Vascular Responses of the Perfused Intestine to Vasoactive Agents during the Development of Two-Kidney, One-Clip Goldblatt Hypertension in Dogs

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SUMMARY We evaluated the potential role of altered vascular reactivity in the pathogenesis of two-kidney, one-clip Goldblatt hypertension (2-KGH) in dogs, in the mesenteric vasculature preparation perfused, in situ, with autologous blood at constant flow. Changes in segmental vascular resistance in response to vasoactive agents were studied 1, 4, and 32 days after unilateral renal artery constriction (URAC) or sham occlusion of the renal artery (SHAM). On day 1 post-URAC, prior to any increase in arterial pressure or resistance, the pressor responses to serotonin (5-HT), angiotensin II (All), and 9,11-epoxymethanoprostaglandin H2 (EMP) were enhanced from pre-URAC values. The major change occurred in small arteries, arterioles, and veins, but not in larger arteries. Mesenteric vascular responses to 5-HT, All, and EMP also were enhanced 4 and 32 days post-URAC; however, at this time, large artery vascular reactivity also was enhanced. Mesenteric vascular responses to NE did not differ from pre-URAC values on day 1 post-URAC. However, 4 and 32 days post-URAC, mesenteric arterial and venous pressor responses to NE also were enhanced. Intestinal smooth muscle responses to 5-HT, EMP, and All also were enhanced within day 1, post-URAC. These data demonstrate that changes in vascular reactivity (1) precede the increased arterial resistance of 2-KGH in dogs and (2) occur first in the smaller arteries, arterioles, and venules as well as in non-vascular smooth muscle of the intestine. Within days 4 to 32 post-URAC, changes are apparent in the larger arteries, and at this time decreases in compliance also contribute to the increase in flow resistance of 2-KGH.


ENHANCED vascular responsiveness to vasopressor substances appears to be characteristic of many forms of experimental and human essential hypertension [Silvertsson, 1970; Folkow et al., 1970; Bohr, 1974; Freidman, 1977; Greenberg et al., in press; S Greenberg, C McGowan, and M Gaida, unpublished observations (and references in all)]. Recent studies demonstrate that enhanced arterial vascular responses to angiotensin II (All) and norepinephrine (NE) occur prior to the increased arterial resistance of deoxycorticosterone acetate (DOCA) hypertension in the rat and pig (Terris et al., 1976; Berecek and Bohr, 1978; Berecek et al., 1980), Grollman hypertension in hamsters (Click et al., 1979), aortic coarctation hypertension in rabbits (Ichikawa et al., 1979) and two-kidney, one-clip Goldblatt hypertension (2-KGH) in dogs (Greenberg et al., unpublished observations). This would suggest that alterations in vascular reactivity participate in the pathogenesis of hypertension in animals and humans. This concept is supported by studies demonstrating enhanced venous tone and reactivity and decreased venous compliance in experimental and human hypertension (Overbeck, 1972; Simon et al., 1975; Greenberg and Bohr, 1975; Takeshita and Mark, 1979). Since the veins demonstrate altered vascular responses in hypertension, the changes in vascular smooth muscle cannot be secondary to an increased intravascular pressure but must reflect a basic abnormality of the vasculature in hypertensive vascular disease.

Two-kidney, one-clip Goldblatt hypertension in dogs results in a small, sustained increase in systemic arterial pressure and total peripheral resistance (Fekete et al., 1971; Lupu et al., 1972; Guyton, 1974). The 2-KGH model of hypertension is characterized by a transient increase in renin release and an increase in cardiac output within the first 4 days after unilateral constriction of the renal artery (URAC) which gives way to an increase in total peripheral resistance [for references, see Ferrario and Page (1978); Guyton (1974); Guyton et al (1976)]. The increase in cardiac output is not a prerequisite for the increase in total peripheral resistance, since occlusion of the vena cavae, which prevents the rise in cardiac output, did not prevent the increase in total peripheral resistance (Greenberg et al., unpublished observations). Although the
mechanism of the hypertension remains unknown, the in vivo pressor responses to vasoactive agents were enhanced before the rise in either cardiac output or arterial resistance. This finding also suggests that changes in the sensitivity of the vasculature also may contribute to the pathogenesis of 2-KGH in dogs.

The mesenteric vasculature is a major contributor to the maintenance of systemic arterial pressure and vascular capacity (Overbeck, 1972; Simon et al., 1975). This study was designed to evaluate the temporal relationship of changes in mesenteric vascular reactivity to the increased arterial resistance of 2-KGH in dogs and also to determine whether the initial changes in vascular reactivity occur in large arteries, small arteries, and/or small veins.

Methods

Hypertensive Dogs

Dogs (22–30 kg) of both sexes were adapted to the laboratory over a period of 3 weeks and then randomly divided into groups of six. The dogs were matched, when possible, for age and breed, but were always matched for sex. Under pentobarbital (25 mg/kg, iv) anesthesia, a flank incision was made, the renal artery exposed, and an electromagnetic flow probe and renal artery occluder placed around the renal artery. A thoracotomy was performed at the level of the 4th intercostal space and a flow probe applied around the ascending aorta. The leads were worked under the skin and externalized at the scruff of the neck and the incisions sutured and closed. Arterial and venous cannulae were placed in the femoral artery and vein and exteriorized. The animals were treated with penicillin G and streptomycin, im, and then allowed to recover. The animals were treated with penicillin G and streptomycin, im, and then allowed to recover. The mesenteric vasculature is a major contributor to the maintenance of systemic arterial pressure and vascular capacity (Overbeck, 1972; Simon et al., 1975). This study was designed to evaluate the temporal relationship of changes in mesenteric vascular reactivity to the increased arterial resistance of 2-KGH in dogs and also to determine whether the initial changes in vascular reactivity occur in large arteries, small arteries, and/or small veins.

Perfusion of the Mesenteric Vasculature

Dogs were anesthetized with pentobarbital sodium (25 mg/kg, iv) supplemented with iv pentobarbital (5 mg/kg/hour, iv drip) to maintain the anesthesia at the induction level. Each animal was ventilated mechanically (Harvard Respiration Pump 607) via an endotracheal tube at 18 breaths/min. The tidal volume was adjusted to give an end-expiratory carbon dioxide tension of approximately 5% as monitored by an infrared analyzer. Central arterial pressure was monitored from the cannula passed into the femoral artery. Heart rate was determined electronically from the arterial pressure pulse. Esophageal temperature was controlled by heat lamp and pad at 39°C and arterial pH adjusted to approximately pH 7.4 by an intravenous drip of 0.5% sodium bicarbonate, at 5 ml/kg per hr.

A laparotomy was performed and a segment of small intestine (with arterial, venous, and nerve supply intact) was isolated. The intestines were sealed off with suture after a saline-filled balloon catheter had been inserted into the lumen to measure intraluminal intestinal pressure. Measurement of intraluminal intestinal pressure was essential since the agonists used to test the integrity of vascular smooth muscle function in normotensive and hypertensive animals may affect the smooth muscle of the small intestines. Contraction or relaxation of the circular muscles of the gut passively will compress or relax, respectively, the intestinal vasculature. By evaluation of this parameter, an intelligent evaluation of the in situ integrity of the vascular smooth muscle of canine mesenteric vasculature in hypertension can be performed.

A small branch (400–450 μm, o.d.) of the mesenteric artery and a medium sized mesenteric vein (1.0 mm o.d.) were cannulated with heparin-filled polyethylene tubes connected to arterial and venous pressure transducers, respectively. The dogs then were given heparin (5 mg/kg, iv) and the large mesenteric artery (2.5–3 mm, o.d.) supplying the intestinal segment was cannulated and perfused with autologous blood obtained from the left femoral artery of the dog. A t-tube, inserted into the perfusion circuit between the pump and the perfused mesenteric vascular segment, was used to measure perfusion pressure. Since flow through the tubing is maintained constant, changes in perfusion pressure reflect changes in arterial and venous vascular resistance. Perfusion pressure was set equal to systemic pressure by adjustment of the blood flow through the preparation. Once the perfusion pressure was set, it did not change during the experiment until such time as the effects of the difference in pressure between the preparations were evaluated.

Vascular Responses to Vasoactive Agents

Responses of the mesenteric vasculature and intestine to intra-arterial injections of norepinephrine bitartrate (NB), serotonin hydrochloride (5-HT) angiotensin II amide (AII), and 9,11-epoxyeicosanoprostaglandin H_2 (EMP) were obtained. All drugs were administered into the perfusion circuit immediately distal to the perfusion pump to allow adequate mixing and dilution prior to their entrance.
into the mesenteric vasculature. All drugs were administered in a volume of 0.05 ml and were made up in 0.9% saline immediately prior to use. EMP was dissolved in ethanol to provide a stock solution of 10 mg/ml and subsequently diluted in saline.

In the perfusion experiments performed on the mesenteric vasculature obtained from SHAM and URAC dogs 32 days after occlusion, the responses to the vasoactive agents were re-evaluated after perfusion pressure was lowered in the URAC dogs by reducing the rate of perfusion so that flow rates equaled those of the SHAM dogs.

Vascular Compliance
At the end of each experiment, blood flow was reduced to provide a rate of 2.5 ml/min and the pressure at this flow was recorded for 5 minutes. The flow rate of the pump was increased to 5, 10, 15, 20, 30, and 40 ml/min for 5-minute intervals and the pressure at each flow rate recorded after stress-relaxation. Pressure-flow curves were constructed.

Analysis of Data
The vascular resistance changes occurring in response to the agonists were calculated according to the method of Zimmerman and Abboud (1963) as

\[ \Delta \text{resistance} = \frac{\Delta \text{pressure (mm Hg)}}{\text{flow (ml/min)}} \]

a. \(\Delta\) Total resistance
\[ = \Delta \frac{\text{change in perfusion pressure}}{\text{flow}} \]
\[ = \Delta \frac{C}{\text{flow}} \]

b. \(\Delta\) Arterial resistance
\[ \frac{\Delta \text{perfusion pressure} - \Delta \text{small artery pressure}}{\text{flow}} \]
\[ = \frac{\Delta C - \Delta D}{\text{flow}} \]

c. \(\Delta\) Arteriolar resistance
\[ \frac{- \Delta \text{simultaneous small vein pressure}}{\text{flow}} \]
\[ = \frac{\Delta D - \Delta E}{\text{flow}} \]

d. \(\Delta\) Venous resistance
\[ \frac{\Delta \text{peak change in small vein pressure}}{\text{flow}} \]
\[ = \frac{\Delta E}{\text{flow}} \]

The change in each perfusion pressure or the difference between the perfusion pressure (as shown in Fig. 1) was divided by the rate of blood flow through the perfusion pump in each experiment.

Results
Development of 2-KGH in Dogs
The time course of the hemodynamic events of 2-KGH hypertension is summarized in Figure 2. Blood pressure increased within 2 days post-URAC and remained elevated throughout the 32-day period of study. Cardiac output was elevated transiently during the 2nd-through 8th days after URAC and returned to normal limits by the 12th
day post-URAC. Total peripheral resistance was elevated by the 8th day after URAC. The increased cardiac output could not be explained by an increased heart rate or plasma or blood volume, since these were essentially normal throughout the study (Greenberg et al., unpublished observations). However, stroke volume was elevated. Therefore, the increased cardiac output, which preceded the increased vascular resistance and pressure rise, was probably due to myocardial factors or to an increased venous return. These data are in agreement with previous findings (Fekete et al., 1971; Lupu et al.; 1972; Guyton, 1974; Greenberg et al., unpublished observations).

The rate of flow necessary to set mesenteric perfusion pressure equal to systemic pressure did not differ between SHAM and URAC animals when evaluated prior to occlusion and days 1, 4, and 32 post-URAC. Therefore, perfusion pressure was greater in the mesenteric vasculature of the hypertensive dogs than SHAM animals only when evaluated 32 days post-URAC (Table 1). When evaluated at flow rates designed to set mesenteric perfusion pressure equal to systemic arterial pressure, small artery pressure and resistance was significantly increased on day 4 post-URAC, and both arterial pressures and venous pressure were elevated on day 32 post-URAC when compared with SHAM animals (Table 1). Intraluminal intestinal pressure did not differ significantly between SHAM and URAC animals at any time period studied (data not shown).

Responses to Vasoactive Agents

When perfused at equivalent pressures and flows, increases in perfusion pressure, small artery pressure, and small vein pressure in response to NE, 5-HT, AII, and EMP were similar among perfused mesenteric preparations when evaluated in four groups of SHAM dogs prior to and on days 1, 4 (not shown), and 32 post-SHAM occlusion of the renal artery (Fig. 3). Vascular responses to each of the agonists tested did not differ between SHAM and URAC animals when evaluated prior to SHAM occlusion or URAC (compare Figs. 3, 4, 5, 7, and 8).

Responses to 5-HT and EMP

Mesenteric vascular responses to 5-HT and EMP were enhanced from pre-URAC values when evaluated within 1 day post-URAC. The pressor responses to 5-HT and EMP were enhanced further with respect to control values when evaluated on day 4 (not shown) and day 32 post-SHAM occlusion of the renal artery (Fig. 3). Vascular responses to each of the agonists tested did not differ between SHAM and URAC animals when evaluated prior to SHAM occlusion or URAC (compare Figs. 3, 4, 5, 7, and 8).
TABLE 1 Characteristics of the Perfused Mesenteric Vasculature of Dogs with Sham Renal Artery Occlusion or 2-KGH

<table>
<thead>
<tr>
<th></th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Mesenteric perfusion pressure (mm Hg)</th>
<th>Mesenteric flow (ml/min)</th>
<th>Small artery pressure (mm Hg)</th>
<th>Small vein pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHAM</td>
<td>96 ± 6</td>
<td>96 ± 7</td>
<td>21.3 ± 1.9</td>
<td>74 ± 3</td>
<td>4.1 ± 0.9</td>
</tr>
<tr>
<td>URAC</td>
<td>94 ± 5</td>
<td>97 ± 6</td>
<td>20.4 ± 2.4</td>
<td>71 ± 4</td>
<td>4.8 ± 1.1</td>
</tr>
<tr>
<td>24 hours post-URAC</td>
<td>99 ± 5</td>
<td>99 ± 4</td>
<td>22.6 ± 1.7</td>
<td>77 ± 4</td>
<td>4.6 ± 1.8</td>
</tr>
<tr>
<td>SHAM</td>
<td>96 ± 6</td>
<td>101 ± 7</td>
<td>21.8 ± 1.5</td>
<td>75 ± 6</td>
<td>4.3 ± 0.5</td>
</tr>
<tr>
<td>URAC</td>
<td>108 ± 7*</td>
<td>99 ± 9</td>
<td>20.6 ± 2.4</td>
<td>73 ± 3</td>
<td>4.3 ± 1.3</td>
</tr>
<tr>
<td>Day 4 post-URAC</td>
<td>SHAM</td>
<td>93 ± 6</td>
<td>20.3 ± 1.8</td>
<td>78 ± 5</td>
<td>6.2 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>108 ± 7*</td>
<td>99 ± 9</td>
<td>21.3 ± 1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 32 post-URAC</td>
<td>SHAM</td>
<td>96 ± 5</td>
<td>22.4 ± 1.3</td>
<td>75 ± 5</td>
<td>4.7 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>129 ± 4*</td>
<td>104 ± 9</td>
<td>21.9 ± 2.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Responses are expressed as the mean values ± SE for six animals. * Differs significantly (P < 0.05) from sham.

The possibility existed that 5-HT- and EMP-induced increases in mesenteric arterial and venous pressures, post-URAC, were secondary to the greater intraluminal gut pressure produced by these substances. As shown in Figure 6, for EMP, the rise in intraluminal gut pressure occurs after the maximum increase in arterial and venous pressures. Similar results were obtained with 5-HT as the agonist (data not shown).

Vascular Responses to All and NE

Angiotensin II amide produced dose-related increases in mesenteric perfusion pressure, small artery pressure, and intraluminal gut pressure but did not affect mesenteric venous pressure. The vasoconstrictor and intraluminal gut pressure responses were enhanced within 24 hours post-URAC, and increased progressively on day 4 and day 32 post-URAC (Fig. 7; Table 2). Analysis of segmental vascular resistance showed that the large arteries responded only to the highest dose of All, whereas the major increase in vascular resistance occurred at the level of the small arteries and arterioles (Table 2). The major site of enhanced resistance to All occurred in the small arteries and arteriolar smooth muscle 24 hours post-URAC. However, by days 4 and 32 post-URAC, the larger arteries also were sensitive to All. Thus, like results for EMP and 5-HT, the first site at which vascular responses to All are enhanced is the arterioles, whereas larger artery involvement appears by day 4 post-URAC, and is fully evident by day 32 post-URAC (Table 2).

NE-induced increases in mesenteric perfusion pressure, small artery pressure, and small vein pressures did not significantly differ from pre-URAC values when evaluated 24 hours post-URAC. By day 4, post-URAC enhancement of NE-induced responses was evident. Further increases in arterial and venous responses to NE were evident on day 32 post-URAC (Fig. 8). NE produced either no change or slightly decreased intraluminal gut pressure. Analysis of segmental vascular resistances demonstrated that, as for All, the increase in resistance produced by NE on day 4 post-URAC occurred in the smaller arteries, arterioles, and venules, whereas an increase in large artery sensitivity occurred by day 32 post-URAC.

Effect of Pressure Reduction on Vasoactivity

On day 32 post-URAC, mesenteric perfusion pressure was elevated. In an attempt to discern the effects of an elevated intravascular pressure on the responses of the vasculature to vasoactive agents,
As flow increased, vascular resistance increased in the large and smaller arteries as well as the venules. The intestine also contracted in response to increases in flow rate and developed a greater intraluminal pressure. Within 24 hours after URAC, large artery resistance was unchanged from pre-URAC values whereas, at higher rates of flow, the pressure-flow curves for the arteriolar and small venous segments of the vasculature were shifted toward the pressure axis. Four days post-URAC, large artery involvement was evident as the pressure-flow curve was shifted toward the pressure-axis at high rates of flow, whereas the small artery and venous curves showed reduced distensibility at lower rates of flow as well. Thirty-two days post-URAC, a decrease in distensibility was evident for the large arteries, arterioles, and venules, as evidenced by a shift in the pressure-flow curve toward the pressure axis. Intraluminal gut pressure, in re-

**Pressure-Flow Curves**

we decreased the blood flow to the perfused intestinal segment, recorded the flow, and reduced the dose of agonist so that the calculated concentrations of agonist in blood, at high and low flows, were equivalent. (The data are summarized in Table 3.) For each of the agonists tested, the change in pressure and resistance on day 32 post-URAC was decreased only slightly from the values obtained when the pressure was elevated. Therefore, it is unlikely that the elevated pressure artifactually enhanced the vasopressor responses to the agonists under study, on day 32 post-URAC.

![Figure 4](image-url)  
**Figure 4** Dose-response curve of the perfused mesenteric arteries and veins to 5-HT prior to (filled circles) 24 hours (unfilled circles) and 32 days (unfilled triangles) after induction of 2-KGH. The ordinate represents the change in pressure to 5-HT. The abscissa represents the dose of agonist. For details of legend, see Figure 3.

![Figure 5](image-url)  
**Figure 5** Vascular and intestinal responses of the perfused mesenteric vasculature to EMP before, and 24 hours and 32 days after, occlusion of the renal artery and induction of 2-KGH. For details of legend, see Figures 2 and 3.
Table 2  Changes in Segmental Mesenteric Vascular Resistance to Intra-arterial 5-HT, All, EMP, and NE during the Development of 2-KGH

<table>
<thead>
<tr>
<th>Δ Resistances</th>
<th>Day post-URAC</th>
<th>Serotonin</th>
<th>Agonist (μg in)</th>
<th>NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large artery</td>
<td>0</td>
<td>0.05 ± 0.01</td>
<td>0.49 ± 0.04</td>
<td>0.03 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.06 ± 0.01</td>
<td>0.51 ± 0.03</td>
<td>0.09 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.15 ± 0.03*</td>
<td>0.62 ± 0.10*</td>
<td>0.21 ± 0.04*</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>0.25 ± 0.04*</td>
<td>0.83 ± 0.13*</td>
<td>0.27 ± 0.05*</td>
</tr>
<tr>
<td>Arteriolar</td>
<td>0</td>
<td>0.25 ± 0.03</td>
<td>2.83 ± 0.14</td>
<td>0.6 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.51 ± 0.07*</td>
<td>3.33 ± 0.17*</td>
<td>1.1 ± 0.16*</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.81 ± 0.14*</td>
<td>3.95 ± 0.23*</td>
<td>1.7 ± 0.23*</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>1.04 ± 0.16*</td>
<td>4.77 ± 0.42*</td>
<td>2.3 ± 0.22*</td>
</tr>
<tr>
<td>Venular</td>
<td>0</td>
<td>0.10 ± 0.02</td>
<td>0.26 ± 0.06</td>
<td>0 ± 0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.15 ± 0.02</td>
<td>0.41 ± 0.08*</td>
<td>0 ± 0</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.33 ± 0.04*</td>
<td>0.67 ± 0.11*</td>
<td>0.05 ± 0.02*</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>0.41 ± 0.05*</td>
<td>0.82 ± 0.13*</td>
<td>0.11 ± 0.04*</td>
</tr>
</tbody>
</table>

Each response represents the mean peak change in segmental resistance [mm Hg/(ml per min)] of six dogs (±SE) after the low and high dose of the agonist. * Differs significantly (P < 0.05) from the corresponding control values attained immediately before unilateral renal artery constriction (day 0 post-URAC).

Discussion

The present study demonstrated that, in 2-KGH hypertension in dogs, increases in mesenteric vascular reactivity: (1) precede the development of the increased cardiac output and arterial resistance of the hypertension, (2) cannot be accounted for by an increase in intravascular pressure or flow, and (3) occur first in the arteriolar and venular smooth muscle and, as the hypertension progresses, in the larger arteries. Enhanced reactivity of the intestinal smooth muscle (nonvascular) is also present in the 2-KGH model of hypertension. In addition, vascular distensibility decreases prior to the increase in arterial vascular resistance in this model of hypertension. These data support the concept that changes in reactivity and compliance precede, and may be...
Difficulties with Mesenteric Vascular Perfusion

The perfused mesenteric artery and vein preparation presents some difficulties in evaluation of the resultant data. Active contraction, or relaxation, of the intestinal smooth muscle can modify passively arteriolar and venous pressures, thereby providing spurious results. This difficulty was minimized by evaluating intraluminal gut pressure and monitoring the time course of the changes in the vascular and gut pressures in response to the vasoactive agents studied.

A second difficulty with this preparation is that, since perfusion pressure is set to equal systemic pressure, perfusion pressures and flows in mesenteric segments could differ between the SHAM and URAC dogs. This could modify the responses of the perfused vasculature in two ways. First, flows might be higher in the URAC preparation early in the hypertension. The concentration of drug injected into the gut segment would be less in the hypertensive animals, since an equal amount of drug administered into a preparation with a greater flow rate would result in a greater dilution of the drug and, thereby, an effectively lower concentration of drug. This possibility appears unlikely in perfused mesentery from animals with 2-KGH hypertension, since blood flow to the intestine was normal (Table 1). This is in agreement with data obtained by Guyton (1974). In addition, the higher perfusion pressure at day 32 post-URAC could modify the responses of the hypertensive vessel itself to the vasoactive agents. Reducing the rate of flow in an attempt to normalize pressures between hypertensive and normotensive intestinal loops will result in a higher effective concentration of injected drug due to the reduction in flow. These difficulties were overcome by assessing the responses of the perfused...
Vascular Responses to 5-HT, EMP, All, and NE

The major sites of the vascular resistance changes produced by 5-HT and EMP appear to be the arterioles and venules. Intestinal compression of the vasculature does not contribute to the increased arterial and venous pressures produced by 5-HT and EMP. All produces mesenteric venoconstriction, probably as a result of increased intestinal contraction. The enhanced responses of the arterioles and venules to 5-HT is consistent with the observations of Haeusler and Finch (1972) in spontaneously hypertensive rats, and in rats with one-kidney, one-clip renal hypertension. The increase in responses to All is consistent with the observations of many investigators in animals with renal, DOCA-saline, and aortic coarctation hypertension (Collis and Alps, 1975; Berecek and Bohr, 1978; Ichikawa et al., 1979; Click et al., 1979). The finding that responses of the mesenteric vasculature to NE are enhanced only slightly on day 4 post-URAC, but greatly increased by day 32 post-URAC, is consistent with the findings of Berecek and Bohr (1978) who were unable to demonstrate an enhanced responsiveness to NE until the 7th day post-DOCA-saline administration to pigs. At this time, arterial resistance and pressure were increased. Similarly, pressure was elevated in our dogs after day 4 post-URAC. These findings indirectly suggest that the α-adrenergic receptor or the transduction mechanism for α-receptor-mediated arterial and venous constriction may be less sensitive to the mechanisms responsible for the early enhancement of the mesenteric responses to 5-HT, EMP, and All in dogs with 2-KGH.

Vascular Reactivity in Hypertension

Current concepts regarding the role of enhanced vascular reactivity in experimental hypertension...
indicate that early vascular reactivity changes may occur independent of pressure changes since (1) enhanced vascular reactivity preceded the increased arterial resistance of various models of experimental hypertension and (2) the study of veins in hypertension demonstrates that venous smooth muscle is less compliant, hypertrophied, and may demonstrate enhanced contractility (Bevan et al., 1976; Greenberg and Bohr, 1975; Takeshita and Mark, 1978; Greenberg et al., 1978).

Folkow et al. (1970) have presented evidence indicating that most, if not all, of the increased vascular resistance and reactivity in the established phase of experimental and human essential hypertension is caused by an increased vascular wall thickness. Concentration-response curves of rats (renal and spontaneously hypertensive to NE) differed from those of the normotensive animals in the same manner as did calculated concentration-response curves of a mathematical model with normal wall thickness, in which it was assumed that medial wall thickness was increased by approximately 30%, and the increase in wall thickness had encroached on the lumen when the smooth muscle was relaxed completely to maximal dilation. Similar conclusions were obtained from the studies of Conway (1963) who observed that maximal dilation of the human forearm vasculature with acetylcholine resulted in a greater resistance in the forearms of hypertensive than of normotensive men. It was suggested that structural vascular changes might be responsible for the increased vascular resistance and vascular reactivity of hypertensive men.

Tobian (1960) suggested that the increased wall:lumen ratio and enhanced vascular reactivity were due in large measure to the increased sodium and water in vascular wall, i.e., “waterlogging.” However, waterlogging does not occur, at least in the rat, until late in the hypertensive process (Folkow and Hallback, 1977). Shibata et al. (1973) and Hansen and Bohr (1975) demonstrated that the increased vascular reactivity and, perhaps, permeability of arterial smooth muscle strips occur prior to, and early in, respectively, the development of hypertension. However, their experiments, like those of Weiderheilm (1967), demonstrated that a reduction in pressure, achieved by occlusion of the femoral artery, was a stimulus sufficient to alter vascular reactivity in normotensive animals as well. Therefore, as suggested by the investigators themselves, the intervention used to assess the importance of functional vs. structural and pressure influences on vascular smooth muscle reactivity in hypertension may have directly affected the smooth muscle function. This possibility has been suggested also by the recent experiments of Bevan et al. (1975), who stated that the increased intravascular pressure of aortic coarctation hypertension was associated with an increased tension development of arteries and veins obtained from high-pressure sites above, but not below, the site of coarctation. The increased tension development was correlated directly with the magnitude of the rise in arterial pressure. Thus, intrinsic changes in vascular smooth muscle function may be masked or modified by the hypertension itself.

In the present study, advantage was taken of the fact that overt hypertrophic changes are absent or minimal within 1 day post-URAC, so that arterial vascular responses would not be influenced by an altered vascular geometry. Second, by the simultaneous measurement of both arterial and venous pressures and responses to vasoactive agents, the deleterious effects of an increased intravascular pressure on the vascular smooth muscle (arterial)
could be accounted for by evaluation of the changes in the vein. Finally, by measurement of intraluminal gut responses, we could evaluate the integrity of nonvascular smooth muscle.

Enhanced vascular responses to 5-HT, AII, and EMP precede the development of the increased arterial pressure and the increased flow resistance of 2-KGH in dogs. Furthermore, as the hypertension progresses and increased resistance to flow occurs, reducing flow to obtain arterial pressures at pre-URAC values still resulted in an enhanced arterial reactivity to the agonists tested. In addition, like the studies by Wood (1961), in which hypertensive patients responded with nausea and increased intestinal motility to concentrations of AII which were inactive in normotensive man, this study demonstrates in enhanced responsiveness of the intestinal smooth muscle to concentrations of 5-HT, EMP, and AII which were inactive in normotensive dogs.

Since flow resistance increases and compliance decreases in the arteriolar smooth muscle, on day 32 post-URAC, we can speculate that hypertrophy must be present, although we did not directly ascertain its existence in this study. Based on the increase in flow resistance at maximal vasodilation (Table 3) and the calculations provided by Folkow and Hallback (1977), we can estimate that the pressor responses of the arteriolar smooth muscle to these agonists should have been enhanced to a much greater value than presented herein. Therefore, it is possible that the altered vascular geometry maintains the exaggerated pressor response to the vasoactive agents tested at a time when an increased intravascular pressure may have damaged the contractile function of the arteriolar smooth muscle. This speculation is supported by the studies of Hansen and Bohr (1975) who demonstrated a decreased contractility of the vascular smooth muscle of renal and spontaneously hypertensive rats at a time when in situ responses were enhanced. Therefore, the data justify the conclusions that (1) an enhanced vascular (arterial and venous) smooth muscle reactivity to 5-HT, EMP, and AII precedes, and may be causal to, the increased arterial pressure and resistance of 2-KGH in dogs, and (2) intestinal (nonvascular) smooth muscle reactivity is enhanced in dogs with 2-KGH prior to the elevated vascular resistance of the hypertension. One can assume that the enhanced arterial reactivity in the established phase of hypertension may be maintained by the greater mechanical advantage offered by a hypertrophied arteriolar smooth muscle, in part to offset the deleterious effects of an elevated intravascular pressure on the arterial wall.

Site of Enhanced Vascular Reactivity

Friedman et al. (1971) demonstrated that the early vascular structural changes that occur in experimental hypertension occur also in vessels larger than 100 μm in external diameter. The smaller arterioles and resistance vessels do not appear to be affected to any significant extent. Friedman et al. (1971) believe that this indicates that a primary change occurs in the reactivity of the small resistance vessels: these vessels constrict and increase the pressure upstream, producing the structural changes that occur in hypertension. The intraluminal pressure downstream does not increase, because these vessels are constricted; hence their structure is not altered. These studies would seem to indicate that the changes in vascular reactivity and electrolyte metabolism in vessels larger than 100 μm o.d. are secondary to the increased intravascular pressure of hypertension and reflect changes in smaller vessels.

Our data support, in part, the concept of Friedman et al. (1971). Enhanced reactivity of vascular smooth muscle occurred in the small arterioles and venules before it was exhibited by the larger arteries. Although the exact sizes of the vessels involved were not measured, the arterial pressure measured responses of the precapillary sphincters, up to the 450-μm (o.d.) vessels which were cannulated for measurement of this pressure. This larger artery should roughly correspond to a 100-μm vessel in the rat of the aforementioned Friedman study. Although our data also demonstrate that the changes in the large arteries occur later in the hypertensive process than do the arteriolar changes, it is difficult to accept the hypothesis that they reflect only the elevated vascular pressure since (1) pressure is elevated only slightly in the systemic circulation and is not altered in the perfused mesenteric vascular segments, and (2) the changes in vascular reactivity are not uniform for each of the agonists tested.

Vascular Distensibility and 2-KGH

A decrease in vascular distensibility in hypertension is believed to result from an increase in connective tissue elements and from a hypertrophied and/or waterlogged smooth muscle, as well as a state of partial contraction of the vasculature (Tobian, 1960; Folkow et al., 1970; Wolinsky, 1971). The increased synthesis of collagen and elastin by the smooth muscle cells of the vasculature, which form the connective tissue of both the media and adventitia (Ross and Klebanoff, 1971), is believed to result from the increased wall stress and intravascular pressure. The incipient stages of decreased vascular distensibility are apparent within small arteries and arterioles by day 1 post-URAC (Fig. 9). However, the veins and intestinal smooth muscle are spared these changes. Within 4 days, post-URAC venous distensibility changes are also evident and become more pronounced as the hypertension progresses. These data support the conclusion that vascular distensibility may decrease prior to the increase in systemic arterial resistance and pressure in 2-KGH. Since decreased distensibility was still evident when maximal vasodilation was induced with prostacyclin, the data support the conclusion that both
active constriction and changes in the structural proteins, collagen and elastin, contribute to the decreased vascular compliance. The existence of changes in the small venules, as well as the arterioles, would support the concept that the early changes in vascular distensibility cannot occur as a result of the pressure changes and may result from circulating factors. The mechanism for the decreased vascular distensibility remains to be elucidated.

In summary, the results of this study demonstrated that enhanced vascular reactivity precedes the increased arterial resistance of 2-KGH in dogs. The primary changes occur in the arterioles and venules and, within 4 to 32 days post-URAC, are found in the larger arteries. The enhanced reactivity also is found in the nonvascular smooth muscle of the small intestines. Decreases in vascular compliance also occur in the mesenteric vasculature of dogs with 2-KGH prior to the increase in arterial vascular resistance. The decrease in compliance is due, in part, to both active contraction and structural changes, i.e., a stiffer vasculature. These data clearly show that changes in vascular function occur prior to any increase in arterial pressure in 2-KGH and therefore may play a pathogenetic role in the development of 2-KGH in dogs.

References

Vascular responses of the perfused intestine to vasoactive agents during the development of two-kidney, one-clip Goldblatt hypertension in dogs.

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