Autoregulation and Vasoconstriction in the Intestine During Acute Renal Hypertension

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SUMMARY The purpose of this study was to investigate whether local mechanisms of blood flow autoregulation mediate vasoconstriction during the early development of renal hypertension. Anesthetized rats were instrumented with Doppler flow probes on the celiac (CA), superior mesenteric (SMA), and renal arteries to measure flow velocity in these vessels. Acute two-kidney, one clip renal hypertension was produced by inflating a pneumatic occluder on the left renal artery to reduce flow velocity by 50%. Two hours after renal artery stenosis (RAS), femoral artery pressure (AP) was increased by 35%, CA resistance by 45%, and SMA resistance by 57%. No increases were observed in AP or in CA and SMA resistances for sham-operated, control rats. To determine if autoregulation contributed to the increase in SMA resistance, we protected the SMA vasculature from the increased arterial pressure by servocontrolled inflation of a pneumatic cuff implanted around the SMA. Although normalizing SMA pressure with the protective cuff significantly reduced (p < 0.05) the increase in SMA resistance that occurred after RAS, SMA resistance remained elevated above control levels. These results suggest that (1) reduced intensity of SMA constriction produced by protection of the SMA is due to inhibition of a local autoregulatory mechanism that is contributing to the increase in SMA resistance during the acute development of renal hypertension, and (2) maintenance of elevated SMA resistance during protection from increased AP is the result of pressure-independent mechanisms that are activated subsequent to renal artery stenosis. (Hypertension 7: 364–373, 1985)

KEY WORDS • two-kidney, one clip Goldblatt hypertension • acute renal artery stenosis • splanchnic hemodynamics • local blood flow regulation

THE mechanisms of vasoconstriction responsible for the elevated peripheral resistance associated with the development and maintenance of hypertension have been the subject of intensive investigation. For the most part, these investigations have focused on the participation of the renin-angiotensin system and sympathetic nervous system. In this regard, there is a convincing body of evidence pointing to the participation of these systems in the pathophysiology of arterial hypertension. By comparison, much less attention has been given to the participation of local mechanisms of blood flow regulation as potential contributors to the hemodynamic events that circumscribe acute and established hypertension.

There is little debate that autoregulation is a powerful vasomotor mechanism that can appropriately alter vascular resistance from moment to moment to regulate flow when tissues are challenged with changes in perfusion pressure. Moreover, the property of autoregulation appears to be a characteristic intrinsic to nearly all peripheral vascular beds and is particularly apparent in the renal, cerebral, coronary, and splanchnic circulations. In hypertension there is a frank increase in arterial pressure, yet the impact of the altered pressure per se on local mechanisms of autoregulation has not been studied. The key question is whether autoregulatory mechanisms act synergistically to amplify the neurohumoral disturbance or act antagonistically to oppose the neurohumoral mechanisms. If autoregulation contributes to the increase in local resistance, then it seems reasonable to hypothesize that a portion of an organ's vascular resistance will reflect the prevailing level of arterial pressure.

The involvement of autoregulation as a process contributing to vasoconstriction in hypertension was proposed in 1963 by Borst and Borst-DeGeus and Led-
were tracheostomized to ensure a patent airway and overanesthetized. After rats were anesthetized, they of anesthetic supplements consisting of 10 to 20% of the initial anesthetic dose. Supplements were given by intraperitoneal injection at intervals not less than 30 minutes apart. This anesthetic regimen maintained a stable level of anesthesia and prevented rats from being overanesthetized. After rats were anesthetized, they were tracheostomized to ensure a patent airway and placed on a heating pad to maintain rectal temperature between 36 and 37.5°C, as measured by a rectal probe. Mean arterial pressure was monitored from the cannulated left femoral artery, and heart rate was determined from electrocardiogram recordings. After completion of the short-term experiments the rats were killed with an intravenous injection of saturated potassium chloride solution.

**Directional Pulsed Doppler Flow Velocity Measurement**

Flow velocities were measured in the celiac, superior mesenteric, and renal arteries with a pulsed Doppler flow velocity measurement system. Briefly, this technique uses miniaturized flow probes that are constructed with lumen diameters similar to the diameter of the artery on which they are used. The procedures describing the methods for construction of the flow probes and use of the pulsed Doppler flowmeter have been described elsewhere. Flow velocity signals from the flow probes were recorded on a physiological recorder as kHz Doppler shift. The flow velocity signal has been previously reported to be directly proportional to blood flow. Zero flow for this flow velocity measurement system was verified by mechanically occluding the artery distal to the location of the Doppler flow probe. The electrical zero of the pulsed Doppler instrument was also obtained by momentarily switching off the ultrasonic signal used to excite the piezoelectric crystal contained in the flow probe. In our studies, the mechanical and electrical zeros were identical.

**Surgical Preparation**

To produce acute two-kidney, one clip renal hypertension, the abdomen was incised along the midline and the left renal artery was isolated to expose a 4-mm segment. A Doppler flow probe and an inflatable pneumatic occluder were then placed around the isolated segment of renal artery. The methods for construction of the pneumatic occluder have been described previously. The flow probe was closed snugly around the artery with silk suture, and the thin wire leads leaving the flow probe were anchored with silk suture to surrounding muscle tissue to secure the flow probe and maintain its orientation with respect to the flow axis of the artery. The vascular occluder was also anchored to muscle tissue with silk suture and then connected to a servocontrolled infusion pump (ServoAmplifier, Model 2990, Harvard Apparatus Company, Inc., South Natick, MA). The infusion pump was adjusted to reduce renal artery flow velocity to 50% of its resting value and to maintain the reduced renal flow over an extended period. The resting value for renal flow was determined during a 30-minute control period immediately before stenosis of the renal artery. The right kidney was not disturbed during any of these procedures.

Following placement of the renal artery flow probe and vascular occluder, an appropriately sized Doppler flow probe was placed on an isolated segment (2 mm long) of the celiac and superior mesenteric artery respectively. The flow probes were then snugly closed.
around these vessels and anchored to surrounding muscle tissue with procedures similar to those described for placement of the renal artery flow probe. Leads from the celiac, superior mesenteric, and renal artery flow probes were collected together with the tubing for the vascular occluder and were brought out the abdominal incision. The incision was then closed with silk suture. Celiac and superior mesenteric artery resistances were calculated by dividing mean femoral artery pressure by mean Doppler flow velocity in kHz for each artery.

Arterial pressure was prevented from increasing in the superior mesenteric vascular bed by placing an inflatable pneumatic occluder around an isolated segment (2 mm long) of the superior mesenteric artery. The occluder was positioned on the superior mesenteric artery downstream from the location of the Doppler flow probe. To measure pressure downstream from the superior mesenteric artery, we cannulated a small jejunal artery that traversed the mesentery to feed a segment of the jejunum. The vascular occluder was connected to a servocontrolled pump that was set to control pressure in the jejunal artery at normotensive resting values. The normotensive jejunal artery pressure was determined during a 30-minute control period that immediately preceded renal artery stenosis. In these experiments, superior mesenteric artery resistance was calculated by dividing jejunal artery pressure by the Doppler flow velocity (kHz) measured in the superior mesenteric artery.

Experimental Protocols

To quantitate the changes in celiac and superior mesenteric artery resistance following short-term renal artery stenosis, two groups of 10 rats were instrumented for production of acute renal hypertension and for measurement of splanchnic circulatory changes, as described in the previous section. One group of rats underwent the renal artery stenosis procedure, whereas the second control group did not. Each experiment consisted of a 30-minute control period during which measurements of femoral artery pressure and renal, celiac, and superior mesenteric artery flow velocities were made at 5-minute intervals. Immediately following the control period the renal artery was stenosed by activating the servocontrolled infusion pump, which reduced renal flow velocity to 50% of its resting value. Measurements were then continued at 5-minute intervals throughout 2 hours of renal artery stenosis. After a 2-hour period of renal artery stenosis, the renal artery vascular occluder was deflated and observations were continued at 15-minute intervals for a 45-minute recovery period. The control group of rats was subjected to similar surgical handling and to a similar protocol regimen but did not undergo renal artery stenosis.

To study the effect of controlling pressure in the superior mesenteric vascular bed at normotensive values on the changes in superior mesenteric artery resistance after short-term renal artery stenosis, a group of 10 rats was instrumented as previously described for controlling perfusion pressure within the superior mesenteric vascular bed. Each short-term experiment consisted of a 30-minute control period during which measurements of femoral and jejunal artery pressure and of renal and superior mesenteric artery flow velocity were recorded at 5-minute intervals. After the control period, renal artery flow was reduced by 50% compared with its resting control value. Following 30 minutes of renal artery stenosis, the vascular occluder on the superior mesenteric artery was slowly inflated to reduce jejunal artery pressure to the normotensive control period value. After achieving a steady state, the protective cuff was deflated, which permitted jejunal artery pressure to return to hypertensive values. Steady state measurements were made before and after normalizing jejunal artery pressure. This protective procedure was repeated after 60, 90, and 120 minutes of renal artery stenosis.

The effect of a step increase in perfusion pressure was examined by quickly deflating the protective cuff on the superior mesenteric artery. This procedure produced a sudden step increase in superior mesenteric artery pressure from normotensive to hypertensive levels and allowed us to study the transient changes in pressure, flow, and resistance.

The reactions of the splanchnic circulation following renal artery stenosis in rats that had been deprived of food for 24 hours before short-term experimentation also were examined. The rationale for this procedure was based on a previous study that found the degree of autoregulation in the superior mesenteric artery was less in fasted dogs than in fed dogs. Thus, it was hypothesized that fasting would reduce any contribution of autoregulation to the increase in resistance associated with the development of hypertension. All rats used in this protocol had free access to water during the 24-hour fasting period. The two groups of rats (10 fed and 12 fasted rats) used for this experiment were surgically prepared and instrumented as described previously for controlling perfusion pressure within the superior mesenteric vascular bed. The short-term experiments performed were identical to those described for protection of the superior mesenteric vascular bed from elevated arterial pressure in fed rats.

Data Handling and Analysis

For each protocol the measurements that were made at 5-minute intervals during the control period were averaged to provide a mean resting value for a given animal. These control values were then used to express the hemodynamic changes following renal artery stenosis as a percentage of the control period value. The data were normalized to percentage of control values with the equation: Percentage of control = Experimental value after renal artery stenosis/Control period mean × 100

Data that were collected to quantitate the splanchnic circulatory changes following short-term renal artery stenosis were analyzed with statistical procedures for a repeated measurements experimental design. These statistical methods tested for overall differences over time and trends over time with the program BMDP2V.
of the BMDP series. The data collected to analyze the effects of protecting the superior mesenteric artery from increased pressure and the effects of fasting rats on the response to renal artery stenosis were tested for significant differences with paired or unpaired t tests. Analysis of variance procedures were used for comparisons involving more than two groups. Group differences that were indicated by significant F tests were individually identified by the use of Duncan's new multiple range test. All differences were considered to be significant at p < 0.05.

Results
Response of the Splanchnic Circulation to Short-term Renal Artery Stenosis
The objective of these studies was to determine the extent and time course of the changes in celiac and superior mesenteric artery resistance after short-term unilateral renal artery stenosis. The resting control period values that were obtained during the 30-minute period immediately preceding renal artery stenosis are summarized in Table 1 for the sham-operated normotensive rats without renal artery stenosis and the hypertensive rats that underwent renal artery stenosis. After the 30-minute control period, renal artery flow velocity was reduced to 50% of its resting value by controlled inflation of the renal artery pneumatic occluder.

Table 1. Resting Control Values During a 30-Minute Period Before Renal Artery Stenosis or Sham Renal Artery Stenosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sham-operated normotensive rats (n = 10)</th>
<th>Hypertensive rats with RAS (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>85 ± 3</td>
<td>79 ± 3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>418 ± 20</td>
<td>358 ± 12</td>
</tr>
<tr>
<td>Celiac artery flow velocity (kHz shift)</td>
<td>3.0 ± 0.4</td>
<td>3.3 ± 0.5</td>
</tr>
<tr>
<td>Celiac artery resistance (mm Hg/kHz)</td>
<td>34 ± 5</td>
<td>30 ± 4</td>
</tr>
<tr>
<td>Superior mesenteric flow velocity (kHz shift)</td>
<td>2.7 ± 0.2</td>
<td>3.5 ± 0.4</td>
</tr>
<tr>
<td>Superior mesenteric artery resistance (mm Hg/kHz)</td>
<td>32 ± 2</td>
<td>25 ± 3</td>
</tr>
<tr>
<td>Renal artery flow velocity (kHz shift)</td>
<td>3.3 ± 0.3</td>
<td>3.3 ± 0.3</td>
</tr>
</tbody>
</table>

All values are means ± SEM. RAS = renal artery stenosis.

Recorder tracings from a representative experiment illustrate the short-term changes in mean arterial pressure, celiac artery flow velocity, and superior mesenteric artery flow velocity after stenosis of the renal artery (Figure 1).

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

**Figure 1.** This record shows the changes that occurred in the celiac and superior mesenteric arteries and mean femoral artery pressure following a short-term, 50% reduction (dotted line) in renal artery flow velocity. To calculate artery resistance, the pressure in the femoral artery was divided by the flow velocity in the celiac or superior mesenteric artery respectively. The calculated resistances for each artery are shown beneath the flow velocity panels.
Mean arterial pressure was significantly increased ($p < 0.05$) within 5 minutes following renal artery stenosis. After 2 hours of renal stenosis, pressure was elevated by 35% as compared with the pressure recorded during the prestenosis control period (Figure 2). Removal of the renal artery stenosis was characterized by a return of mean arterial pressure toward its prestenosis control value (see Figure 2). Mean arterial pressure in the sham-operated normotensive rats remained between 90 and 100% of its control value throughout a period equivalent to 2 hours of renal artery stenosis and 45 minutes of recovery (see Figure 2).

The rise in mean arterial pressure following renal artery stenosis was accompanied by a corresponding rise in celiac artery and superior mesenteric artery resistances (see Figure 2). After 2 hours of renal artery stenosis, celiac artery resistance was increased by 45% and superior mesenteric artery resistance by 57%. In sham-operated normotensive rats, which did not undergo renal artery stenosis, vascular resistance in the celiac and superior mesenteric arteries remained within 5% of their control resting values throughout a period comparable to that used to study the effects of renal artery stenosis. After removal of the renal artery stenosis, resistance in the celiac and superior mesenteric arteries returned toward the prestenosis control values (see Figure 2).

Protection of the Superior Mesenteric Vascular Bed from Elevated Arterial Pressure

To test the hypothesis that the elevated perfusion pressure associated with short-term renal artery stenosis was acting as a stimulus to increase superior mesenteric artery resistance, the superior mesenteric artery was protected from the elevated arterial pressure by controlling the inflation of a protective cuff around the superior mesenteric artery. As can be seen in Figure 3, the protection procedure did not significantly alter mean arterial pressure in the rats. During protection jejunal artery pressure was reduced below the prevailing level of systemic arterial pressure and maintained at a pressure similar to the control pressure recorded before renal artery stenosis (see Figure 3).

The increase in superior mesenteric artery resistance that accompanied the 2 hours of renal artery stenosis was significantly attenuated ($p < 0.05$) but not abolished by reducing jejunal artery pressure to control levels (see Figure 3). Furthermore, the attenuation response could be reproduced throughout the 2-hour period of renal artery stenosis (see Figure 3). Vascular resistance remained approximately 10% greater during protection than during the prestenosis control period. Protection of the superior mesenteric vascular bed also reduced superior mesenteric artery flow velocity compared with the unprotected state (see Figure 3).

The hemodynamic effects of a step increase in superior mesenteric artery pressure were studied in the hypertensive rats by quickly deflating the protective cuff that was implanted around the superior mesenteric artery. This procedure produced a step increase in superior mesenteric artery pressure from the prestenosis control level to the hypertensive level without significantly altering mean arterial pressure (Figure 4). The step increase in pressure resulted in a rapid increase in superior mesenteric artery flow velocity to a peak value 41% above the protected level. The peak flow increase was then followed by a decrease to a new steady state value 15% above the protected flow velocity level (see Figure 4). After deflation of the protective cuff, the superior mesenteric artery resistance fell transiently, then rose to a new steady state value 45% above the vascular resistance in the protected state (see Figure 4).
AUTOREGULATION IN HYPERTENSION

MEAN ARTERIAL PRESSURE (% of Control)

MEAN JEJUNAL ARTERY PRESSURE (% of Control)

SUPERIOR MESENTERIC ARTERY FLOW VELOCITY (% of Control)

SUPERIOR MESENTERIC ARTERY RESISTANCE (% of Control)

MINUTES AFTER RENAL ARTERY STENOSIS

PROTECTION REMOVED (N = 10)

HYPERTENSIVE RATS WITH UNPROTECTED SUPERIOR MESENTERIC ARTERY (N = 10)

HYPERTENSIVE RATS WITH PROTECTED SUPERIOR MESENTERIC ARTERY (N = 10)

FIGURE 3. A pneumatic occluder implanted around the superior mesenteric artery in hypertensive rats was inflated to protect the intestinal vasculature from the elevated mean arterial pressure. This protective procedure was performed 30, 60, 90, and 120 minutes after stenosis of the renal artery to induce acute hypertension. Effective protection was evidenced by normal pressure in a jejunal artery located downstream from the superior mesenteric artery. The protection significantly (p < 0.05) reduced resistance in the superior mesenteric artery compared with the unprotected state; however, during protection vascular resistance remained significantly above (p < 0.05) the resistance in the control state. Data are mean percent of control values ± SEM. The asterisks indicate a significant difference between the unprotected and protected states.

FIGURE 4. The effects are shown of suddenly deflating the protective cuff around the superior mesenteric artery to produce a step change in jejunal artery pressure from normotensive to hypertensive levels. Following sudden occluder deflation (dotted line), jejunal artery pressure abruptly increased, which produced a transient surge in superior mesenteric artery flow velocity and then a return of flow velocity toward the protected level. The return of flow velocity toward the protected level was the result of a significant increase in superior mesenteric artery resistance. The asterisks indicate a significant (p < 0.05) difference between the steadystate protected values and the steady state unprotected values. Data are means ± SEM.

Effects of Fasting Before Renal Artery Stenosis

The control resting values for the fasted and fed rats are summarized in Table 2. Short-term renal artery stenosis in fasted rats resulted in a significant increase (p < 0.05) in mean arterial pressure. After 2 hours of renal artery stenosis, however, mean arterial pressure was significantly lower (20% increase versus 43%; p < 0.05) in fasted rats than in fed rats (Figure 5). Superior mesenteric artery resistance also increased in the fasted group of rats, but after 2 hours of renal artery stenosis vascular resistance was also lower (28% increase versus 55%) than that observed in the fed rats (see Figure 5).

In the fasted rats, protection of the superior mesenteric artery from elevated perfusion pressure significantly attenuated (p < 0.05) the increase in resistance associated with short-term renal artery stenosis (Figure 6). During protection, however, the superior mesenteric artery resistance remained approximately 10% above the prestenosis control period resistance (see
TABLE 2. Resting Control Values Collected During a 30-Minute Period Before Renal Artery Stenosis in a Group of Fed and 24-Hour Fasted Rats

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fed rats (n = 10)</th>
<th>Fasted rats (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>81 ±3</td>
<td>84 ±2</td>
</tr>
<tr>
<td>Jejunal artery pressure (mm Hg)</td>
<td>65 ±4</td>
<td>68 ±4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>310 ±10</td>
<td>334 ±12</td>
</tr>
<tr>
<td>Superior mesenteric flow velocity (kHz shift)</td>
<td>2.5 ±0.1</td>
<td>3.4 ±0.2</td>
</tr>
<tr>
<td>Superior mesenteric artery resistance (mm Hg/kHz)</td>
<td>27 ±2</td>
<td>20 ±1</td>
</tr>
<tr>
<td>Renal artery flow velocity (kHz shift)</td>
<td>1.9 ±0.3</td>
<td>2.0 ±0.2</td>
</tr>
</tbody>
</table>

All values are means ± SEM.

FIGURE 5. Rats fasted for 24 hours had significantly (p < 0.05) reduced mean arterial pressure and superior mesenteric artery resistance compared with fed rats following short-term renal artery stenosis. Data are mean percent of control values ± SEM. The asterisks indicate a significant difference between the fed and fasted rats.

FIGURE 6. Protection of the superior mesenteric artery from the increased arterial pressure significantly (p < 0.05) reduced resistance in the fasted rats. Data are mean percent of control values ± SEM. The asterisks indicate a significant difference between the unprotected and protected states.

Figure 6). Rapid deflation of the protective cuff to produce a step change in superior mesenteric arterial pressure (Figure 7) resulted in a transient surge (29%) in superior mesenteric artery flow velocity followed by a decrease to a new steady value 15% above the protected level (see Figure 7). Resistance fell transiently and then rose to a new steady state level 20% above the protected level (see Figure 7).

The responses to the step increase in perfusion pressure produced by rapidly deflating the protective cuff were compared for fasted and fed animals by calculating the percent compensation of the vascular bed to the step increase in pressure. Percent compensation was calculated with the formula 1 - (%Δ flow/Δ pressure). The percent compensation (mean ± SEM) was significantly less (p < 0.05) for the fasted rats (53 ± 10%) than for the fed rats (77 ± 5%).

Discussion
The major goal of this study was to determine whether an autoregulation-induced vasoconstriction may mediate a component of the increase in splanchnic
vascular resistance during the early development of renal hypertension. The ability of the splanchnic circulation to autoregulate is well documented, and we rationalized that the elevated arterial pressure associated with the development of hypertension may provide a fundamental stimulus that leads to autoregulatory adjustments that elevate vascular resistance. To test this hypothesis, we quantified the vascular resistance in the small intestine when the vascular bed was exposed to the elevated arterial pressure produced by short-term renal artery stenosis and when the perfusion pressure was normalized with a pneumatic vascular cuff to protect the superior mesenteric vasculature from the acute hypertension.

**Splanchnic Vascular Changes After Renal Artery Stenosis**

For short-term renal artery stenosis to produce hypertension, a hemodynamic irregularity involving cardiac output or total peripheral resistance must occur. Using radiolabeled microspheres we recently have found that the rise in mean arterial pressure following 90 minutes of renal artery stenosis was the result of an increase in total peripheral resistance, as cardiac output was unchanged (unpublished observations, 1984). Similar reports of the early hemodynamic alterations that accompany the early development of renal hypertension also indicate that the primary disturbance appears to be directed at producing peripheral vasoconstriction. To assess the importance of the splanchnic circulation as a site of increased resistance during the early developmental phase of renal hypertension, we calculated the changes in celiac and superior mesenteric artery resistance immediately following renal artery stenosis. Our results show that there was a pronounced increase in vascular resistance in the celiac and superior mesenteric artery immediately following a 50% reduction in renal artery flow. Furthermore, the magnitude and time course of the changes in resistance were similar to those observed for the increase in mean arterial pressure. Taken together, these circulatory changes imply that the splanchnic circulation makes an important hemodynamic contribution to the early development of renal hypertension.

Only a few studies have examined the role of the splanchnic circulation in acute renal hypertension. In a recent investigation, conscious rats were instrumented with Doppler flow probes and resistance was measured in the superior mesenteric and renal arteries and the splanchic organ vascular resistance.26 Whatever the reasons for this variability, we are presently unable to assess the importance of the splanchnic vascular reactions we report here continue into the more established phases of renal hypertension.

**Evidence for a Contribution by Autoregulation to the Increase in Splanchnic Vascular Resistance**

The major finding of this study was that protection of the superior mesenteric vascular bed from the elevated pressure that occurs during the development of the hypertension markedly blunted the increase in superior mesenteric artery resistance. Thus, a portion of the increase in resistance appeared to be a consequence of the increase in arterial pressure. We have interpreted this blunted vasoconstrictor response as being caused by the elimination of a pressure-dependent, local autoregulatory mechanism.
We believe that two lines of evidence support this interpretation. First, resistance in the superior mesenteric vascular bed rapidly increased to a new steady state level when the protective cuff around the superior mesenteric artery was deflated, which permitted the perfusion pressure to quickly rise from normotensive to hypertensive levels. The transient behavior and time course of the changes in flow velocity and vascular resistance in response to this step increase in pressure were identical to the autoregulatory reactions reported to occur in vascular beds exposed to a step increase in perfusion pressure.

Second, to further demonstrate that an autoregulatory component was present, a group of rats was fasted for 24 hours before the short-term experiment. Dogs fasted for 24 hours have been shown to autoregulate intestinal blood flow less well in response to changes in perfusion pressure. Although the mechanism of the diminished autoregulatory capacity is unknown, it is thought to possibly result from alterations in the local concentration of vasodilator metabolites or in the sensitivity of arterioles to these substances. Provided this was true in the rat, we hypothesized that the percent decrease in superior mesenteric artery resistance following protection would be reduced in fasted rats, and we expected to find a smaller increase in superior mesenteric artery resistance after renal artery stenosis. Our observations confirmed both of these expectations, which suggests that the fasting had reduced the autoregulatory gain of the superior mesenteric vascular bed and therefore reduced the contribution of the autoregulatory component to the total increase in superior mesenteric artery resistance. As a measure of the autoregulatory gain in the fasted rats, the percent compensation was calculated from the data obtained when the protective cuff was quickly deflated to produce a step increase in pressure. The calculated percent compensation in the fasted rats was found to be significantly less (p < 0.05) than the gain in fed animals. Thus, this descriptor indicated that for a given increase in pressure the ability of the superior mesenteric vascular bed to return flow toward normal or compensate was reduced in the fasted state. Based on our data, it appears that as much as 74% of the increase in intestinal resistance for the fed rats and 64% for the fasted rats may be attributable to a local pressure or flow-dependent autoregulatory mechanism.

Although protection of the superior mesenteric artery during the acute hypertension significantly blunted the vasoconstriction (p < 0.05), vascular resistance remained elevated above the prestenosis control level. This finding strongly indicates that other vasoconstrictor mechanisms are operating to increase vascular resistance. In this regard, acute two-kidney, one clip renal hypertension is typically thought of as a renin-angiotensin-dependent form of hypertension. In addition, more recent data from several laboratories indicate that sympathetic vasoconstrictor activity is increased during renal hypertension and may in fact be increased during the earliest stages of the hypertension. Thus, in the present study it seems reasonable to implicate these two vasoconstrictor mechanisms as candidates that could account for the component of increased resistance that was not eliminated by normalizing perfusion pressure. Further experimentation with our model is required to warrant this conclusion.

**Autoregulation and Hypertension: Mechanisms and Implications**

We have identified what we believe to be a pressure-dependent autoregulatory process that is contributing to the increase in vascular resistance during the development of renal hypertension. It is not possible to determine from the data collected the precise local mechanism responsible for the reduced intensity of vasoconstriction when the superior mesenteric artery was protected from the increase in arterial pressure. Certainly the metabolic (flow-related) and myogenic (pressure-related) mechanisms traditionally thought to be responsible for autoregulation could account for the observed phenomenon. Another possible explanation for our results is that the arterial pressure per se may affect the ability of the vascular smooth muscle to generate tension. In this regard, the increased pressure associated with the development of hypertension may enhance the capacity of the vasculature to respond to vasoconstrictor activity through length-tension relationships. There is also some evidence to suggest that splanchnic afferents are capable of eliciting local reflex vasocostriction in the splanchic circulation when arterial pressure is elevated. Therefore, in our study it is possible that the development of hypertension could have evoked a local mechanoreceptor reflex that induced vasoconstriction. As such, normalizing pressure would inhibit the reflex increase in resistance.

Whether the short-term autoregulatory phenomenon we have identified persists into more established phases of renal hypertension remains to be demonstrated. It has been suggested that the short-term mechanisms of autoregulation that involve active changes in vessel caliber may be slowly replaced by local mechanisms requiring longer time constants to express themselves. For example, structural adaptations of the vasculature involving an increased thickness of the media and a reduced lumen size may slowly supplant the active vasoconstriction. Thus, short-term autoregulation may, through a series of intermediate events, give rise to a longer term or structural autoregulation. It appears that the component of resistance we have identified with a local regulatory process is secondary to the increase in mean arterial pressure. As a secondary event, it would represent a local compensatory reaction to a disturbance in blood pressure control and therefore cannot account for the genesis of the hypertension. Based on our observations we propose that the developmental phase of renal hypertension is the result of an interaction between local autoregulatory mechanisms and mechanisms set in motion by renal artery stenosis. According to this proposal, the increase in mean arterial pressure is initiated by mechanisms activated by renal artery stenosis. As the pressure rises it...
triggers a local, pressure-dependent autoregulatory phenomenon to increase resistance. The goal of the autoregulatory phenomenon may be to minimize local disturbances in microvascular flow or pressure; however, by amplifying the effects of extrinsic vasoconstrictor mechanisms responsible for the initiation of the hypertension, autoregulation may potentiate the overall disturbance in blood pressure control.

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