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Increased Mesenteric Blood Flow and Decreased Mesenteric Venous Compliance in Dogs with Chronic Perinephritic Hypertension (40560)

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In dogs with early (less than 2 weeks) one-kidney perinephritic hypertension there are coexisting rises in cardiac output (1) and mesenteric blood flow (2) and decreases in mesenteric venous compliance (2). After 4 weeks of this form of hypertension, cardiac output returns to normal, the hypertension then being sustained by increased total peripheral resistance (1). Similar observations of whole body hemodynamics led to the hypothesis that the elevated total peripheral resistance in established hypertension results from a vascular autoregulatory response to early increases in blood flow through the peripheral vascular beds (3). If this hypothesis is correct, one would expect that, in the chronic phase or perinephritic hypertension, mesenteric blood flow would return toward normal levels and mesenteric vascular resistance would rise in conjunction with total peripheral resistance. Thus, in the present study we investigated mesenteric blood flow, pressures, and resistances in the chronic (>4-week duration) stages of perinephritic hypertension in dogs. We also studied pressure–volume relationships in mesenteric veins.

Materials and Methods. To allow comparison of results with our previous study in early hypertension (2), we used essentially identical methods. Briefly, healthy conditioned male mongrel dogs weighing 19–28 kg and maintained on standard dog chow and water *ad libitum* were trained to lie quietly during femoral artery punctures for blood pressure measurements; normal baseline pressures were documented. Under sodium pentobarbital anesthesia, a left-flank incision was made and the left kidney dissected free from its fat pad and, in the 10 dogs of the experimental group, wrapped in silk. The silk wrapped kidney in turn was wrapped in Saran Wrap to minimize adhesions. In 10 control dogs the kidney was merely dissected and Saran Wrap laid down alongside. One week later the right kidney was removed from all dogs. Postoperatively, femoral arterial blood pressures were measured weekly until the time of the hemodynamic studies.

After 4 to 5 weeks of sustained hypertension in the experimental group and at a similar time interval in the control group, the dogs were fasted overnight and then anesthetized with sodium pentobarbital (35 mg/kg, iv), intubated, and mechanically ventilated to maintain measured arterial blood pH at 7.39–7.43. Heparin (12,000 USP units) was administered iv.

After a midline abdominal incision, we prepared a collateral-free innervated, naturally perfused intestinal loop from a similar anatomic location in each dog, corresponding to the midportion of the ileum. This loop plus its mesentery was used for the study of mesenteric blood flow and pressures, as previously described (2). A venous outflow catheter (PE 240) was inserted and pressure measured through a T-tube and identified as large vein pressure (P_{LV}). By adjusting the level of the venous catheter, this pressure was set at 7 mm Hg in all dogs. Small artery (P_{SA}) and small vein (P_{SV}) pressures were monitored through catheters (PE 10) inserted into a small artery and retrograde into a small vein near the junction of the mesentery and the ileal wall. A femoral artery was cannulated (PE 240) for monitoring large-artery pressure (P_{LA}). The preparation was kept at 37–38° and moist.

Beginning 90 min after the initial anesthesia in all dogs, repeated measurements of intravascular pressure, by strain gauge, and mesenteric venous outflow, by stopwatch and graduated cylinder, were obtained for 30 min. At the conclusion of these measurements, the ileal loop and its mesentery were excised and weighed.

We used steady-state measurements in our calculations, as previously (2). Blood flow

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was expressed as ml/min 100 g^{-1} ileum. As previously, we divided intravascular pressure gradients by blood flow to calculate steady-state total and segmental vascular resistances: mesenteric total resistance (R_T); mesenteric large artery resistance (R_{LA}); mesenteric small vessel resistance (R_{SV}); and mesenteric large vein resistance (R_{LV}).

We compared flows, pressures, and calculated resistances in dogs of the hypertensive group with those of controls by Student's t test, rejecting the null hypothesis at probability values $P \leq 0.05$.

For measurement of mesenteric vein pressure–volume relationships *in vivo*, we then prepared an ileal vascular arcade as previously described (1), taking care to select an arcade from a similar anatomic location in each dog. Except for the point of cannulation (PE 200) the standardized (4 × 4 × 1.5-cm) venous segment used was left intact and temperature and humidity were controlled. Small holes were made in the avascular portion of the mesentery on the two sides of the vein so that the segment and its supplying artery could be temporarily occluded by atraumatic clamps for the pressure–volume studies. After occlusion, the venous segment was drained of its blood content through the indwelling catheter until intrasegmental pressure, monitored through a T-tube arrangement, was atmospheric. Then, to produce step increases in intrasegmental pressure up to 50 mm Hg, we injected 0.05-ml samples of the dog's own blood at 37–38° into the distal end of the indwelling catheter. A 10-sec pause after each injection was allowed to establish steady-state pressures. The time required for each pressure–volume study was less than 5 min, and then circulation through the venous segment was restored by removing the clamps. This pressure–volume measurement was repeated after a waiting period of 25 min. Using the average of two or three series of measurements in each dog, injection-phase volumes producing intrasegmental pressures of 5, 15, 25, and 35 mm Hg in the hypertensive dogs were compared by Student's t test with respective values in the control normotensive dogs. Entire pressure–volume curves were also assessed with profile analysis (4).

Results. At the time of the hemodynamic studies, mean arterial blood pressure in dogs of the hypertensive group had risen from a preoperative value of 118 to 173 mm Hg ($P < 0.001$). From a preoperative value of 120 mm Hg in the control group no change in arterial pressure occurred. There was no statistically significant difference in body weight, hematocrit, serum electrolytes, or creatinine between hypertensive and control groups. The general health of all dogs remained good.

Table I presents group means ±SEM of mesenteric blood flows, pressures, and calculated resistances in the two groups of dogs. The weight of the ileal segment studied was similar in the two groups. Ileal blood flow (ml/min 100 g^{-1}) in the hypertensive dogs was 20% greater than in normotensive dogs ($P < 0.02$). Intraarterial pressures (P_{LA}, P_{SA}) in hypertensive dogs were significantly increased compared with those in control dogs. In contrast, there were no significant changes

TABLE I. BODY WEIGHTS, ILEAL SEGMENT WEIGHTS, BLOOD FLOWS, PRESSURES, AND RESISTANCES[a]

	Hypertensive group	P	Normotensive group
N	10		10
Body weight, kg	24.1 ± 1.1	>0.5	24.3 ± 1.0
Weight of ileal segment, g	49.8 ± 3.5	>0.5	51.2 ± 3.6
Blood flow, ml/min 100 g^{-1}	50.8 ± 2.6	<0.02	42.2 ± 2.1
Pressure, mm Hg			
Large artery (P_{LA})	181.2 ± 4.8	<0.001	142.4 ± 3.0
Small artery (P_{SA})	140.1 ± 3.9	<0.001	106.8 ± 3.7
Small vein (P_{SV})	13.2 ± 0.4	>0.1	11.6 ± 0.5
Large vein (P_{LV})[b]	7		7
Resistance, mm Hg/ml min^{-1} 100 g^{-1}			
Total (R_T)	3.51 ± 0.24	>0.4	3.29 ± 0.17
Large artery (R_{LA})	0.84 ± 0.10	>0.4	0.75 ± 0.08
Small vessel (R_{SV})	2.56 ± 0.15	>0.4	2.39 ± 0.16
Large vein (R_{LV})	0.12 ± 0.01	>0.1	0.16 ± 0.03

[a] All values are mean ± SEM.
[b] P_{LV} held constant at 7 mm Hg.

in venous pressure (P_{SV}). Calculated ileal vascular segmental resistances (R_T, R_{LA}, R_{SV}, and R_{LV}) of hypertensive dogs were not significantly different from those of normotensive control dogs.

Table II presents pressure–volume data obtained from the temporarily isolated mesenteric veins *in vivo* during the injection phase. The means (±SEM) of total volumes (ml) which produced intravenous pressures of 5, 15, 25, and 35 mm Hg are tabulated. In hypertensive dogs, the total volumes producing intravenous pressures of 15, 25, and 35 mm Hg were significantly lower than in normotensive control dogs. These conclusions were supported by profile analysis (4).

Gross examination of the kidneys at autopsy revealed no abnormality of the sham-wrapped kidney of normotensive control dogs. The capsule of the silk-wrapped kidney of hypertensive dogs was thickened, but the parenchyma appeared normal.

Discussion. Venous pressure–volume measurements in the present study indicate that the decreased mesenteric venous compliance we observed in dogs in the early stages of perinephritic hypertension (2) persists into the chronic phases of this form of experimental hypertension. This finding confirms our previous observation that femoral venous compliance in dogs with chronic hypertension is also decreased (5). Because the mesenteric veins contain a major portion of venous volume, our present findings add strong support to our previous conclusion that the normalization of cardiac output in these dogs (1) cannot be attributed to a return of venous compliance to normal (5).

Results of the present study indicate that mesenteric blood flow is elevated by 20% in these dogs with chronic perinephritic hypertension. There are no other reports in the literature of studies of mesenteric hemodynamics in chronic perinephritic hypertension. However, mesenteric blood flow has been studied in other forms of established hypertension. Unfortunately, major differences in experimental techniques make the data extremely difficult to interpret. Differing anesthetic agents were used, or no anesthesia at all. In many cases fractional, rather than absolute, flow was reported (6–8). In other cases blood flow was measured with excessively large (50 μm) microspheres (9) or Rb^{86} (8, 10), the diffusion of which is a function of blood velocity as well as flow. Similar to our observations in one-kidney perinephritic hypertension in dogs, gut blood flow is reported by one group (6) to be elevated in two-kidney Goldblatt hypertension and in DOCA-salt-uninephrectomy hypertension in the rat. However, normal or reduced gut flow is reported in the rat with one- and two-kidney Goldblatt hypertension (6–8). In other forms of experimental hypertension, including SHR (9, 11, 12) and neurogenic hypertension in rabbits (10, 13), normal or reduced gut flow is also reported. In patients with hypertension, the dye clearance techniques used for flow measurement do not allow separation of hepatic and mesenteric flow. These patients are found to have normal or decreased total splanchnic flows (14–17).

TABLE II. *In Vivo* Mesenteric Vein Pressure–Volume Relationships[a]

Intravenous pressures (mm Hg)	Hypertensive group ($N = 9$)	Normotensive group ($N = 9$)	P
	Volume (ml)		
5	0.124 ± 0.012	0.172 ± 0.035	>0.2
15	0.245 ± 0.021	0.369 ± 0.048	<0.05
25	0.328 ± 0.025	0.536 ± 0.059	<0.01
35	0.379 ± 0.029	0.596 ± 0.064	<0.02

[a] All values are mean ± SEM.

The abnormal increases in mesenteric blood flow we have observed in dogs in the early stages of perinephritic hypertension (2) thus persist 2–3 weeks into the chronic phases of this hypertension. Therefore, mesenteric blood flow fails to reflect the return of cardiac output to normal levels (1). Nor is there evidence for increases in mesenteric arterial resistance that reflect the increased total peripheral resistance in these dogs with chronic hypertension.

Figure 1 compares flow and resistance values observed in our present and previous (2) studies and illustrates graphically that no significant changes occurred in mesenteric blood flow or resistances over the 2- to 3-week period of development of the established stages of this form of hypertension. It should, however, be pointed out that our findings do not exclude the possibility that similar measurements made several weeks later in these dogs might have revealed normal blood flow and elevated resistance.

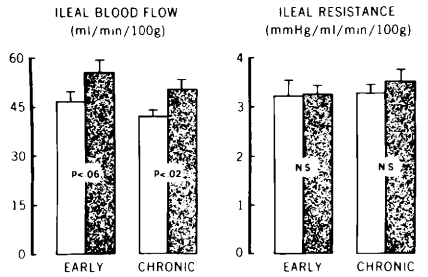

FIG. 1. Ileal blood flow (ml/min/100 g) and ileal vascular resistance (mm Hg/ml/min/100 g) in dogs in early (<2 weeks) and chronic (>4 weeks) stages of one-kidney perinephritic hypertension. Stippled bars and clear bars represent mean + SEM for hypertensive and normotensive dogs, respectively.

Our observations in the mesenteric vascular bed clearly indicate that whole-body hemodynamics may not be used to predict the hemodynamics of any specific vascular bed in hypertension. Thus, the validity of hypotheses conceived on the basis of observations of whole-body hemodynamics must be tested in the individual vascular beds.

In this regard, data from our two studies of mesenteric hemodynamics, one in early and one in the later established phases of hypertension, appear not to support the concept of long-term, whole-body autoregulation (3). Increases in mesenteric blood flow occurring in early hypertension persist, apparently unchanged, for at least 2–3 weeks into the chronic stages. These prolonged increases in blood flow are unaccompanied by evidence for the increases in mesenteric vascular resistance that would be predicted by the hypothesis. It is possible, however, but not investigated in the present study, or in any other study of which we are aware, that long-term autoregulation occurs more slowly in the mesenteric than in most other vascular beds. The effects of chronic hyperperfusion on the various regional vascular beds clearly requires study.

Our experiments also have not excluded the possibility that the increased mesenteric flow we observed may be entirely appropriate for this vascular bed, serving to maintain normal relations between blood flow and tissue demands. It is possible, for example, that there could be underlying increases in the metabolic rate of these mesenteric tissues in hypertension requiring increased blood flow. Alternatively, diffusion barriers, due, for example, to tissue "waterlogging" (18), might impair movement of respiratory gases, nutrients, and metabolites between blood and tissue. Thus, more blood flow would be required for normal levels of exchange. As a third possibility, the increased flow may merely indicate that the proportion of flow shunted through arterio–venous anastomotic connections in the mesentery in hypertension is elevated for some unexplained reason—perhaps passive dilation of these channels. Blood flows that are increased, but yet remain in proportion to tissue metabolic demands would not argue against the concept of long-term, whole-body autoregulation in hypertension.

These possible explanations for the chronic increases in mesenteric flows in this form of experimental hypertension must be tested. The results of such investigations may have relevance to the underlying mechanism of the elevations of cardiac output occurring in perinephritic and other forms of hypertension.

Summary. In 10 dogs with chronic (>4 weeks) one-kidney perinephritic hypertension and in 10 uninephrectomized normotensive control dogs anesthetized with pentobarbital we measured mesenteric pressures, flows, and venous pressure–volume relationships in the collateral-free, innervated, naturally-perfused ileal loop preparation. In hypertensives, compared to normotensives, arterial pressure ($P < 0.001$) and mesenteric blood flow/100 g ($P < 0.02$) were elevated, and venous compliance was decreased. In contrast, there were no significant changes in venous pressures and total and segmental resistances in hypertensives. Mesenteric pressures, flows, resistances, and compliances in these chronically hypertensive dogs did not differ significantly ($P > 0.05$) from values in dogs with early (<2 weeks) perinephritic hypertension that we previously reported. Together these results indicate that in the mesentery the normal vascular resistance and increased blood flow occurring in the early stages of perinephritic hypertension in dogs persist for several weeks into the established stages, without the development of increasing resistance and decreasing flow as would have been expected if "long-term autoregulation" had taken place.

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