<td>V (µl/min-g kidney wt)</td>
<td>0.61 ± 0.21</td>
<td>2.98 ± 0.30</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Values are means ± SEM.
TABLE 2. Hemodynamic Values in the Steady State

<table>
<thead>
<tr>
<th>Duration of renal artery stenosis</th>
<th>6 to 9 days</th>
<th>10 to 13 days</th>
<th>14 to 17 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clip</td>
<td>Sham</td>
<td>Clip</td>
</tr>
<tr>
<td>ABP (mm Hg)</td>
<td>92 ± 3</td>
<td>74 ± 1</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Iliac venous pressure (mm Hg)</td>
<td>1 ± 0</td>
<td>2 ± 0</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output (ml/min-kg body wt)</td>
<td>165 ± 9</td>
<td>156 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>278 ± 6</td>
<td>277 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke volume (ml/kg bw)</td>
<td>0.59 ± 0.04</td>
<td>0.60 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Hindleg flow (ml/min-kg bw)</td>
<td>6.2 ± 0.4</td>
<td>7.9 ± 0.4</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Hindleg vascular resistance (mm Hg/ml/min-kg bw)</td>
<td>15.6 ± 2.0</td>
<td>9.4 ± 0.8</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Blood volume (ml/kg bw)</td>
<td>63 ± 2</td>
<td>62 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiopulmonary volume (ml/kg bw)</td>
<td>13.1 ± 1.2</td>
<td>8.5 ± 0.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Right hindleg volume (ml/kg bw)</td>
<td>10.2 ± 0.6</td>
<td>9.2 ± 0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

was not sufficient to cause significant blood volume differences between clipped and nonclipped animals. Therefore, the degree of expansion and its subsequent decline was similar in all animals. At 90 minutes, the increase of blood volume above control was 24 ± 2 ml/kg; at 150 minutes, it was 22 ± 4 ml/kg.

In spite of the identical changes in intravascular volume, there were differences in the arterial blood pressure patterns (fig. 1) and in the caval pressure patterns (fig. 2): In each of the three groups the hypertensive animals showed greater postinfusion arterial pressure increases than did the corresponding normotensive sham group. In addition, their caval pressure increased more than it did in sham animals, the difference being too small for significance in early hypertension (fig. 2), but becoming significant by the 10th day.

There were no significant differences between experimental and control animals with respect to mean pulmonary arterial pressure (fig. 3) or mean left atrial pressure (fig. 4). Hypertensive animals showed the greater arterial pressure increase after volume expansion in the face of cardiac output increases that were smaller than those produced in sham animals (fig. 5) by an identical blood volume change. The implication is that hypertensive animals had a significantly reduced ability for compensatory vasodilation. This was, indeed, seen in the hindleg vasculature (fig. 6) in the 6- to 9-day group, though not in animals that had been clipped longer than 9 days (fig. 6).

In addition to the differences in vascular resistance changes implied by figures 1 and 5, there were significant changes in the ability of the hypertensive circula-
tion to accommodate blood volume. Figures 7 and 8 show that, in the normotensive circulation, added blood volume was not preferentially distributed either to the cardiopulmonary region (fig. 7) or to the hindleg region (fig. 8). In sham animals, both regions appeared to accept their steady-state proportions of blood volume so that the fractional volumes were not changed by the infusion. Hypertensive animals, on the other hand, showed altered regional volume storage capacities. In them the fraction of blood volume that was measured as cardiopulmonary volume decreased during and after blood volume expansion (fig. 7). The decrease in 6- to 9-day hypertensives was smaller than in hypertensives of longer duration.

The hindleg vascular bed, on the other hand, decreased in fractional volume in animals with a renal artery stenosis of 6 to 9 days' duration (fig. 8) but increased significantly above the volume seen in sham animals at both the 10- to 13-day stage and the 14- to 17-day stage (fig. 8).

**FIGURE 2.** Acute changes in iliac venous pressure in animals with real arteries clipped for various lengths of time (•••) and in sham-clipped animals (O--O). Values are means ± SEM.

**FIGURE 3.** Mean pulmonary artery pressure in animals with renal stenosis of various durations (••••) and in sham-clipped animals (O--O). Values are means ± SEM.

**FIGURE 4.** Mean left atrial pressure in clipped (••••) and sham-clipped (O--O) animals. Values are means ± SEM.
It has been suggested that cardiopulmonary volume is a determinant of cardiac filling and of cardiac function. We found the correlation coefficients between cardiopulmonary volume (CPV) and stroke volume (and between CPV and cardiac output) to be significant in most animals, clipped or sham. However, the slope of the regression line correlating cardiac output with cardiopulmonary volume was significantly smaller in hypertensive animals than in normotensives. Thus, in normotensives, each ml/kg change in cardiopulmonary volume correlated with a 14 ml/min-kg change in cardiac output. This decreased to 9 ml/min-kg in 6- to 9-day hypertensives ($p < 0.001$ by F test), to 2 ml/min-kg at 10 to 13 days ($p < 0.001$) and to 3 ml/min-kg at 14 to 17 days ($p < 0.001$).

The cause of the reduced cardiopulmonary storage capacity in hypertensives (fig. 7) appeared to have been a progressive increase in the effective elasticity of the cardiopulmonary region. This is shown in table 3 as the pressure increase per unit change in volume. As the duration of clipping increased, the cardiopulmonary area seemed to increase its effective elasticity from a value of 0.022 mm Hg per ml/kg at 6 to 9 days to 0.443 mm Hg per ml/kg at 14 to 17 days. The hindleg region, on the other hand, showed an effective elasticity that was about three times that of the cardiopulmonary region (sham, table 3). It was not significantly changed in any of the three hypertensive groups.

**Discussion**

The thermal dilution technique has been widely used, and loss of indicator during pulmonary transit has been shown to be a negligible problem in animals up to the size of the dog. In our study, flows calculated from pulmonary arterial thermodilution curves correlated highly with those calculated from left atrial thermodilution curves ($r = 0.965; p < 0.001$), and they agreed well with values reported by others.
Therefore, heat loss in the pulmonary bed must have been insignificant. However, thermal indicator does distribute in a volume greater than that contained within the blood vessels. As a result, thermal transit times are greater than those of intravascular dyes, yielding a thermodilution volume greater than true intravascular volume. Cardiopulmonary vascular volume has not been reported for the rabbit, but has been reported for normotensive humans and for the dog to range between 15% and 26% of total blood volume. Our values of 14% to 25% (fig. 7) are within this range. Therefore, we believe that in rabbits the intravascular space forms the major component of the cardiopulmonary thermodilution space.

Values for hindleg volumes do not appear to be available in the literature. Our results show that the right hindleg contained approximately 16% of total blood volume. Given that the splanchnic bed contains 20% of blood volume and that the cardiopulmonary bed holds 20% of blood volume, these two regions plus the hindlegs together account for about 70% of blood volume. This makes a hindleg volume of 16% of blood volume a reasonable value.

Extravascular heat diffusion would have affected the estimates of absolute volume only. Changes in regions

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**Table 3.** Slopes of the Regression Lines of Pressure (y) vs Volume (x) in the Cardiopulmonary or Hindleg Regions

<table>
<thead>
<tr>
<th>Duration of renal artery stenosis</th>
<th>6 to 9 days</th>
<th>10 to 13 days</th>
<th>14 to 17 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clip</td>
<td>Sham</td>
<td>F Value</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>0.022</td>
<td>0.071</td>
<td>0.44 (104)*</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hindleg</td>
<td>0.181</td>
<td>0.211</td>
<td>3.75 (104)*</td>
</tr>
</tbody>
</table>

The slope represents effective elasticity, its units are mm Hg/ml/kg.

*Degrees of freedom, DF2. DF1 = 1 in all cases.
al thermodilution volumes could have been caused by changes in thermal diffusion coefficients of tissues or by changes in the intravascular volumes. We believe the latter to have been the major factor because changes in diffusion coefficients during the time of the experiments cannot have been large.

The terms, compliance or capacitance, when applied to a whole vascular region, have been interpreted differently by different authors and the difficulties encountered when making comparisons among their results have been described by Hainsworth and Linden.11 We chose a definition that relates to the change in vascular pressure accompanying a change in the vascular volume of the region. Subject to its known limitations, we have taken the local thermodilution volume as an approximation to intravascular volume. By measuring absolute volumes and by changing total blood volume at the same rate in all animals, we have avoided the difficulties engendered by looking at small portions of different sections on a nonlinear pressure-volume curve,11 and we have avoided differing rates of stress relaxation as a factor leading to the interpretation of apparent changes in capacitance.11 In the hindleg we chose iliac venous pressure, measured at the bifurcation, as the pressure distending the capacitance vessels in that region.11 In the lungs we followed Milnor et al.12 by choosing the average of mean pulmonary arterial and mean left atrial pressure as the pressure distending the pulmonary capacitance vessels.

Neither pressure exactly measures the average pressure distending all capacitance vessels in the region. The pulmonary pressure, because it is based on both arterial and venous pressure, is a better estimate of distending pressure for pulmonary capacitance than is the iliac venous pressure for hindleg capacitance. Many of the smaller hindleg storage vessels would have had a hydrostatic pressure greater than iliac venous pressure because our observations were made under conditions in which there was flow through the region. This in itself would not have influenced our calculations of effective compliance because they were based on changes in pressure rather than absolute values. However, during the nonsteady state of blood volume expansion, the pressure change in small capacitance vessels might have been different from that measured in the large vessels.12 Furthermore, these inaccessible regions might have behaved differently in clipped and sham-clipped animals. For example, if all of a given volume change occurred in the smaller vessels without changes in large vessel pressure, the effective compliance of the area will appear to be high because it is based on large vessel measurements. If, on the other hand, the same volume change resulted in at least some change in large vessel pressure then the effective compliance of the area will appear to be lower. Accordingly, our measurements cannot distinguish between changes in effective compliance of the whole capacitance bed and changes in the compliances of small regions without necessarily a change in the average compliance of the whole bed.

It should be noted that the origin of the pressure changes is not important in these considerations because vessel distension will happen equally in response to pressure generated by smooth muscle activity, pressure transmitted "forward" through the capillaries following changes in vasomotor tone or pressure transmitted "backward" from a heart that varies in performance.

The hemodynamic sequelae of one-kidney Goldblatt hypertension have been studied more extensively in dogs,26-29 than in rabbits.14,20 The progression in arterial blood pressure shown in table 2 is not different from that reported by Brooks and Muirhead,14 and the control values for cardiac output, heart rate, stroke volume, and blood volume are similar to those found by Siripaisarnpipat.20 However, the progressive changes in blood volume and in cardiac output (table 2) are different from those seen in the dog. In that species, the increase in mean arterial blood pressure to 120% of control value by Day 7 was accompanied by increases in plasma volume, cardiac output, and total peripheral resistance.26 Ferrario18 has reported that, in the dog, increased cardiac output plays an important role during the first 28 days of hypertension due to renal artery constriction.

Our model showed a pressure increase to 124% of control over 7 days without changes in blood volume or cardiac output (table 2). This suggests that increased peripheral resistance alone accounted for the pressure rise. After 14 to 17 days of clipping, total peripheral resistance had apparently increased so much that only a fall in cardiac output could prevent arterial pressure from increasing further (table 2). The mechanism for this was a fall in heart rate without change in stroke volume (table 2). The most likely cause was increased vagal drive, but we have no direct evidence for this.

The cardiopulmonary volume of about 8 ml/kg in sham-clipped animals (table 2) compares well with values obtained in other species by methods different from thermodilution. For example, a value of 7.6 ml/kg was found in the rat,7 7.65 ml/kg in the dog,31 and about 9 ml/kg in the normotensive human.18 The values reported by Marshall and Shepherd22 for the dog (16 ml/kg) and for male human subjects (17 to 24 ml/kg) were higher, but their measurement included the left heart in dogs and both left and right hearts in humans. The fact that all these studies were performed with such completely intravascular indicators as labelled erythrocytes5 or cardiogreen dye16,31 further supports our argument that intravascular volume is likely to be the major compartment in the cardiopulmonary thermodilution space in the rabbit.

At steady-state, all hypertensive groups had significantly larger cardiopulmonary volumes than their matched sham-clipped groups (table 2, fig. 7), while the hindleg, consisting mostly of skeletal muscle, showed no change in steady-state volume (table 2, fig. 8). The changes in central blood volume are a common finding in hypertensives.5,23 In humans, increased fractional cardiopulmonary blood volume has been reported to be directly correlated with cardiac output or stroke volume in normotensives as well as in essential
and renovascular hypertensives.\textsuperscript{9, 18, 23} We did not see a positive correlation between steady-state stroke volume and steady-state cardiopulmonary volume (table 2) although we did find them to be significantly correlated during volume transients. A possible interpretation of these observations is that the mechanism by which increased cardiopulmonary volume leads to enhanced cardiac function is via an increase in cardiac filling pressure. At steady state, the increased volume in clipped animals (table 2) was not associated with increased left atrial pressure (fig. 4). During blood volume expansion, however, there were elevations in cardiopulmonary volume and in cardiac filling pressure (fig. 4).

Acute blood volume expansion to identical degrees in all groups resulted in transient changes of pressures (figs. 1 and 2) and of regional volumes (figs. 7 and 8) that differed between normotensive and hypertensive animals. Consequently, there must have been differences between them in their abilities to alter peripheral resistance or to distribute excess volume in response to an acute stimulus. Normotensive animals responded to blood volume expansion with large increases in cardiac output (fig. 5) but insignificant changes in mean arterial pressure (fig. 1). Hypertensive animals, on the other hand, showed smaller changes in cardiac output (fig. 5) and larger changes in arterial pressure (fig. 1). Therefore, it appears that normotensives were capable of complete vasoconstrictor compensation for increased output while hypertensives displayed impaired vasodilator capability. This was observed in the hindleg vasculature at 6 to 9 days (fig. 6) although it was not evident there at later longer durations of clipping.

Similar findings have been reported by others in two forms. Some have observed enhanced reactivity of the hypertensive circulation,\textsuperscript{22, 35} and others have observed reduced vasodilator capacity in hypertension.\textsuperscript{24} Enhanced cardiovascular reactivity expresses itself as an augmented blood pressure response of the hypertensive circulation to various stimuli. One of its causes, particularly on the arterial side where innervation is extensive, might have been neurogenic factors or increased responsiveness to them.\textsuperscript{35} However, on the venous side of the circulation there is less sympathetic innervation\textsuperscript{35} so that the purely mechanical effects of decreased vascular distensibility are a likely factor explaining the steeper rise in iliac venous pressure following blood volume expansion in hypertensive animals (fig. 2). This is explored further in the regional volume changes shown in figures 7 and 8. Hypertensive animals displayed a decreasing ability to store transiently increased blood volume in the cardiopulmonary space (fig. 7), but a gradually increasing ability to store volume in the hindleg region during later stages of hypertension (fig. 8).

Two explanations might be offered for the decreased regional volumes seen in figures 7 and 8. Either the decrease resulted from translocation of volume out of the regions secondary to increased arteriolar resistance\textsuperscript{11, 35} or the decrease resulted from regional changes in storage vessel elasticity.\textsuperscript{2, 8, 36, 37}

The first possibility is ruled out on two grounds. First, both regions in all animals showed vasodilation, not vasoconstriction. Second, the techniques employed here yielded *"needle-to-needle"* volumes and, therefore, included both arterial and venous volumes. Even though reduced vasodilator capacity in some tissues, including the hindleg in 6- to 9-day hypertensives (fig. 6) and the lungs in all three groups of hypertensives,\textsuperscript{*} would have caused some translocation of volume to the arterial side from the venous side, the major portion of the measured volumes were on the venous side.\textsuperscript{11}

Consequently, we believe that the observed volume changes are more likely to have resulted from changes in regional elasticity. It is not known whether these were caused by structural vascular changes or by altered neurogenic factors. Both of these have been reported as causes of the reduced venous distensibility that is seen in various forms of hypertension. For example, it has been found in isolated veins of dogs with one-kidney perinephritic hypertension,\textsuperscript{2} in plethysmographic studies of the forearm\textsuperscript{8} or of the index finger\textsuperscript{36} in essentially hypertensive humans, and in the portal vein of spontaneously hypertensive rats.\textsuperscript{37}

We have no data showing the importance of neurogenic factors. However, analysis of the pressure-volume data for both the cardiopulmonary region and the hindleg (table 3) showed the importance of changes in cardiopulmonary elasticity. With increasing duration of renal artery clipping, there was an increase in cardiopulmonary elasticity so that a given change in regional volume produced greater changes in intrapulmonary pressure than it did in normotensive control rabbits. No significant change in elasticity was demonstrated in the hindleg (table 3). Accordingly, with increasing duration of hypertension, the lungs were no longer a reservoir of the first order\textsuperscript{38} during acute volume changes. The hindleg became a reservoir of higher order even though there appeared to be no significant change in its effective elasticity (table 3).

The functional significance of these changes may be that they protect the heart during periods of volume overload. The peak change in stroke volume with the infusion was 0.4 ml/kg in the 6- to 9-day clipped group, 0.2 ml/kg in the 10- to 13-day group, and 0.1 ml/kg in the 14- to 17-day group, compared with 0.5 ml/kg in each of the sham-clipped groups. It may therefore be that, in the hypertensive circulation, increased cardiopulmonary elasticity minimized transient cardiopulmonary volume changes and thereby maintained stroke volume and cardiac output at a lower level than it otherwise would. Therefore, cardiopulmonary compliance may be an important factor in regulating transient loads on the heart. In hypertension, this mechanism could be a major factor in the control of blood pressure because the vasodilator capacity of the hypertensive circulation is impaired.

\textsuperscript{*}Reduced pulmonary vasodilator capacity is suggested by the markedly lower cardiac output during volume expansion in hypertensives (fig. 6) in the absence of significant differences between pulmonary arterial pressure (fig. 3) and left atrial pressure (fig. 4).
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References

Regional vascular capacitance in rabbit one-kidney, one clip hypertension.
U Ackermann and S R Tatemichi

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