Whole Body Autoregulation in Reduced Renal Mass Hypertension


Whole body autoregulation in conscious rats can be shown in the absence of the rapid acting neural and hormonal controllers of blood pressure. It is hypothesized that this phenomenon is responsible for the gradual rise of vascular resistance observed in volume-dependent forms of hypertension such as reduced renal mass–salt-induced hypertension. To examine the hypothesis, we evaluated the gain of whole body autoregulation at various stages of reduced renal mass hypertension to determine if acute autoregulatory capacity is altered during chronic hypertension. Rats underwent reduced renal mass surgery (nephrectomy plus 70% reduction of remaining kidney) and were studied at 2 (n=8), 4 (n=6), and 6 (n=7) weeks after high salt diet. Control rats (n=6) underwent nephrectomy and sham surgery and were studied after 2 weeks of high salt diet. All reduced renal mass rats showed progressive hypertension (2 weeks, 136±5; 4 weeks, 157±8; and 6 weeks, 171±10 mm Hg) compared with sham rats (113±4 mm Hg). We observed an increase in basal level of total peripheral resistance index after neurohumoral blockade in reduced renal mass rats (2 weeks, 1.64±0.06; 4 weeks, 1.79±0.10; and 6 weeks, 1.89±0.09 mm Hg · 100 g⁻¹ · min⁻¹ · ml⁻¹) compared with sham rats (1.56±0.10 mm Hg · 100 g⁻¹ · min⁻¹ · ml⁻¹). Blood volume expansion in the four groups during neurohumoral blockade caused significant whole body autoregulation in all rats as indicated by the slopes of the pressure–flow relations: 0.38 in sham, 0.41 in 2-week, 0.45 in 4-week, and 0.43 in 6-week reduced renal mass rats (slope=6, perfect autoregulation; slope=1, rigid vasculature). There were no significant differences in the autoregulatory capacity between the reduced renal mass rats and sham rats. We conclude that chronic reduced renal mass hypertension does not modify whole body autoregulation in response to acute volume expansion. (Hypertension 1992;29:659–665)

Key Words • cardiac output • vascular resistance • blood pressure • plasma volume • hypertension, volume-dependent • homeostasis

The hypothesis of whole body autoregulation, initially proposed by Ledingham and Cohen¹ and Borst and Borst-de Geus,² predicts that an expansion of blood volume causes an initial increase in cardiac output that results in overperfusion of the systemic circulation. This overperfusion triggers local autoregulatory mechanisms to increase vascular resistance to return blood flow back to normal. We have shown that whole body autoregulation can be clearly demonstrated in conscious areflexic rats.³,⁴ When neurohumoral reflex controllers of blood pressure are eliminated, a small 5% increase in blood volume caused approximately a 20% increase in vascular resistance. Our studies also indicate that the increase in vascular resistance is locally mediated and independent of neurohumoral and central nervous system control.⁵

Whole body autoregulation is of interest because it has been proposed as the mechanism for the hypertension that develops when animals with 70% reduction of renal mass (RRM) are fed a high salt diet (RRM hypertension).⁶ The hemodynamic pattern of this volume-dependent form of hypertension is consistent with that predicted by whole body autoregulation. RRM hypertension in dogs⁷ and rats⁸ is characterized by two phases. The acute phase is associated with an increase in cardiac output and no change in total peripheral resistance. The chronic phase is associated with cardiac output only slightly elevated above normal and a sustained increase in total peripheral resistance.

The complex cardiovascular responses to changes in blood volume have made the evaluation of long-term whole body autoregulation very difficult. A theoretical analysis of blood flow regulation has predicted estimates of whole body autoregulation in response to short-term volume expansion and to long-term volume expansion.⁹ It was observed that in the chronic phase of volume expansion, total peripheral resistance increased more than was predicted by the response during the acute phase of volume expansion. The cause of this difference between short-term and long-term autoregulation could not be determined from the mathematical model. We hypothesized that structural alterations in the systemic vasculature associated with chronic hypertension may enhance the autoregulatory response.

Studies by Folkow and his group¹⁰–¹² indicate that chronic hypertension is associated with structural

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changes in the systemic circulation that contribute to the elevated vascular tone. It has been proposed that structural changes in resistance vessels that cause a narrowing of the vessel act as a "geometric amplifier." Thus, hypertrophied hypertensive vessels will respond to a given vasoconstrictor stimulus with a greater increase in vascular resistance than normal vessels.

RRM hypertension has been shown to be associated with closure of microvessels during the first 2 weeks of hypertension. Anatomical rarefaction occurred during the fourth through sixth week of hypertension. Calculations showed that wall thickness of gracilis muscle arteries was increased after 6 weeks of RRM hypertension, but was not different from normotensive vessels after 2 weeks of hypertension. The extent to which these functional and structural changes in the vasculature could alter the autoregulatory responsiveness of the autoregulatory geometric amplifier concept, if these microcirculatory alterations result in vessel narrowing, would suggest autoregulatory vasoconstriction responses in hypertensive animals to be greater than in normotensive animals. The purpose of the present study was to evaluate the autoregulation response to an acute volume expansion in unanesthetized normotensive and hypertensive rats.

Methods

Animal Preparation

Male Sprague-Dawley rats weighing 225–250 g (King Animal Labs, Madison, Wis.) were anesthetized with a mixture of ketamine (50 mg/kg i.m.) and acepromazine (5 mg/kg i.m). The left kidney was exposed through a flank incision, and the poles of the kidney were surgically removed. Sham surgery consisted of exposing the left kidney without removal of the poles. After 2 weeks of recovery, sham-operated and RRM rats were anesthetized using the ketamine-acepromazine mixture, and the right kidney was removed. After a 1-week recovery period, the animals were fed a 4% NaCl diet to trigger the development of the hypertension. The rats were given water ad libitum and housed in animal rooms with a temperature of 23°C and a 12-hour light/dark cycle.

The rats were studied 2, 4, and 6 weeks after the initiation of hypertension with the 4% NaCl diet. Approximately 5 days before the experimental protocol the rats were surgically instrumented for hemodynamic monitoring, which has previously been described in detail. Briefly, the rats were instrumented with an electromagnetic flow probe (series 100, Carolina Medical Electronics, King, N.C.) placed around the ascending aorta and allowed to recover for 3 days; catheters were then placed in the left femoral artery, left femoral vein, and right jugular vein. The rats were allowed to recover for 1–2 days before the experimental protocol.

Experimental Protocol

During the experiment, the rats were placed in a Plexiglas restrainer inside a soundproof ventilated chamber. Arterial pressure was measured in the arterial catheter with a pressure transducer (model P23 Db, Statham Instruments Division, Gould Inc., Oxnard, Calif.), and cardiac output was measured by an electromagnetic flowmeter (model 201D, Carolina Medical Electronics). Measurements of mean arterial pressure (MAP) and cardiac output were recorded on a Grass polygraph recorder (model 7D, Grass Instruments Co., Quincy, Mass.). Cardiac index (CI) and total peripheral resistance index (TPRI) were calculated to normalize the values with respect to the weight of the animal. TPRI was calculated as the ratio of MAP to CI.

Neurohumoral reflex function was abolished pharmacologically, as described previously. Ganglionic transmission of the autonomic nervous system was blocked with chlorisondamine chloride (10 mg/kg) and methscopolamine bromide (0.5 mg/kg). Angiotensin II synthesis was inhibited by captopril (1 mg/kg). The vasoconstrictor effects of vasopressin were prevented by a specific vascular vasopressin receptor antagonist, [d(CH2)5Tyr(Me)]-arginine vasopressin (10 µg/kg). The drugs were first administered intravenously as a bolus injection and were then continuously infused throughout the experimental protocol at a rate of 0.015 ml/min. The concentrations of the blocking agents in the solution were calculated to deliver the initial blocking dose of each agent over a 1-hour period. Hemodynamic measurements were monitored immediately after neurohumoral blockade to determine basal hemodynamic characteristics.

Blood pressure in areflexic rats was then maintained with a constant infusion of norepinephrine (0.5–1.0 µg · kg⁻¹ · min⁻¹). In sham-operated normotensive rats, blood pressure was maintained at the level observed before neurohumoral blockade. In the hypertensive rats, norepinephrine was infused at a similar rate as in normotensive rats. The purpose of setting the norepinephrine infusion rate the same in all rats was to keep the level of adrenergic tone constant between groups and to maintain blood pressure in the RRM rats within the physiological operating range of the heart and systemic vasculature. This would allow for an accurate evaluation of the autoregulatory ability between groups based on the comparison of the ratio of change of pressure and flow in the areflexic state. Autoregulation

Table 1. Hemodynamic Values and Autoregulation Slopes in Normotensive Rats During Three Infusion Doses of Norepinephrine

<table>
<thead>
<tr>
<th>NE dose (µg · kg⁻¹ · min⁻¹)</th>
<th>MAP (mm Hg)</th>
<th>CI (ml · min⁻¹ · 100 g⁻¹)</th>
<th>TPRI (mm Hg · 100 g⁻¹ · min⁻¹ · ml⁻¹)</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.36±0.04</td>
<td>149±2</td>
<td>31±2</td>
<td>5.1±0.3</td>
<td>0.33±0.04</td>
</tr>
<tr>
<td>0.73±0.01</td>
<td>124±1</td>
<td>31±1</td>
<td>4.3±0.2</td>
<td>0.30±0.02</td>
</tr>
<tr>
<td>0.37±0.01</td>
<td>100±2</td>
<td>30±1</td>
<td>3.4±0.1</td>
<td>0.31±0.02</td>
</tr>
</tbody>
</table>

NE, norepinephrine; MAP, mean arterial pressure; CI, cardiac index; TPRI, total peripheral resistance index; slope, autoregulation slope. n=5 rats. Values are mean±SEM.
Table 2. Resting Hemodynamic Values in Conscious Rats During Intact and Areflexic Conditions

<table>
<thead>
<tr>
<th>Group</th>
<th>Intact</th>
<th>Areflexic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (n=6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>113±4</td>
<td>112±4</td>
</tr>
<tr>
<td>CI (ml · min⁻¹ · 100 g⁻¹)</td>
<td>32.4±1.6</td>
<td>30.7±2.3</td>
</tr>
<tr>
<td>TPRI (mm Hg · 100 g⁻¹ · min⁻¹ · 100 g⁻¹)</td>
<td>3.52±0.21</td>
<td>3.78±0.35</td>
</tr>
<tr>
<td>2-week RRM (n=8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>136±5*</td>
<td>129±4</td>
</tr>
<tr>
<td>CI (ml · min⁻¹ · 100 g⁻¹)</td>
<td>37.8±1.7*</td>
<td>38.1±1.5*</td>
</tr>
<tr>
<td>TPRI (mm Hg · 100 g⁻¹ · min⁻¹ · 100 g⁻¹)</td>
<td>3.61±0.11</td>
<td>3.44±0.20</td>
</tr>
<tr>
<td>4-week RRM (n=6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>157±8*</td>
<td>130±2†</td>
</tr>
<tr>
<td>CI (ml · min⁻¹ · 100 g⁻¹)</td>
<td>32.9±1.1</td>
<td>31.2±0.9</td>
</tr>
<tr>
<td>TPRI (mm Hg · 100 g⁻¹ · min⁻¹ · 100 g⁻¹)</td>
<td>4.76±0.09*</td>
<td>4.21±0.16†</td>
</tr>
<tr>
<td>6-week RRM (n=7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>171±10*</td>
<td>135±6†</td>
</tr>
<tr>
<td>CI (ml · min⁻¹ · 100 g⁻¹)</td>
<td>35.7±2.0</td>
<td>34.6±2.1</td>
</tr>
<tr>
<td>TPRI (mm Hg · 100 g⁻¹ · min⁻¹ · 100 g⁻¹)</td>
<td>4.86±0.31*</td>
<td>3.96±0.26†</td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure; CI, cardiac index; TPRI, total peripheral resistance index. Values are shown before (intact) and after (areflexic) neurohumoral blockade and norepinephrine infusion in sham-operated and 2-, 4-, and 6-week reduced renal mass (RRM) hypertensive rats. Values are mean±SEM.

* Significant difference when compared with sham group.
† Significant difference between intact and areflexic values.

Responses were tested in normotensive animals during consecutive infusion rates of norepinephrine, and no differences were found in those responses among the various norepinephrine infusion doses. The results of these tests are summarized in Table 1.

After neurohumoral reflex blockade, the rats were subjected to an acute blood volume expansion. Donor blood was infused through a venous catheter at a rate of 0.15 ml/min using an infusion pump (model 355, Sage Instruments, Boston, Mass.) with a total volume of 0.9 ml donor blood infused in 6 minutes. Approximately 3–5 minutes after blood volume expansion, 0.9 ml blood was withdrawn through the arterial catheter to restore blood volume to control levels.

Donor blood was prepared as a mixture of washed blood cells and a plasmalike solution to eliminate any vasoactive agents as previously described. The proportions of blood cells and plasmalike solution were calculated to match the hematocrit of the experimental recipient rat. Before use in an experimental protocol, donor blood electrolytes, gases, and pH were analyzed and verified to be within a normal physiological range.

Statistical Analysis

The results of the present study were expressed as mean±SEM. Differences between baseline hemodynamic variables during intact and areflexic conditions were assessed with a Student's t test for paired values. Differences in basal hemodynamics between groups after neurohumoral blockade were determined by a one-way analysis of variance followed by a Newman-Keuls comparison test. Changes in MAP, CI, and TPRI during acute increases in blood volume in RRM and sham-operated rats were evaluated by a two-way analysis of variance for repeated measures. The Dunnett’s multiple range test was used to determine significant differences in these hemodynamic changes as compared with control values. Linear regression analysis was used to determine the slope of the pressure–flow relations followed by an unpaired Student’s t test to compare the slopes of the lines. A probability value of p<0.05 was considered statistically significant for all tests.

Results

Baseline Hemodynamics

Table 2 shows the baseline hemodynamics in sham-operated and RRM rats before and after neurohumoral blockade and norepinephrine infusion. MAP in the three RRM groups was significantly higher than that in the sham-operated group. The hypertension in 2-week RRM rats was a result of an elevated CI, whereas the hypertension in 4- and 6-week RRM rats was a result of an elevated TPRI. After neurohumoral blockade in the sham rats, norepinephrine was infused to return MAP to intact levels. This also resulted in CI and TPRI values that were not different from intact values. After neurohumoral blockade in RRM rats, norepinephrine was infused at the same rate as in the normotensive rats. In 2-week RRM rats, this resulted in hemodynamic values that were not significantly different from those observed in the intact state. In 4- and 6-week RRM rats, norepinephrine maintained MAP and TPRI at levels that were significantly lower than those before blockade.
FIGURE 1. Bar graphs show mean arterial pressure (MAP), cardiac index (CI), and total peripheral resistance index (TPRI) after neurohumoral blockade of the sympathetic nervous system, renin-angiotensin system, and vasopressin in normotensive rats (n=21) and 2-week (n=14), 4-week (n=9), and 6-week (n=11) reduced renal mass (RRM) rats. *Significant difference when compared with normotensive rats (p<0.05). Data are expressed as mean±SEM.

Basal Hemodynamics During Neurohumoral Blockade

Hemodynamic values were recorded for 1–2 minutes after combined blockade of the sympathetic nervous system, the renin-angiotensin system, and the vasopressin system before the initiation of norepinephrine infusion in normotensive sham-operated rats (n=6), 2-week RRM (n=14), 4-week RRM (n=9), and 6-week RRM (n=11). In addition, a second group of normotensive rats fed a normal sodium diet (n=15) in which only basal hemodynamic measurements were evaluated was included in these results. There were no differences in the responses between the two normotensive groups; therefore, their responses were pooled. Figure 1 shows that neurohumoral blockade decreased CI to the same level in all groups; however, MAP and TPRI in the 4-week and 6-week RRM rats (56±3 mm Hg and 1.79±0.10 mm Hg · 100 g⁻¹ · min⁻¹ · ml⁻¹; 55±2 mm Hg and 1.89±0.09 mm Hg · 100 g⁻¹ · min⁻¹ · ml⁻¹, respectively) were significantly higher than the normotensive group (45±2 mm Hg and 1.56±0.10 mm Hg · 100 g⁻¹ · min⁻¹ · ml⁻¹, respectively).

Hemodynamic Responses to Blood Volume Expansion

We measured hemodynamic changes as they occurred during a steady infusion of donor blood. Since neurohumoral controllers of blood pressure were eliminated, we assumed that increases in TPRI observed during volume expansion were indicative of local autoregulation responses. Not all rats exhibited significant increases in TPRI during volume expansion, i.e., autoregulation. We have consistently observed that approximately 25% of the rats do not demonstrate autoregulation. Therefore, as in previous

FIGURE 2. Line graphs show mean arterial pressure (MAP), cardiac index (CI), and total peripheral resistance index (TPRI) before and during a 6-minute infusion of blood in sham-operated (n=6) and 2-week (n=8), 4-week (n=6), and 6-week (n=7) reduced renal mass (RRM) rats. *Significant difference from 0 minutes (p<0.05). Data are expressed as mean±SEM.
studies,3-5 only responses from autoregulating rats were included in these results. Figure 2 represents the average hemodynamic values observed before and during a 6-minute infusion of donor blood in sham-operated rats and RRM rats. MAP, CI, and TPRI increased significantly during volume expansion, reaching a plateau during the last 2 minutes of blood infusion. Evaluation of hemodynamic values during 3-5 minutes after blood infusion revealed no further increases, indicating that peak autoregulation responses occurred during the infusion period. Hemodynamic responses were therefore calculated at the end of infusion. Volume expansion caused small but significant increases in CI of 9±1% in sham-operated, 7±1% in 2-week RRM, 9±1% in 4-week RRM, and 9±2% in 6-week RRM rats. Blood infusion also caused significant increases in MAP of 23±2% in sham-operated, 18±3% in 2-week RRM, 21±1% in 4-week RRM, and 20±2% in 6-week RRM rats. When TPRI was calculated, we observed significant increases in all groups of rats indicating that both normotensive and hypertensive rats were responding to the volume expansion by systemic vasoconstriction via local autoregulatory mechanisms. TPRI increased by 13±3% in sham-operated, 10±2% in 2-week RRM, 11±1% in 4-week RRM, and 10±1% in 6-week RRM rats.

Pressure-Flow Relations

An index of the autoregulatory strength of the systemic circulation is the normalized pressure-flow relation. Assuming Poiseuille's law prevails with a nondisensible vasculature and no systemic autoregulation, this pressure-flow relation is characterized by a regression line with a slope equal to 1. Complete autoregulation is characterized by a pressure-flow relation with a slope equal to 0. Figure 3 represents the pressure-flow relations for normotensive and hypertensive rats. The fractional change in pressure (ΔP/P) is plotted against the fractional change in flow (ΔF/F) during each minute of blood infusion. The ratios ΔP/P and ΔF/F were determined before volume expansion and at 1-minute intervals during the 6-minute protocol. The regression lines for the systemic pressure-flow relations were determined by seven points in each rat by linear regression analysis. The calculated slopes were 0.38±0.02 (r=0.77) in sham-operated, 0.41±0.03 (r=0.69) in 2-week RRM, 0.45±0.04 (r=0.64) in 4-week RRM, and 0.43±0.03 (r=0.78) in 6-week RRM rats. There were no significant differences among these slopes, which indicates that hypertensive RRM rats had a similar autoregulatory strength in response to an acute volume expansion as compared with normotensive rats.
Discussion

We have previously characterized the hemodynamic and microcirculatory changes during the acute and chronic phases of RRM hypertension in rats. It was observed that during the first 4 days of salt loading, the hypertension was related to an elevated cardiac output. Six weeks after salt loading, cardiac output was normal, and the hypertension was maintained by an elevated total peripheral resistance. The results of the present study indicate that an elevated CI persists through the second week of hypertension and that sometime between the second and fourth weeks of hypertension CI returns to normal and TPRI increases. We also determined the basal hemodynamic characteristics after neurohumoral blockade at the various stages of the hypertension. Basal vascular tone, characterized in the present study by TPRI in the absence of tone from the sympathetic nervous system, the renin-angiotensin system, and vasopressin, progressively increased during the development of the hypertension. There was a statistically significant elevation in basal vascular tone in rats after 4 and 6 weeks of RRM hypertension.

The present study therefore confirms the sequence of hemodynamic events related to salt-induced hypertension in RRM rats obtained in our previous study using thermodilution techniques. These observations are also consistent with the sequential events first seen in RRM dogs in that the hypertension is initiated by an elevation of cardiac output followed by a chronic phase of hypertension associated with an elevated total peripheral resistance and a nearly normal level of cardiac output. As pointed out by earlier investigators, this hemodynamic pattern would be predicted by regional autoregulatory events of the systemic vasculature. This concept has come to be known as the “whole body autoregulation” theory of hypertension.

We have proposed that the response of the cardiovascular system to sustained increases in body fluid volume is a complex series of events whereby the initial rise of systemic vascular resistance is a result of the well-characterized autoregulatory responses that have been observed in nearly every organ and tissue in response to elevations of perfusion pressure. We have shown in a theoretical analysis that the degree of whole body autoregulation seen with acute (6-minute) elevations of blood volume is similar to that predicted from the individually determined regional responses. However, the so-called “long-term autoregulation” response observed with chronic blood volume expansion exceeds that which can be predicted from measured “short-term autoregulation” experiments.

Figure 4 characterizes the long-term autoregulation responses to chronic volume expansion during 2, 4, and 6 weeks of RRM hypertension. These pressure–flow relations were determined using the data presented in Table 1 by computing the ratio (slope) of the fractional increase of CI to the fractional increase of MAP. From these relations, it can be seen that at 2 weeks, most of the fractional increase of pressure far exceeds that of flow and is therefore due to increases in resistance.

We evaluated the whole body autoregulation responses to acute volume expansion in normotensive and hypertensive rats. We observed that despite chronic hypertension, the short-term autoregulatory ability in these animals was not different from normotensive rats. These results indicate that the rise in vascular resistance (long-term autoregulation) seen with chronic volume expansion was not due to altered short-term autoregulation responses.

The most likely explanation is that these time-dependent increases of resistance are related to vascular structural changes. Hypertension at 4 and 6 weeks was associated with an increase in basal vascular tone. We expected that this would be the case, but we also expected that such vascular structural changes would act to enhance the gain of whole body autoregulation. Folkow et al. first recognized that medial hypertrophy of small resistance vessels associated with established hypertension would allow the arteries to amplify vascu-
lar resistance during stimulation. However, we observed no differences in acute autoregulation responses between normotensive and hypertensive animals.

We have, however, observed other types of structural changes specific to the microcirculation during the development of RRM hypertension in which there is a total disappearance and reduction in the number of small precapillary (3A and 4A) arterioles, a phenomenon called rarefaction.

Functional rarefaction (vessel closure) of cremasteric arterioles was observed as early as 36 hours after the onset of hypertension and progressed to anatomical rarefaction (vessel loss) after 4 and 6 weeks of hypertension. The structural basis of this anatomical rarefaction was shown to be irreversibly degenerated or severely atrophied microvessels. An evaluation of the structure of microvascular smooth muscle cells in vessels that had not undergone rarefaction revealed extreme vasoconstriction in some arterioles of RRM rats between 3 days and 2 weeks after salt loading, but not in 4-week RRM rats. In addition, this study revealed evidence of focal hyperplasia of vascular smooth muscle cells but no evidence of vascular hypertrophy. Calculations of vessel wall thickness indicate an increase in thickness in 6 week RRM rats but not in 2-week RRM rats. However, no calculations of vessel internal diameters are available.

Based on these microvascular studies it appears that the predominant structural alteration associated with the development of RRM hypertension is vessel rarefaction with little evidence of medial hypertrophy. This type of structural alteration has been shown to contribute to an increase in vascular resistance and probably accounts for the increased basal tone observed at 4 and 6 weeks of hypertension in the present study. Such structural changes, however, are not believed to cause a vascular amplification effect. Thus, our findings of an elevated basal vascular resistance in RRM rats and no difference in acute autoregulatory response between normotensive and hypertensive rats are consistent with the development of rarefaction during the hypertension. Thus, our results indicate that although structural alterations do not act to amplify acute autoregulatory vasoconstrictor responses, they are responsible, at least in part, for the gradual rise of total peripheral resistance observed in the chronic stages of RRM and probably of other volume-dependent forms of hypertension.

In summary, we have shown that RRM hypertension in rats is characterized by a hemodynamic pattern predicted by the whole body autoregulation hypothesis, i.e., an acute phase of hypertension initially maintained by an elevated cardiac output followed by a chronic phase of hypertension maintained by an elevated total peripheral resistance. Observed elevations of basal vascular resistance after 4 and 6 weeks of hypertension do not appear to be a result of vascular structural enhancement of acute autoregulatory responses. Rather, the progressive rise of peripheral vascular resistance appears to be a result of the anatomical rarefaction that occurs during this phase of hypertension.

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