Hemodynamic Characteristics of the Intestinal Microcirculation in Renal Hypertension

GERALD A. MEININGER, KAREN L. FEHR, MIRIAM B. YATES, JEFFREY L. BORDERS, AND HARRIS J. GRANGER

SUMMARY This study investigated the microvascular changes that affect vascular resistance in the rat small intestine during two-kidney, one clip renal hypertension 4 weeks after renal artery stenosis. To study the intestinal microcirculation, a loop of the small intestine was exteriorized with intact circulation and innervation and a section of the bowel wall was prepared for observation with an intravital video microscopy system. Microvascular diameter, pressure, and flow velocity were measured for first, second, and third branch order arterioles and venules, using an image shearing monitor, servo-null micropipette system, and an optical Doppler velocimeter, respectively. The diameters of the first order arterioles and venules were significantly \( p < 0.05 \) reduced in hypertensive rats; however, diameters were unaltered in smaller second and third order arterioles and venules as compared with normotensive vessels. In hypertensive rats, mean arterial pressure was significantly \( p < 0.05 \) elevated (47%) and pressures also were elevated significantly \( p < 0.05 \) throughout the microcirculation, although by a proportionally smaller amount. Total network flow (i.e., first order arteriole flow) was significantly \( p < 0.05 \) reduced (40%) in hypertensive rats, but volume flows in individual second and third order arterioles were similar to flows measured in normotensive rats. Calculated total network resistance was increased (124%) in hypertensive rats. Thus, the intestinal microcirculation in rats with two-kidney, one clip Goldblatt hypertension is disturbed by elevated pressure and decreased total flow. The presence of normal flows in individual second and third order arterioles without any demonstrable difference in their diameters suggests that the predominant cause of elevated resistance across this segment of the intestinal microcirculation is a reduction in the number of perfused small arterioles. (Hypertension 8: 66-75, 1986)

KEY WORDS • microvascular pressures • microvascular flows • microvascular diameters • vascular resistance • splanchnic circulation • two-kidney, one clip Goldblatt hypertension

The microvascular characteristics that determine vascular resistance in hypertension have received increased attention over the last decade. This is principally because the microcirculation is a primary site of peripheral resistance and is controlled by neural and hormonal mechanisms of blood pressure regulation, which are well known to be altered in various forms of experimental hypertension. It has been reasoned, therefore, that a better understanding of the microvascular changes occurring in hypertension should improve our understanding of the abnormalities that produce and sustain hypertension.

Substantial experimental evidence indicates that the elevated total peripheral resistance in renovascular hypertension is not necessarily the result of a uniform increase in vascular resistance among the various regional circulations. In addition, different vascular beds vary in their degree of neural control, sensitivity to vasoactive humoral agents, and capacity to autoregulate blood flow. Thus, it seems reasonable to hypothesize that during hypertension the mechanisms that produce increased vascular resistance in different regional circulations will express themselves in quantitatively or qualitatively different ways on the microcirculation. As such, it may not be valid to infer that changes observed in one vascular bed are characteristic...
of the changes that occur in another. In this regard, the majority of our information concerning the microcirculation in hypertension has been derived from studies of skeletal muscle.11-14 Several features of the splanchnic circulation suggest that hemodynamic changes in this regional vascular bed could have a major effect on overall cardiovascular homeostasis. For example, the splanchnic circulation 1) receives approximately 25% of the cardiac output, 2) contains between 20 and 35% of the total blood volume, and 3) is important in total body fluid and electrolyte balance. In addition, the hepatic clearance of hormones, such as renin and aldosterone, that are capable of altering circulatory hemodynamics is dependent on splanchnic flow.15-18 Therefore, alterations in splanchnic circulatory homeostasis could have a profound impact on systemic hemodynamics.

For these reasons, our goal was to characterize the microvascular hemodynamics of the small intestine in the rat with two-kidney, one clip renal hypertension. To accomplish this, our study was designed to quantify microvessel pressure, flow velocity, and diameter for arterioles and venules located across several consecutively branching segments of the jejunal microcirculation.

Materials and Methods

All studies were performed on male Sprague-Dawley rats that were fed rat chow ad libitum and allowed free access to water. The rats were housed in pairs and maintained in a room with a 12-hour light/dark cycle.

To produce two-kidney, one clip renal hypertension, 4-week-old rats (weight, 70-100 g) were first anesthetized with an intraperitoneal injection of sodium pentobarbital (50 mg/kg). The right renal artery was then exposed through a flank incision, and a silver clip with a gap width of 200 μm was placed around the artery. The left kidney was not disturbed during this procedure. Normotensive control rats underwent similar surgical treatment except that a silver clip was not compressed. The entire preparation was then transferred to the stage of a Zeiss ACM trinocular microscope (San Antonio, TX, USA) for observation of the microcirculation.19 20 The pedal was also constructed such that it was surrounded by a water-jacketed Plexiglas block through which warmed (37°C) Krebs solution was continuously circulated. A small bath chamber with a hole in the bottom was then placed over the intestine to restrain it in a flat position against the optical pedestal. The chamber was sealed with silicone grease and care was taken that the vessels feeding the intestinal wall were not compressed. The entire preparation was then transferred to the stage of a Zeiss ACM trinocular microscope (San Antonio, TX, USA) for observation of the microcirculation using a closed-circuit video system.

The Krebs solution that was used to keep the intestine moist was warmed to 37 ± 0.5°C and was composed of 25.5 mM NaHCO3, 112.9 mM NaCl, 4.7 mM KCl, 2.55 mM CaCl2, 2H2O, 1.19 mM KH2PO4, 1.19 mM MgSO4·7H2O, and 11.6 mM dextrose. This Krebs composition resulted in an osmolality of approximately 290 mosm. Nitrogen and carbon dioxide gas were bubbled at controlled rates through the Krebs solution to maintain pH between 7.35 and 7.45, carbon dioxide tension between 40 and 50 mm Hg, and oxygen tension between 30 and 40 mm Hg. This Krebs solution was suffused continuously over the intestinal wall at a rate of 5 to 6 ml/min.

During short-term microvascular experiments, microvessel lumen diameter, pressure, and flow velocity were measured. The lumen diameter measurements were performed on line using an image shearing monitor (Model 907, Instrumentation for Physiology and
Microvascular pressure measurements were made using a servo-null micropuncture system (Model 4A, Instrumentation for Physiology and Medicine). The techniques employed for determination of pressure have been described previously. Microtipettes for this system were sharpened to an outside tip diameter of 1 to 2 μm and were filled with a 2 M NaCl solution by immersing them in a reservoir of heparinized, filtered 2 M NaCl solution. Heparin (10 U/ml) was used to reduce the formation of platelet aggregates at the pipette tip, which sometimes occurred after puncture of a microvessel. The pipettes were sharpened by lowering their tip onto a rotating surface layered with abrasive 0.3 μm aluminum particles. The abrasive surface was covered with a thin layer of 2 M NaCl solution. Micropipettes were inserted into selected microvessels with a micromanipulator. Measurements of centerline blood flow velocity were made with an optical Doppler intravital velocimeter (Microcirculation Research Institute, College Station, TX, USA). The details describing this measurement device have been published previously. The velocimeter was displayed as a continuous trace on a chart recorder. The velocimeter was calibrated against a rotating Plexiglas wheel that had a blood-smeared surface. The output of the velocimeter was found to be linear over a range of known wheel rotation rates.

Volume flow (nl/sec) was calculated from measurements of microvessel diameter and flow velocity by using the following equation: flow = \( \left( \frac{v}{1.6} \right) \times \left( \pi r^2 \right) \times (0.001) \), where \( v \) is centerline flow velocity (mm/sec), 1.6 is a correction factor that converts centerline velocity to an average cross-sectional flow velocity, \( r \) is the microvessel radius (μm), and 0.001 is a conversion factor used to express flow (in nl/sec).

Microvessels selected for study were defined according to their branch order location within the microvascular network. This classification scheme has been described previously in detail for the small intestine microcirculation. Briefly, first order arterioles (1A) and venules (1V) arise from a small artery and small vein pair that traverse the mesenteric border of the intestine. The 1A and 1V vessels penetrate through the muscle layers of the intestinal wall to the submucosal layer. Within the submucosa the 1A and 1V give rise to a second order arteriole (2A) and venule (2V). The 2A and 2V generally lie along the longitudinal axis of the intestine. Third order arterioles (3A) branch at right angles from the 2A and give rise to smaller arterioles that feed the muscle layers. Also, the 3A continues into the mucosa and becomes the central villus arteriole. Third order venules (3V) arise from the 2V and typically travel a short distance within the submucosa before penetrating into the muscle layers. In our study, measurements were obtained from the first through third order arterioles and first through third order venules.

Micropunctures of the 1A and 1V were performed as near to their entry point into the intestinal wall as possible. The puncture of the 2A, 2V, and 3A were performed within the midpoint regions of these vessels as they course through the submucosa. Punctures of the 3V were performed within the short segment of the venule that lie in the submucosa before it penetrates into the muscle layers. Punctures of the microvessels were performed in sequence beginning with a randomly selected 3A arteriole. After the 3A had been punctured, the pipette was moved upstream to the parent 2A for pressure measurement and then upstream to the parent 1A. Venules also were punctured in a sequential fashion beginning with the 1V and moving upstream to the 2V and 3V. This sequential micropuncture procedure was used to permit more accurate determination of the pressure gradient between adjacent branch order vessels and to minimize the effect of any platelet aggregates on the downstream pressure distribution. In some animals it was not possible to obtain sequential measurements throughout the microvascular network.

During the short-term microcirculation experiments, microvessel diameter and flow velocity were measured in a group of 13 normotensive and 15 two-kidney, one clip hypertensive rats. In these experiments a selected microvessel was observed for 3 minutes, during which diameter and flow velocity were continuously recorded. This procedure was used to obtain measurements of diameter and flow velocity for the 1A arteriole. A 2A vessel branching from the 1A was then randomly selected for study. The 2A measurements were then followed by random selection of a 3A vessel that branched from the selected 2A arteriole. A similar sequence of measurements was obtained from the venules beginning with the 1V vessel and moving upstream to a selected 2V and 3V. In each animal measurements were obtained from one vessel in each branch order category. In seven of the 13 normotensive rats and in 12 of the 15 hypertensive rats, adenosine (1 × 10^{-4} M) was added to the Krebs suffusion solution to maximally dilate the intestinal microvasculature. Maximal adenosine dilation was tested by suffusing the preparation with Krebs solution containing 5 × 10^{-4} M or 1 × 10^{-3} M adenosine. At each of these concentrations no further dilation was noted over that produced by 1 × 10^{-4} M adenosine. In these preparations the measurements of diameter were made before and after adding adenosine to the suffusion solution.

In a second group of 15 normotensive and 18 two-kidney, one clip hypertensive rats, microvessel pressure was measured in the first through third order arterioles and venules. For these experiments, a selected microvessel was first observed for a 2-minute control period to obtain a prepuncture measurement of the microvessel's resting diameter. After this initial period the vessel was punctured with a pipette for measurement of microvascular pressure. A minimum of 30 seconds of pressure recordings was required to consider the pressure measurement valid. Also, a valid measurement required that the diameter of the microvessel being punctured did not change significantly (i.e., >5%) from the diameter of the vessel during the control period. In addition, measurements of pressure
were discarded if platelet aggregation obstructed the vessel flow or the pipette tip.

A short-term microcirculation experiment typically required 90 to 120 minutes to complete. Microvascular preparations were evaluated and discarded before or during an experiment if the preparation showed excessive sticking of leukocytes to the walls of small venules, vessels with stasis, petechial hemorrhages, or excessive movement of the intestinal wall.

To determine if the number of 1A vessels in the gut wall differed, the number of 1A vessels was visually counted in a group of 12 normotensive and 14 hypertensive rats. To count the number of 1A vessels, three sections of the small intestine (each section approximately 4 cm long) were excised and the 1A vessels penetrating the bowel wall were counted. These counts were then expressed as the number of 1A vessels per gram of tissue weight.

To reduce intestinal motility during the microcirculatory experiments sufficiently to measure diameter, velocity, and pressure, isoproterenol was added to the Krebs solution suffusing the intestine. The concentration of isoproterenol required to quiet the intestinal motility ranged from $0$ to $4.7 \times 10^{-7}$ g/ml and averaged $1.9 \times 10^{-7} \pm 1.3 \times 10^{-8}$ g/ml. The concentration of isoproterenol required to reduce motility did not differ between the hypertensive and normotensive rats. At these concentrations the motility could be reduced without producing any detectable microvascular effects. The observations we made to confirm the absence of an isoproterenol effect on intestinal microvessels included the following: 1) no detectable arteriolar dilation for any of the arterioles studied unless the concentration of isoproterenol exceeded $1 \times 10^{-6}$ g/ml; 2) no detectable change in 1A flow (i.e., total network flow) when isoproterenol was added to the suffusion solution; and 3) no change in mean arterial pressure in the rat, which indicates an absence of any systemic effect. Similar findings for isoproterenol in the small intestine have been reported by others.19, 20

Measurements of diameter, flow velocity, and pressure were taken from the chart record at 10-second intervals and averaged to provide the measured values for a selected microvessel. Comparisons between the hypertensive and sham-operated normotensive rats were made using the nonpaired t test. Differences between the two groups were considered significant at a 5% confidence level. Comparisons of the microvascular responses within the hypertensive group or within the sham-operated before and after treatment with adenosine were made using the paired t test.23 Results are given as means ± SEM.

Results

Microvascular Diameters

Lumen diameters of the first order arterioles ($72 \pm 5 \mu m$) and first order venules ($155 \pm 10 \mu m$) in the hypertensive rats were significantly reduced compared with those of the first order arterioles ($87 \pm 7 \mu m$) and venules ($185 \pm 12 \mu m$) in sham-operated normotensive rats ($p < 0.05$; Figure 1). However, there were no differences between the two groups in the diameters of the smaller second and third order arterioles and venules (Figure 1).

The addition of $10^{-4}$ M adenosine to the Krebs solution suffusing the intestinal wall produced significant dilation at all three arteriolar branch levels in the hypertensive rats and at the second and third order arterioles in the normotensive rats ($p < 0.05$; Table 1). Excluding the IV, the adenosine-dilated vessels in normotensive and hypertensive rats had comparable diameters. No significant differences were observed, however, between the hypertensive and normotensive rats in the evoked raw change or in the percent change in arteriolar diameters produced by adenosine (see Table 1). In our study, adenosine did not significantly dilate the venules at any branch level in the normotensive or hypertensive rats (see Table 1).

![Figure 1](https://hyper.ahajournals.org/)

**Figure 1.** Microvessel lumen diameters are shown for the small intestine of normotensive rats and two-kidney, one clip hypertensive rats. Arterioles and venules are designated as 1, 2, and 3 for the first, second, and third branch order vessels, respectively. These data are plotted as the mean ± SEM. Asterisks designate a significant ($p < 0.05$) difference between hypertensive and normotensive rats.
TABLE 1  Control and Adenosine-Dilated Diameters in the Small Intestine from Seven Normotensive and 12 Two-Kidney, One Clip Hypertensive Rats

<table>
<thead>
<tr>
<th>Vessel category</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resting (µm)</td>
<td>Passive (µm)</td>
</tr>
<tr>
<td>1A</td>
<td>86±11</td>
<td>92±7</td>
</tr>
<tr>
<td>2A</td>
<td>33±3</td>
<td>47±2*</td>
</tr>
<tr>
<td>3A</td>
<td>15±1</td>
<td>24±2*</td>
</tr>
<tr>
<td>3V</td>
<td>22±2</td>
<td>22±2</td>
</tr>
<tr>
<td>2V</td>
<td>57±2</td>
<td>61±4</td>
</tr>
<tr>
<td>1V</td>
<td>186±19</td>
<td>188±16</td>
</tr>
</tbody>
</table>

Values are means ± SEM. The first, second, and third order arterioles and venules are given as 1A, 2A, 3A and 1V, 2V, 3V, respectively. *p < 0.05, compared with resting diameter values.

Mean Arterial Pressure and Microvascular Pressures

Four weeks after unilateral renal artery stenosis, mean arterial pressure (147 ± 3 mm Hg) in hypertensive rats was significantly elevated compared with that in the sham-operated normotensive rats (100 ± 3 mm Hg; p < 0.05). Compared with those in normotensive rats, microvascular pressures were also significantly elevated in the hypertensive rats for the first (101 ± 4 vs 77 ± 3 mm Hg), second (83 ± 4 vs 61 ± 2 mm Hg), and third (55 ± 6 vs 48 ± 2 mm Hg) order arterioles (p < 0.05; Figure 2). Similarly, pressures were significantly increased in the first (11 ± 0.5 vs 9 ± 0.4 mm Hg), second (14 ± 0.5 vs 11 ± 0.6 mm Hg), and third (21 ± 1 vs 16 ± 1 mm Hg) order venules (p < 0.05; see Figure 2).

Although pressures were elevated throughout the...
microcirculation, they were increased proportionally less than the rise (47%) in mean arterial pressure. For instance, intravascular pressures were increased 31%, 36%, and 15% in the first, second, and third order arterioles, respectively, and 22%, 27%, and 31% in the first, second, and third order venules, respectively. Thus, a significant fraction of the increased mean arterial pressure in the hypertensive rats was dissipated proximal to the microcirculation of the intestinal wall \( (p < 0.05) \).

**Microvascular Flows**

In the hypertensive rats, flow velocities measured in the first through third order arterioles and the first through third order venules were similar to those measured in the sham-operated normotensive rats (Figure 3). However, calculated volume flow for the total microvascular network, as measured in the first order feeder arteriole, was significantly reduced (40%) in the hypertensive rats (82 ± 13 nl/sec) as compared with that in the normotensive rats (140 ± 21 nl/sec; \( p < 0.05 \)). We also counted the number of 1A vessels in weighed segments of the small intestine (Table 2). By multiplying the number of 1A vessels per gram by 1A flow (in ml/min), it was possible to calculate the blood flow per unit weight of the intestine. This calculation yielded a flow of 62.8 ± 9.4 ml/min/100 g for the normotensive rats and of 35.3 ± 5.6 ml/min/100 g for the hypertensive rats. Thus, flow per unit weight of intestine was also reduced by approximately 40%. In comparison, microvessel flows in downstream second (13 ± 4 nl/sec) and third (2 ± 0.4 nl/sec) order arterioles were similar to second (16 ± 4 nl/sec) and third (2 ± 0.4 nl/sec) order arteriole flows in the normotensive rats (see Figure 3). Microvessel flows in the third (4 ± 1 nl/sec) and second (30 ± 7 nl/sec) order ven-

![Figure 3](image-url)
ules of the hypertensive rats were also similar to the flows in third (5 ± 1 nl/sec) and second (29 ± 6 nl/sec) order venules of the normotensive group, however, flow was significantly reduced (36%) in the IV of the hypertensive rats (205 ± 28 nl/sec) compared with that in the normotensive group (311 ± 29; p < 0.05; see Figure 3).

In both the hypertensive and normotensive rats, 1V flow was found to exceed 1A flow (see Figure 3). Although the reasons for this difference are not entirely clear, there are several possibilities. It may be the result of anastomosing connections between neighboring IA networks within the intestinal wall. In this regard, in a group of four rats we found that the number of 1V vessels per centimeter of intestine length was reduced 11% compared with the number of 1A vessels. Thus, the 1V would carry a higher fraction of the total flow. However, this does not account for 1A flows that are approximately 50% less than the 1V flows. Another more likely possibility is that the 1V venules are not cylindrical but somewhat elliptical in cross-section.

Network Resistance

Using the pressure and flow data for the normotensive and hypertensive rats we were able to calculate how the increase in total network resistance ([femoral pressure − 1V pressure]/1A flow) was distributed between the small arteries ([femoral pressure − 1A pressure]/1A flow) and the microcirculation ([1A pressure − 1V pressure]/1A flow). However, because these data were collected in different groups of animals, albeit similarly treated, they cannot be expressed as the mean ± SEM and cannot be compared statistically. Even so, the calculations from the averaged flow and pressure data are useful in that they suggest that the increase in total network resistance was the result of an increase both in the resistance of the small arteries upstream of the 1A arteriole and in the microcirculation of the intestinal wall (Figure 4). The calculated increase in the small artery resistance is consistent with the presence of an increased pressure gradient across the small artery compartment (i.e., femoral pressure − 1A pressure) in the hypertensive rats (see Figure 3). Consequently, a smaller fraction (1A pressure/femoral pressure) of systemic pressure is transmitted to the 1A arteriole in the hypertensive rats (69 ± 2.5%) as compared with that in the normotensive rats (78 ± 2.9%).

Vessel Number

The number of 1A vessels per gram of tissue weight of intestinal wall did not differ between the hypertensive and normotensive rats (see Table 2). To estimate the number of perfused 2A, 3A, 3V, and 2V microvessels, 1A flow was divided by microvessel flow. This technique is based on the assumptions that the intestinal network is composed of series-coupled vascular segments and that the 1A flow is distributed equally to all second order arterioles and downstream vessel segments. When this estimation technique was used, the number of 2A, 3V, and 2V microvessels per 1A vessel did not differ significantly between the hypertensive and normotensive rats (see Table 2). However, there was a significant reduction in the calculated number of perfused 3A vessels per 1A and in the number of 3A vessels per 2A (2A flow/3A flow) in the hypertensive rats (p < 0.05; see Table 2).

<table>
<thead>
<tr>
<th>Group</th>
<th>1A (vessels/g)</th>
<th>2A per 1A</th>
<th>3A per 1A</th>
<th>3V per 1A</th>
<th>2V per 1A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>74 ± 2 3</td>
<td>11 5 ± 2 1</td>
<td>85 2 ± 15</td>
<td>7 4 ± 1 1</td>
<td>70 ± 2 9 0</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>71 7 ± 3 3</td>
<td>8 8 ± 1 7</td>
<td>53 2 ± 14*</td>
<td>4 4 ± 0 7*</td>
<td>77 5 ± 1 7 0</td>
</tr>
</tbody>
</table>

Values are means ± SEM. See Table 1 for key to abbreviations. The number of 2A, 3A, 3V, and 2V microvessels per 1A was calculated using the equation (1A flow/microvessel flow), and the number of 3A vessels per 2A was calculated from the ratio of 2A flow/3A flow. *p < 0.05, compared with values in normotensive rats.
Discussion

The goal of this study was to characterize the microvascular changes that occur in the intestinal circulation during two-kidney, one clip renal hypertension. Specifically, our objective was to use measurements of microvascular pressure, flow, and diameter to quantify alterations in total and segmental microvascular resistance in the small intestine. Our study demonstrated that vascular resistance in the intestine was significantly elevated 4 weeks after stenosis of the renal artery (see Figure 4). Moreover, we found that the increased resistance was associated with microvascular alterations that included 1) increased intravascular pressures throughout the vascular network (see Figure 2), 2) reduced total network blood flow (i.e., first order arteriole feeder flow) with normal flows in smaller downstream arterioles (see Figure 3), and 3) reductions in the microvessel diameters of large but not small arterioles and venules in hypertensive rats (see Figure 1). Because intestinal vascular resistance increased proportionally more than the rise in arterial pressure, these results indicate that the intestinal circulation may be a significant site of the increased total peripheral resistance that is associated with established two-kidney, one clip renal hypertension.

One of the prominent questions that continues to receive attention in studies of the microcirculation during hypertension is whether the increase in vascular resistance is the result of reduced lumen diameters in resistance vessels and/or rarefaction of arterioles. In our study, we observed a significant diameter reduction in the large first order arterioles of the hypertensive rats (see Figure 1). The increased dilation of the first order arteriole with adenosine may reflect the presence of increased vascular tone or an altered wall/lumen ratio in this vessel (see Table 1). In addition, we observed 1) normal flows (see Figure 3) and 2) elevated pressures (see Figure 2) in the small arterioles (second and third order arterioles) in the absence of a significant reduction in diameter for these vessels (see Figure 1). We have interpreted the presence of the normal flows in these vessels to suggest that the elevated vascular resistance across this segment of the microcirculation is primarily the result of a reduction in the number of perfused arterioles. In this regard, if the number of open arterioles had not been reduced, then the reduction in network flow would have been accompanied by corresponding reductions in small vessel flow. Using an estimation technique, which assumed that each arteriolar segment is coupled in series and that all first order arteriolar flow must therefore pass through each segment, we determined that the number of second order arterioles was unchanged, whereas the number of third order arterioles was reduced by approximately 40% (see Table 2). We have interpreted the elevated intravascular pressure in the absence of a significant change in lumenal diameter to imply that wall tension is increased in these smaller vessels. This interpretation suggests that a vascular wall abnormality must be present to permit the normal internal diameters of the vessels to be maintained. Two possibilities that would explain this abnormality include an increased activation of the contractile elements of muscular smooth muscle or an increase in the wall/lumen ratio of the arterioles.

To our knowledge, there are no other studies available for comparison that have directly examined the intestinal microcirculation during renal hypertension. However, one recent study investigated the microcirculation of the small intestine in spontaneously hypertensive rats. Compared with our results, Bohlen observed that the diameters of the first order feeder arteriole and small downstream fifth order arterioles were significantly reduced in 18- to 21-week-old spontaneously hypertensive rats. Furthermore, Bohlen found, by direct visual counting of microvessels, that the number of perfused second and third order arterioles per milligram of tissue was reduced by 31% and 8% respectively. When combined with our results, these findings indicate that diameter reduction and arteriolar rarefaction may be common methods of expressing increased resistance in the intestinal microcirculation; however, there may very well be some site-specific differences in the mechanisms responsible for the microvascular changes between these two experimental forms of hypertension.

Another issue of concern in studies of the microcirculation during hypertension is how the normal distribution of resistance is altered in consecutively coupled segments of the vascular network. In other words, is the increase in vascular resistance uniformly distributed across the microvasculature, or are certain vascular segments preferentially involved? The vascular changes identified in our study suggest that the increase in resistance was not confined to the microcirculation itself but also involved an elevation in resistance for the small arteries that are upstream from the intestinal wall (see Figure 4). Evidence for the selective involvement of the small arteries upstream from the cremaster muscle and larger cremaster arterioles has also been reported for rats with two-kidney, one clip renal hypertension.

It has been suggested that these larger vessels in skeletal muscle undergo a process of narrowing during early hypertension and that this process may advance down the arterial tree as the hypertension progresses.

In addition to recognizing that differential changes occur within a vascular bed, it is also important to consider whether or not the mechanisms that induce hypertension produce common microvascular disturbances in different regional circulations. In a previous study, the cremaster muscle microcirculation was investigated in rats 4 weeks after unilateral renal artery stenosis to produce two-kidney, one clip renal hypertension. In the cremaster microcirculation, the diameters of larger first and second order arterioles (80–120 μm) were reduced, whereas the diameters of small...
third order arterioles (25-30 \(\mu\)m) were unchanged compared with those in normotensive control rats. This selective increase in large arteriole resistance appeared to protect the microvasculature from the elevated mean arterial pressure, since microvascular pressures were not significantly elevated despite a 43% increase in systemic pressure. Taken together with the results of our present study, these data indicate that the mechanisms that produce two-kidney, one clip renal hypertension interact in different ways with the skeletal muscle and intestinal microcirculations.

Several studies have provided evidence concerning the role of the splanchnic circulation during the early developmental stages of two-kidney, one clip renal hypertension. During the first several hours following renal artery stenosis in the rat, vascular resistance was found to increase comparatively more in the splanchnic circulation than in the skeletal muscle, and the greatest increases in resistance occurred within the small intestine. Proportionally greater increases in splanchnic organ resistance, compared with those in skeletal muscle, have also been reported for the dog during the early development of two-kidney, one clip renal hypertension. Taken together, these findings indicate that the splanchnic circulation is an important site of vasoconstriction during the developmental phase of two-kidney, one clip renal hypertension.

Comparison of our findings of increased resistance and reduced flow in the intestinal microcirculation with whole organ studies of splanchnic hemodynamics in established two-kidney, one clip renal hypertension, Dahners et al found that the fraction of cardiac output reaching the liver through the hepatic artery was reduced, whereas the portal venous fraction was elevated. By comparison, Flohr et al found that the fraction of cardiac output reaching the entire splanchnic circulation was reduced. The lack of consistent findings concerning the role of the splanchnic circulation in established two-kidney, one clip renal hypertension is most likely attributable to the use of different experimental methods for assessing flow, to differences in the anesthetics employed, and to the use of animals at different developmental stages of hypertension. It is interesting, however, that in hypertensive patients with renal artery stenosis splanchnic blood flow was significantly reduced due to a marked increase in splanchnic vascular resistance.

Increased intravascular pressures (see Figure 2) throughout the intestinal microcirculation could have an important impact on transcapillary fluid exchange. An increased capillary hydrostatic pressure would be consistent with available reports of increased protein and fluid movement in hypertensive patients and animals. However, the precise effect of altered pressure and permeability on exchange may differ depending on the form of hypertension examined.

In conclusion, our findings indicate that the microcirculation of the small intestine is significantly disturbed during two-kidney, one clip renal hypertension by elevated resistance, decreased flow, and increased pressure. The marked increase in intestinal vascular resistance further suggests that the intestinal circulation may be particularly sensitive to the mechanisms responsible for sustaining hypertension.

Acknowledgments

The authors express their appreciation and thanks to Dr. Robert F. Gore, Department of Physiology, University of Arizona for his time, assistance, and technical advice concerning the preparation of the rat intestine for study of the microcirculation. The authors also thank Cynthia L. Hrachovy and Carrie L. Byington for their technical assistance and Debra Dillard and Helen Higginton for their typing of the manuscript.

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Hemodynamic characteristics of the intestinal microcirculation in renal hypertension.
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Hypertension. 1986:8:66-75
doi: 10.1161/01.HYP.8.1.66

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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