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THE EFFECTS OF CHRONIC ONE KIDNEY PERINEPHRITIC HYPERTENSION AND INTRAVENOUS ANGIOTENSIN II INFUSION ON REGIONAL SPLANCHNIC HEMODYNAMICS IN THE DOG

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Michael Craig Maier

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Major professor

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THE EFFECTS OF CHRONIC ONE KIDNEY PERINEPHRITIC HYPERTENSION AND INTRAVENOUS ANGIOTENSIN II INFUSION ON REGIONAL SPLANCHNIC HEMODYNAMICS IN THE DOG

BY

Michael Craig Maier

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ABSTRACT

THE EFFECTS OF CHRONIC ONE KIDNEY PERINEPHRITIC HYPERTENSION AND INTRAVENOUS ANGIOTENSIN II INFUSION ON REGIONAL SPLANCHNIC HEMODYNAMICS IN THE DOG

By

Michael Craig Maier

Regional splanchnic blood flows were measured in dogs using microspheres labeled with ^{85}Sr, ^{51}Cr and ^{141}Ce during chronic hypertension (Series I) and before and after infusion of low (0.05 μg/Kg/min) and high (1.0 μg/Kg/min) doses of angiotensin II (Series II).

During chronic hypertension blood flow remained unchanged in the adrenal gland, spleen and liver but increased in the pancreas. Blood flow was unchanged in the mucosal layers but elevated in submucosal and muscularis layers of the stomach, duodenum, jejunum, ileum and colon.

Both doses of angiotensin II descreased blood flow in the pancreas, adrenal gland and spleen but liver was unchanged. Angiotensin II decreased blood flow in all mucosal and submucosal layers of all regions of the gastrointestinal tract and produced an increase in muscularis blood flow in the duodenum and jejunum, while flow remained unchanged in the muscularis of the ileum and colon, and blood flow decreased in the stomach muscularis.

DEDICATION

To my mother and father for

their continued support and guidance

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I would like to take this opportunity to thank my advisor, Dr. Thomas E. Emerson, Jr., for the guidance and assistance he has provided in the pursuit of this research. I would also like to thank Dr. Jerry B. Scott and Dr. Ching Chung Chou for their assistance in the preparation of this manuscript. Finally, I would like to express my thanks and appreciation to Ms. Bonnie Beck for her support and patience.

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INTRODUCTION

The use of the radioactive microsphere dispersion technique in chronic vascular research would prove to be very valuable because it would allow the measurement of regional hemodynamic parameters which cannot be measured by other means. To date, concrete data assessing the stability of microspheres lodged within vascular beds for an extended period of time is sparse. The report of Hales (1974) suggests that microspheres are not displaced from their initial sites of lodging during en eight-week chronic observation period. However, since the microsphere represents a foreign particle within an experimental animal, their ability to remain stationary after lodging within a vascular bed must be questioned. One purpose of the present study is to determine the stability of radioactive microspheres lodged within regional vascular beds of the splanchnic circulation during an eight-week chronic observation period.

The effect of chronic renovascular hypertension on the splanchnic circulation has not been clearly established. To date, investigations concerned with the role of the splanchnic circulation during chronic renal hypertension has produced conflicting results and a compartmental hemodynamic analysis of the gastrointestinal tract during the chronic hypertensive state is lacking. A second purpose of the present study is to investigate possible regional splanchnic hemodynamic changes within the mucosal, submucosal and muscularis layers of the gastrointestinal tract.

While the effect of angiotensin II on the splanchnic circulation has been investigated somewhat extensively, a compartmental hemodynamic

analysis of the response of the gastrointestinal tract to this vasoconstrictor is lacking. Since angiotensin II is elevated for a period following severe hemorrhage and during early renal hypertension, a regional hemodynamic analysis might prove to be valuable in assesssing the role of angiotensin II during these pathophysiological states. A third purpose of the present study is to determine the effect of low and high pharmacological doses of angiotensin II on the splanchnic circulation and to provide a hemodynamic analysis of the response of the mucosal, submucosal and muscularis layers of the gastrointestinal tract.

SURVEY OF THE LITERATURE

THE USE OF RADIOACTIVE MICROSPHERES IN CHRONIC VASCULAR RESEARCH

The radioactive labeled microsphere dispersion technique is an accepted technique for acute determination of blood flow to discrete regions of the body provided prescribed procedural criteria are adhered to strictly and microspheres of appropriate size are used (Wagner et al. 1969). To date, two studies exist which suggest that the use of radioactive microspheres in chronic vascular research is feasible.

Kaihara et al. (1968) measured possible loss of 50 μ radioactive microspheres in dogs for a period of two weeks. Using external detectors urine and fecal material were monitored for a period of five days and total body radioactivity was measured for a period of two weeks. No change in total body radioactivity was found and radioactivity in urine and feces was negligible. These findings were indirectly supported by Hales (1974) in a comprehensive study which monitored microspheres in microcirculation of the rabbit ear for an eight-week period. Using a microscope and the ear window technique, he found that during the eight-week chronic period the spheres were not phagocytized, dislodged or otherwise removed from the area studied. While the microcirculation of the rabbit ear is different from other regional vascular beds, this study suggests that the use of microspheres in chronic vascular research is a feasible and valuable approach because, it enables each animal to serve as its own control thus minimizing variance.

EXPERIMENTAL RENOVASCULAR HYPERTENSION

Two models of hypertension can be produced using the classical methods of Goldblatt et al. (1943): 1) Two kidney Goldblatt hypertension is produced by constriction of only one renal artery which produces a renin-dependent, mild, transient evaluation in arterial blood pressure; 2) One-kidney Goldblatt hypertension is produced by either constricting both renal arteries or by constricting one renal artery and removing the contralateral kidney. A volume-dependent state of hypertension is produced which is much more severe than that produced by the two-kidney model.

The original Goldblatt method was modified in 1939 by Page, who found that wrapping one kidney in silk or cellophane, with or without contralateral nephrectomy produces a one-kidney or two-kidney Goldblatt model of hypertension, respectively. This method is called perinephritic hypertension and is apparently caused by an inflammatory reaction around the kidney resulting in a fibrotic encapsulation. While the actual mechanism of hypertension is unknown, it has been demonstrated that perinephritic hypertension and the classical Goldblatt hypertension are similar in every aspect (Pickering, 1972). This technique is often preferable since it does not involve clamp adjustment to obtain proper constriction of the renal artery.

CARDIAC OUTPUT

Extensive studies in animal models of experimental renovascular hypertension have shown that cardiac output is elevated during the first four weeks of hypertension, and total peripheral resistance remains normal. Subsequently, cardiac output gradually returns to normal while total

peripheral resistance increases.

Ledingham et al. (1964, 1967) used electomagnetic flowmeters placed around the arch of the aorta to monitor cardiac output in anesthetized rats, before and after clipping one renal artery with contralateral nephrectomy, (one-kidney Goldblatt model). Cardiac output fell below control values for a period of five days after clipping, then increased transiently to a level above control values for the 35 day observation period. Interestingly, total peripheral resistance and blood pressure rose within two hours following renal artery constriction and remained elevated for the duration of the experiment.

Ferrario et al. (1970) used an electromagnetic flowmeter implanted around the aortic arch to monitor cardiac output in unanesthetized dogs before and after the induction of perinephritic hypertension. They produced a two-kidney model of Goldblatt hypertension by wrapping one-kidney in cellophane and leaving the contralateral kidney untouched. After a period of two weeks they converted the two-kidney model into a one-kidney model by contralateral nephrectomy. Cardiac output was elevated and total peripheral vascular resistance slightly decreased during the two-week period when the two-kidney model was in effect. Following the conversion to a one-kidney model, cardiac output rose further until it reached a maximum of 18% greater than the control level two weeks after nephrectomy. During this period, arterial blood pressure and for the first time, total peripheral resistance began to rise. Cardiac output transiently returned to normal by the fourth to sixth week post-nephrectomy and total peripheral resistance maintained the hypertensive state.

Ferrario et al. (1974) compared the one-kidney Goldblatt hypertension model, produced by renal artery constiction, to his earlier studies of the one-kidney Goldblatt perinephritic hypertension model in unanesthetized dogs. One renal artery was constricted by a chronically implanted, externally adjustable clamp and the contralateral kidney was removed. Cardiac output rose during the first two weeks and remained elevated for a period of four weeks. An increased heart rate and, to a lesser extent, an increased stroke volume was responsible for the elevated cardiac output. During the first two weeks total peripheral resistance remained normal and the elevated arterial blood pressure was maintained solely by an increased cardiac output. Total peripheral resistance began to rise during the third week following renal artery constriction while cardiac output began declining. By the fifth week, cardiac output had returned to normal and hypertension was maintained solely by an elevated total peripheral resistance. These studies of Ferrario demonstrate that hemodynamic changes which occur in the perinephritic one-kidney hypertensive model and the one-kidney Goldblatt model produced by renal artery constriction are similar.

In contrast to the findings of Ferrario, Bianchi et al. (1970, 1972) found that cardiac output of dogs with one-kidney and two-kidney models of Goldblatt hypertension measured by dye dilution, rose more transiently. In the one-kidney model cardiac output was significantly increased on the fourth and seventh day following renal artery constriction. Also, total peripheral resistance rose immediately after renal artery constriction but returned to normal after 24 hours. In the two-kidney model of hypertension, cardiac output was elevated for only one day following renal artery constriction and returned to normal by the sixth

and seventh days. Total peripheral resistance rose immediately after renal artery constriction and remained elevated throughout the one-week duration of the study.

Elevated cardiac output with normal total peripheral resistance in the early hypertensive stage, and normal cardiac output with an associated increased total peripheral resistance in the chronic hypertensive state led to the "autoregulation theory" as an explanation for the development of hypertension (Coleman and Guyton 1969; Coleman et al. 1971). Accordingly, vascular resistance increases in some or all peripheral regional vascular beds in response to the increased blood flow, eventually, resulting in a chronically elevated total peripheral resistance.

To date, the regional autoregulatory function of various vascular beds is based upon short term animal experiments. The renal vascular bed maintains a relatively constant level of blood flow in the arterial blood pressure range of 80-200 mmHg. In the splanchnic circulation, autoregulation is present in the spleen, intestine, and hepatic artery circulation of the liver. There is no apparent autoregulation in the stomach (Texter et al. 1968). However, the regional autoregulation of various vascular beds which occurs in response to the elevated cardiac output and arterial blood pressure is presently undefined. Therefore, it is uncertain how short-term regional autoregulation relates to long-term body autoregulation that has been suggested to occur in the course of the development of hypertension.

VASCULAR COMPLIANCE

Medial hypertrophy of arterial and arteriolar walls, thickening of the elastic intima, and an associated reduction in arterial compliance

are well established features of chronic experimental renal hypertension (Goldblatt 1938, Feigl, et al. 1963).

Recently, investigators have looked into the venous side of the circulation since a decrease in venous compliance could increase venous return to the heart and contribute to the elevated cardiac output during early hypertension.

Overbeck (1972) studied pressure-volume relationships in the isolated, temporarily occluded segment of the jugular and femoral vein in dogs during the early (less than four weeks) stage of perinephritic hypertension. The pressure-volume curve of the femoral vein was shifted toward the pressure axis, suggesting a reduced compliance, while the pressure-volume curve of the jugular vein remained unchanged.

These findings were supported by Simon et al. (1975), who studied pressure-volume curves of mesenteric veins in two different models of hypertensive dogs during the early hypertensive stage. The pressure volume curve of the four week, one-kidney model suggested a decreased venous compliance while the pressure volume curves of the eleven day, two-kidney model remained unchanged.

BLOOD VOLUME

Ledingham and Cohen (1964) measured plasma volume and extracellular fluid volume in rats with one-kidney Goldblatt hypertensions using the Evans blue distribution and thiocyanate method, respectively. Plasma volume and extracellular fluid volume tended to increase in both the hypertensive and the sham-operated controls, although the increases were significantly greater in the hypertensive rats at days three and seven. Plasma volume and extracellular fluid returned to normal by the fifteenth day following surgical induction of hypertension.

These findings were supported by Bianchi (1970), using similar techniques in conscious, unilaterally nephrectomized rats following renal artery constriction. A significant increase in plasma volume and extracellular fluid volume was found on days 1, 3-4 and 6-7 of hypertension; Plasma volume and extracellular fluid volume returned to normal by the twelfth, to fourteenth day.

Ferrario et al. (1970) measured plasma volume and total blood volume in dogs with one-kidney perinephritic hypertension using the radioiodinated serum albumen method. No change was found at 15 days after wrapping one-kidney in cellophane (two-kidney model), 15 days after contralateral nephrectomy (30 days post-wrapping), or after 10-17 months of chronic, one-kidney, perinephritic hypertension. In contrast, Ferrario (1974) measured plasma volume and total blood volumes in conscious dogs with one-kidney Goldblatt hypertension using the 10-minute Evans blue dye dilution technique. He found a small, transient rise in plasma volume and total blood volume, accompanied by a fall in hematocrit, during the first two weeks after renal artery constriction and contralateral nephrectomy.

REGIONAL HEMODYNAMICS IN RENAL HYPERTENSION

There is little data in the literature concerning regional hemodynamics in one-kidney or two-kidney Goldblatt models of renal hypertension. Some investigators believe that in the chronic hypertensive stage, total peripheral resistance is increased uniformly throughout the systemic vascular bed and hence regional blood flows remain unchanged (Overbeck et al. 1971, 1972a; 1972b; Simon et al. 1975). Other investigators support the theory that blood flow is redistributed between vascular beds during Goldblatt hypertension (Bralet et al. 1973; Flohr et al. 1976). The results of long-term, total body autoregulation during an extended period of elevated cardiac output (early stage of hypertension) is also rather poorly understood. A review of available data follows.

RENAL

Bonnous et al. (1962) studied renal hemodynamics in chronic, two-kidney Goldblatt hypertension in anesthetized dogs. Direct measurement suggests that blood flow per unit weight is normal in the non-stenotic kidney and normal or decreased in the stenotic kidney, depending on the post stenotic blood pressure. Vascular resistance was elevated in both the stenotic and non-stenotic kidney, however, the rise was greater in the stenotic kidney. Consequently the rise in perfusion pressure is proportional to the rise in resistance.

Using chronically implanted flowmeters, Ferrario et al. (1973) studied renal blood flow in conscious dogs with one-kidney Goldblatt hypertension produced by varying degrees of renal artery stenosis. Following a mild stenosis (i.e. 20%) of the renal artery, mean renal blood flow decreased during days 1-8, and then returned to or exceeded

control values. Pressure in the renal artery distal to the stenosis was lower than systemic arterial pressure, but greater than control systemic arterial pressure. Therefore, renal vascular resistance was initially elevated, but tended to return to normal after the first week following stenosis. Severe renal artery stenosis (i.e. 45%) produced a sustained reduction in mean renal blood flow and a sustained increase in renal vascular resistance.

Bralet et al. (1973) measured to the fractional distribution of cardiac output using ^{86}Rb in conscious rats that had one-kidney Goldblatt hypertension. Fractional distribution of ^{86}Rb to the kidney of hypertensive was not significantly different from controls at periods of five and ten weeks of hypertension. Renal resistance was not reported.

In a recent study, Flohr et al. (1976) measured the fractional distribution of cardiac output using the radioactive particle dispersion technique in rats that had one-kidney and two-kidney Goldblatt hypertension for a period of eight weeks. In the two-kidney model, the stenotic kidney decreased in weight and received a proportionate decrease in the fraction of cardiac output which was less than normotensive control values. The opposite, untouched kidney increased in weight, received a proportionate increase in the fraction of cardiac output, and exhibited a resistance equal to normotensive controls. However, the total renal fraction of cardiac output for both kidneys in this model was not significantly different from control values. In the one-kidney model there was a considerable hypertrophy of the remaining kidney. The fraction of cardiac output increased, but not to the same extent as did the weight. Therefore, total renal fraction of cardiac

output and flow per weight of renal tissue were decreased when compared to control values in one-kidney Goldblatt hypertension.

CORONARY

Increase in myocardial weight, primarily due to left venticular hypertrophy, and increase in total coronary vascular resistance is a common feature of renovascular hypertension (West et al. L959). Whether coronary blood flow per unit weight of myocardium is altered during hypertension is uncertain.

Dahners et al. (1972) found an increase in fractional distribution of cardiac output to the heart in anesthetized, one-kidney Goldblatt hypertensive rats using labeled macroaggregated albumen. These findings were supported by Bralet et al. (1973) who used ^{86}Rb to measure fractional distribution of cardiac output in conscious rats that had one-kidney Goldblatt hypertension. Furthermore, they felt that cardiac hypertrophy only partly accounted for the increase in myocardial flow fraction; the fraction of cardiac output delivered to 1 gm myocardium was significantly greater in hypertensive rats and was proportional to the severity of hypertension. They hypothesized that the increases in myocardial fraction of blood flow reflects both cardiac hypertrophy and an increased nutritional demand of the myocardium during hypertension.

Conversely, Flohr et al. (1976) measured the fractional distribution of cardiac output to the myocardium using the radioactive particle dispersion technique in rats that had one-kidney and two-kidney models of Goldblatt hypertension. Compared to normotensive controls, the myocardial fraction of cardiac output increased proportionally to the

increase in myocardial weight in both models of hypertension. Hence, flow per gram of myocardium remained in the normal range. The coronary vascular resistance increased proportionally to the total peripheral resistance.

LIMB

Limb hemodynamics have been intensively investigated in the early (less than 4 weeks) and the chronic (more than 4 weeks) stage of perinephritic hypertension in dogs by Overbeck et al. (1971, 1972). They reported that limb hemodynamics in the early stage of hypertension are apparently similar to those in the chronic stage, including normal blood flow and increased vascular resistance. Also, the increase in total limb resistance was equally distributed between the skin and skeletal muscle vascular beds. Skin and muscle venous resistances were normal in both early and chronic hypertension. On the other hand, Bralet et al. (1973) used ^{86}Rb to show that fractional distribution of cardiac output is reduced to the skin vascular bed and increased to the femoral muscle vascular bed in the rat during chronic on-kidney Goldblatt hypertension.

Flohr et al. (1976) measured the fractional distribution of cardiac output to skin and skeletal muscle using the radioactive particle dispersion technique in rats that had one-kidney and two-kidney models of Goldblatt hypertension. They found that the fraction of cardiac output received by the skin was equal to normotensive controls in both models of hypertension, hence skin vascular resistance increased proportionate to the increase in total peripheral resistance. In skeletal muscle, they revealed differences in the fractional distribution of

cardiac output in the one-kidney Goldblatt model, which exhibited a significant reduction in blood flow with an associated elevation in vascular resistance which was proportionately greater than the total peripheral resistance. This suggests a redistribution of blood flow from the muscle vascular bed to other organs in one-kidney Goldblatt renal hypertension. On the other hand, the two-kidney model, they found no significant change in muscle blood flow as resistance increased uniformly with total peripheral resistance.

CEREBRAL

Flohr et al. (1971) studied cerebral hemodynamics in rats with three different types of experimental renal hypertension: two-kidney Goldblatt, one-kidney Goldblatt, and deoxycorticosterone with sodium chloride loading. They used the radioactive microsphere dispersion technique and expressed their results in terms of fractional distribution of cardiac output. Fractional cardiac outputs to the brain in all three hypertensive models were not significantly different from the normotensive control group. In each experimental model cerebral vascular resistance was increased in exact proportion to the increased systolic blood pressure, suggesting that regional vascular resistance of the cerebral vascular bed rises uniformly with total peripheral resistance.

Flohr et al. (1976) later repeated and confirmed these studies using the same blood flow determination techniques in rats with one- and two-kidney Goldblatt hypertension. These studies imply that the cerebral vascular bed exhibits good autoregulation of blood flow during chronic renal hypertension.

Strandgaard et al. (1975) studied the ability of the cerebral vascular beds of normotensive and two-kidney Goldblatt hypertensive

baboons to autoregulate blood flow during acute elevations in blood pressure. Cerebral blood flow was measured using the intracorticord ^{133}Xe clearance method. Mean arterial blood pressure (MABP) was raised in increments of 10-20 mmHg by intravenous infusion of angiotensin II amide. Cerebral blood flow remained constant in the normotensive and hypertensive groups until MABP reached a level of 140-154 mmHg and 155-169 mmHg, respectively. Further evaluation of MABP in either group was associated with a proportionate increase in cerebral blood flow. The study suggests that the upper limit of cerebral blood flow autoregulation is elevated during two-kidney Goldblatt hypertension.

However, a recent study suggests that the upper limit of cerebral autoregulation may be exceeded in chronic one-kidney perinephritic hypertension in dogs (Ely et al. 1977). Regional cerebral blood flow were measured using the radioactive particle dispersion technique in the same dogs before 6-8 weeks after the development of hypertension. Blood flow was significantly increased and vascular resistance was actually decreased in the hypothalamus, thalamus, and cerebellum.

SPLANCHNIC

Simon et al. (1975) studied ileal blood flow and ileal vascular resistance in dogs during the early stage of one-kidney and two-kidney perinephritic hypertension. The one-kidney hypertensive model was hypertensive for a period of four weeks while the two-kidney model was hypertensive for a period of eleven days. Hypertensive animals were compared to sham-wrapped normotensive control dogs. Measuring blood flow directly on a per weight basis, they found ileal blood flow to be elevated by 20% in the one-kidney model. The two-kidney model showed

no significant increase in ileal blood flow. Combined ileal blood flow data from both models of hypertensive dogs resulted in a statistically significant 17% increase in blood flow in the early hypertensive stage. Calculated ileal vascular resistance of both hypertensive models was not significantly different from the normotensive control. This data suggests that a portion of the elevated cardiac output passes through the mesenteric vascular bed during the early stage of hypertension. Since ileal vascular resistance was normal, the authors suggested that passive vasodilation does not occur despite elevated intravascular distending pressures. This finding suggests decreased vascular distensibility in the hypertensive dogs.

To date, two studies assessing regional splanchnic hemodynamic changes during chronic renovascular hypertension are available. Bralet et al. (1973) measured the fractional distribution of cardiac output (^{86}Rb) in normotensive and chronic one-kidney Goldblatt hypertensive rats. Compared to normotensive control values, chronic hypertension was associated with a normal fraction of cardiac output received by the liver, spleen, stomach and small intestine while the colon received an increased fraction of cardiac output during hypertension.

These findings were partially supported by Flohr et al. (1976) who measured the fractional distribution of cardiac output (radioactive particle dispersion technique) in chronic one-kidney and two-kidney Goldblatt hypertensive rats. Compared to normotensive control values, the one-kidney hypertensive model exhibited a normal fraction of cardiac output received by the spleen and an increased fraction of cardiac output received by the colon. These results support Bralet et al. (1973). In contrast, Flohr et al. (1976) reported that chronic one-kidney

Goldblatt hypertension is associated with increased fractions of cardiac output received by the liver, stomach and small intestine while the adrenal gland received a normal fraction of cardiac output. The results of this study also suggest that the pattern of redistribution of cardiac output may also be dependent upon the model of renal hypertension studied. Compared to normotensive values, both models of chronic renal hypertension received normal and increased fractions of cardiac output in the adrenal gland and colon respectively. In contrast to the one-kidney Goldblatt, compared to control values the two-kidney model exhibited decreased fractions of cardiac output by the liver, spleen and pancreas while the fraction of cardiac output to the stomach and small intestine remained unchanged.

ROLE OF THE RENIN-ANGIOTENSIN SYSTEM

EARLY RENOVASCULAR HYPERTENSION

Bianchi et al. (1970) measured plasma renin leves in the conscious, unilaterally nephrectomized dog after renal artery constriction (one-kidney Goldblatt model). Plasma renin levels, systemic blood pressure and total peripheral resistance increased sharply during the first two hours post-constriction. Plasma renin levels gradually returned to normal during 1-14 days following renal artery constriction, total peripheral resistance declined but systemic arterial blood pressure remained elevated. The authors suggested that hypertension might be produced initially by increased plasma renin and hence angiotensin II levels.

Additional strong evidence that angiotensin II is responsible for the initiation of renovascular hypertension was provided by Miller et al. (1972). Injection of a nonapeptide inhibitor of converting enzyme into unilaterally nephrectomized conscious dogs prevented hypertension which usually occurs after renal constriction. Inhibiting the converting enzyme was effective for only four days following renal artery constriction. After this period treatment with converting enzyme inhibition did not prevent the development of chronic hypertension.

Angiotensin II may also play a role in increasing cardiac ouput during the initial days following renal artery stenosis. Angiotensin II stimulates adolesterone production and hence increased intravascular fluid volume in the one-kidney Goldblatt model (Oparil et al. (1974).

Angiotensin II also appears to act directly on the central nervous system. Injection of angiotensin II is pharmacologic concentrations into

the arterial supply to the cross-perfused head of anesthetized dogs causes tachycardia and blood pressure elevation (Bickerton et al. 1961).

Scroop et al. (1971) suspected the central site of action of angiotensin II to be in the area postrema of the medulla since this region lacks a blood-brain barrior. Systemic arterial blood pressure was measured during intravenous injections of angiotensin II and norepinephrine in anesthetized dogs. Ablation of the area postrema significantly reduced systemic pressor responses to angiotensin II but not to norepinephrine.

CHRONIC RENOVASCULAR HYPERTENSION

The role of the renin-angiotensin system in the maintenance of chronic renovascular hypertension is not well established. Since angiotensin II inhibitors are effect only during the first four days following renal artery constriction, and renin is only elevated during the initial onset of the early stage of hypertension, the possible role of the renin-angiotensin system in maintenance of the chronic (more than six weeks) stage of renovascular hypertension remains unanswered. However possible increased vascular sensitivity to normal circulating levels of angiotensin II during the chronic stage has been suggested (Bianchi et al. 1970).

THE EFFECT OF ANGIOTENSIN II ON REGIONAL SPLANCHNIC BLOOD FLOW

The very potent vasoconstrictor angiotensin II is elevated during the first week following renal artery constriction or kidney wrapping in one-kidney and two-kidney models of Goldblatt and perinephritic hypertension respectively. It is also elevated for a period following severe hemorrhage. While there have been many investigations of the effect of angiotensin II on abdominal organs, a compartmental regional blood flow study of the response of the gastrointestinal tract to intravenous infusion of angiotensin II does not exist.

Abell and Page (1942) first described the selective arteriolar vasoconstriction produced by natural angiotensin II. They implanted transparent moat chambers to allow direct microscopic examination of vascular changes in the ears of unesthetized rabbits. They found that with moderate doses of angiotensin, only arterioles constricted while venules and capillaries were uneffected.

Texter et al. (1964) studied the direct effects of several vasoactive agents on the segmental resistance of the mesenteric and portal circulation in dogs. They injected angiotensin II, l-epinepherine, levartenol, vasopressin, acetylcholine, methacholine, histamine and seratonin into the perfused superior mesenteric artery. It was reported that the mesenteric vasculature was more sensitive to vasoconstrictor than to vasodilator substances. Angiotensin II and vasopressin were the most potent vasoconstrictors and caused an increased resistance which was localized to the small vessel segment.

Using in vitro techniques, Bohr and Uchida (1967) demonstrated the response of canine mesenteric arterial vascular smooth muscle to

different doses of angiotensin II. Helical strips of vascular smooth muscle were mounted in a bath of physiological salt solution at 37°C. Vascular responses to angiotensin were measured using a Grass displacement transducer. They reported that the threshold concentration of angiotenin required for tension development was 1-3 μg/L while maximum response was obtained with a concentration of 100 μg/L. When mesenteric vascular smooth muscle was treated with a high concentration of angiotensin, the tension at first increased rapidly, and reached a maximum in one to two minutes. After that period the tissue preparation gradually relaxed and had negligible tension remaining at the end of five minutes. If angiotensin was rinsed from the bath and the tissue allowed to recover for a period of 20 minutes, reexposure of the tissue to the same concentration of angiotensin produced tension development which was only one-third that of the original response. The authors proposed that these results were due to tachyphylaxis.

These findings were supported by Shehadeh et al. (1969) who studied the effects of low and high pharmacological doses of angiotensin II on intestinal blood flow and motility in the dog. Superior mesenteric artery blood flow and intraluminal jejunal pressure were measured using electromagnetic flow meters and fluid-filled baboons respectively. The low dose of angiotensin was infused into the superior mesenteric artery at a rate of 0.05 μg/Kg/min for a period of seven minutes. The infusion rate was then increased to 1.0 μg/Kg/min for a second seven minute period. Vasoconstriction of the mesenteric vascular bed and a decrease in superior mesenteric artery blood flow occurred in a monophasic response which was maximal during the first two minutes while the low dose was infused. During the minutes 2-7 blood flow

increased but remained lower than control values. When the dose of angiotensin was increased during the minutes 7-14, blood flow did not change. Angiotensin increased jejunal motility during the entire duration of the experiment.

To date, mechanisms that explain the effect of angiotensin II on gastrointestinal motility in the canine are lacking. However Khairallah and Page (1961) described possible mechanisms for the contractile response to angiotensin in the isolated guinea pig ileum. Visceral smooth muscle contraction was monitored using a frontal writing lever having fourfold magnifications. Prior to treatment with angiotensin, the guinea pig ileum was exposed to atropine and morphine which are known inhibitors of acetylcholine release at postganglionic parasympathic nerve endings. They found that these drugs inhibited the response of visceral smooth muscle to angiotensin as ileal motility was decreased by about 60-70%. These results suggest that angiotensin II increases GI motility primarily through an indirect manner, by increasing acetylcholine release at postganglionic parasympathetic nerve endings in the myenteric plexus of Auerbach and plexus of Meissner.

SUMMARY

Currently available evidence suggests that the use of the radioactive microsphere dispersion technique in chronic vascular research is a feasible and valuable method.

The responses of regional vascular beds to an extended period of increased cardiac output during one-kidney and two-kidney Goldblatt hypertension are quite variable. Investigators tend to agree that vascular resistance in the kidney and cerebral vascular beds rises proportionately with the general rise in total peripheral resistance during the chronic hypertensive state. They also tend to agree that during chronic renal hypertension, the increase in vascular resistance in the heart and colon is proportionately less than the rise in total peripheral resistance (hence increased blood flow). Studies of hemodynamics in other vascular beds are conflicting. It may be that the model of Goldblatt hypertension (one-kidney or two-kidney) used may also effect the results.

A first purpose of this study is to investigate the hemodynamics of the splanchnic circulation during chronic one-kdieny perinephritic hypertension and to assess possible hemodynamic changes within the mucosal, submucosal and muscularis (muscle + serosal) layers of the gastrointestinal tract.

Generalized vasoconstriction with an associated decrease in superior mesenteric arterial blood flow following the administration of angiotensin II is a consistant finding. In the canine and guinea pig angiotensin causes contraction of visceral smooth muscle resulting in an increased gastrointestinal motility. To date, the hemodynamic effect of angiotensin

II on the three layers of the canine gastrointestinal tract is lacking.

A second purpose of this study is to measure the hemodynamic response of various abdominal organs and the mucosal, submucosal and muscularis layers of the gastrointestinal tract to the intravenous infusion of low and high pharmacological doses of angiotensin II.

METHODS

SERIES I. CHRONIC RENAL HYPERTENSION

Healthy, conditioned male mongrel dogs (n=7) weighing 24 ± 1 Kg were trained to lie quietly during femoral artery punctures for blood pressure measurements, which were conducted once each week throughout the study. Animals exhibiting resting mean arterial blood pressures of less than 140 mmHg on two separate occasions were accepted for surgical induction of hypertension. These criteria were established by Overbeck (1971). Conditioning included vaccination against rabies, distemper, leptospirosis, hepatitis, and examination of the stool for parasites. The dogs were maintained on a diet of standard dog chow (Wayne Dog Food., Allied Mills Inc., Chicago, IL) pre and post-operatively and water *ad libitum*.

SURGICAL PREPARATION FOR INJECTION OF MICROSPHERES INTO NORMOTENSIVE DOGS

Regional splanchnic blood flows were calculated using the radioactive particle distribution technique (Wagner *et al*. (1969). Animals fasted for 24 hours were anesthetized with sodium pentobartibal, (25 mg/Kg IV) and a cuffed endotracheal tube was inserted. Supplemental doses of sodium pentobarbital (50-100 mg) were given later if necessary, but no measurements were made during the first 30 minutes following administration. Mechanical ventilation was maintained with a Harvard positive pressure respiration pump (Model No. 607 Dover, Mass.). Respiratory rate was held constant at ten per minute, and tidal volume adjusted according to body weight. Room temperature was maintained at 23°C throughout all experimental procedure.

Anesthetized animals were placed in a right lateral recumbency and

held in position by towel clamps attached to the webbing of the respective limbs. Under sterile conditions, a polyethylene cannula (PE 240) filled with normal saline was inserted into the abdominal aorta via the right femoral artery. This cannula was used for monitoring mean systemic arterial pressure when connected to a Stratham pressure transducer (Model 23Gb), obtaining arterial blood samples for analysis, and for reference blood samples collection during microsphere injection. A similar cannula, connected to a second Stratham pressure transducer, (Model 23 Gb) was inserted into the left ventricle via the left common carotid artery for the documentation of intraventricular placement and injections of microspheres. Pressure recordings were made using a Sanborn direct writing recorder (Model No. 7700).

PREPARATION AND DESCRIPTION OF STOCK SOLUTIONS OF MICROSPHERES

Three stock solutions of microspheres 15 $\pm$ 5 μ in diameter (3M Company, St. Paul, Minn.) were labeled with either ^{85}Strontium, ^{51}Chromium or ^{141}Cerium and suspended in a 10% dextran solution)1 millicurie/10 ml) which contained one drop of Tween 80 polyethylene sorbitan mono-oleate) to prevent microsphere aggregation. The specific activities for these isotopes were 13.73 mCi/gm for ^{85}Sr, 10.42 mCi/gm for ^{51}Cr, and 7.61 mCi/gm for ^{141}Ce. One milligram of the microspheres contained approximately 440,000 microspheres. Each dog received one ml of each type of microsphere which represented an injection of approximately 3.2 X 10^6 microspheres with the ^{85}Sr label, 4.4 X 10^6 microspheres with the ^{51}Cr label and 5.7 X 10^6 microspheres with the ^{141}Ce label.

INJECTION OF CONTROL (CHRONIC) MICROSPHERES INTO NORMOTENSIVE DOGS

One ml of preagitated, carbonized microspheres labeled with ^{85}Sr (15 $\pm$ 5 μ; 3M Company, St. Paul, Minn.) was withdrawn from the stock solution using a 3 ml syringe. This suspension was placed into a glass tube which contained 2 ml of a 20% dextran solution and mixed thoroughly using an ultrasonic sonifier cell disruptor (Branson Instrument Co., Long Island, NY) to achieve uniform dispersion of the microspheres. The microsphere suspension was then drawn into a 3 ml syringe and connected to the left ventricular cannula. Immediately prior to injection, mean systemic arterial pressure was recorded and an arterial blood sample was taken for analysis and recording of pO_2, and pCO_2 using a radiometer blood gas analyzer. Blood hematocrit was determined using a centrifuged heparinized capillary tube. The microspheres were then injected as a bolus into the left ventricle and flushed with 5-8 ml of saline. At the time of injections, a three minute reference blood sample was withdrawn from the abdominal aorta into a heparinized syringe with a Harvard withdrawal pump at a rate of 3.88 ml/min. The reference blood was then divided into 12 gamma counting tubes (5 ml capacity) at 1 ml/tube. The blood was frozen for later counting. The cannulae were removed, and the arteries were repaired with 7-0 cardiovascular suture. The incisions were closed with silk and ventafil suture.

SURGICAL INDUCTION OF PERINEPHRITIC HYPERTENSION

Immediately following the microsphere injection, perinephritic hypertension (Page 1939) was produced surgically. A left flank incision was made and the left kidney was exposed using a retroperito-

neal approach. The kidney was dissected free from it's perirenal fascia and fat and wrapped in silk. The silk-wrapped kidney, in turn, was wrapped in Saran Wrap to minimize the amount of adhesion between the kidney and the surrounding tissues. It was then restored to it's normal anatomical position and the wound closed by suturing tissues by layer. Procanine penicillin (60,000 units) and steptomycin (0.5 g) were administered intramuscularly for 3 days postoperatively. One week following the first surgery, a contralateral nephrectomy was performed under sodium pentobarbital anesthesia (25 mg/Kg IV) and sterile conditions. Animals were again treated 3 days postoperatively with antibiotics as described above. Aniamls were then maintained for a period of six weeks following the first documentation of sustained arterial hypertension (> 140 mmHg mean arterial pressure) recorded via direct puncture of the femoral artery in the conscious dog.

INJECTION OF MICROSPHERES DURING THE CHRONIC HYPERTENSIVE STATE

Following a six week period of documented hypertension the terminal study was performed. Animals fasted for 24 hours were anesthetized with sodium pentobarbital (25 mg/Kg IV) and a cuffed endotracheal tube was inserted. Similar supplemental doses were administered under the same restrictions as mentioned above. Room temperature was held constant at 23°C. Ventilation was maintained by a Harvard positive pressure respiration pump, at the same settings used during the initial (^{85}Sr) microsphere injection. A polyethylene cannual (PE 240) containing normal saline was inserted into the abdominal aorta via the right femoral artery for measurement of mean systemic arterial pressure, arterial blood gas sampling, and for withdrawal of the 3 minute reference

blood sample. A different procedure was used to enter the left ventricle of the heart for the 2nd and 3rd microspheres injections, prior surgery resulted in occlusion of the left common carotid artery. Unsuccessful attempts at placing the cannula into the ventricle via the right common carotid and brachial arteries in an unrelated group of practice dogs necessitated opening the left side of the chest in the fourth intercostal space for direct left ventricular puncture. Ely (1977) showed that cerebral blood flow was not effected by opening the thoracic cavity. The left common carotid artery, which was almost always occluded, was re-isolated and clamped to insure that no blood was flowing in this artery (as was the case when the artery was cannulated during the initial injection). A polyethylene tube (PE 240), attached to a pressure transducer and equipped with a 3-way stopcock and 13 gauge needle, was preparted for left ventricular puncture, documentation of intraventricular position, and injection of the second microsphere respectively.

After the dogs stabilized, arterial blood gases were measured using a radiometer. The respiratory rate was either increased or decreased until the arterial pCO_2 was identical to the pCO_2 recorded during the initial microspheres injection. When the initial pCO_2 was reached, a suspension of either ^{141}Ce or ^{51}Cr (15 $\pm$ 5 μ; 3M Company) was prepared as before, the selection being random. The syringe containing the microsphere suspension was then inserted into the 3-way stopcock and left ventricular puncture was performed. When intraventricular position was documented and mean systemic pressure was recorded, the microsphere suspension was injected into the left ventricle and a 3 minute reference blood samples was withdrawn at a rate of 3.88 ml/min

using a Harvard withdrawal pump. The reference blood sample was placed into gamma counting tubes as before and frozen. The animals, which now contain both ^{85}Sr microspheres to measure normotensive regional blood flows and either ^{141}Ce or ^{51}Cr microspheres to measure hypertensive regional blood flows were sacrificed by sodium pentobarbital overdose.

TISSUE COLLECTION AND MEASUREMENT OF RADIOACTIVITY

The abdominal cavity was opened through a ventral midline incision and the internal organs were exposed. Duplicate tissue samples were taken from the adrenal gland, spleen, liver, head of the pancreas, tail of the pancreas, fundus of the stomach, duodenum at the level of the pancreatic duct, proximal jejunum, terminal ileum and descending colon.

The segments of the intestinal tract were cut longitudinally and the lumens were exposed. All samples were washed with cold running tap water. Any external fat, fascia or mesentery which remained on the tissues were trimmed off. Each sample from the intestinal tract was then separated into three portions, i.e., the mucosa, submucosa, and the muscle plus serosa (muscularis). This dissection was accomplished by scraping the mucosa and muscularis from the submucosa with a blunt instrument. Each tissue sample, in duplicate, was placed into a preweighted plastic counting tube. The actual weight of each tissue sample was calculated after reweighing the counting tube. The tubes containing reference blood and tissues samples were placed in a Searle (Model 1185) gamma counter, and counted at the following settings:

ISOTOPE	BASE	WINDOW	ATTENUATION
^{85}Sr	464	100	8
^{141}Ce	380	400	2
^{51}Cr	preprogrammed setting by Searle Co.		

The raw counts obtained from the Searle gamma counter were entered into a Wang Model 700 preprogrammed computer which removed overlap of the energy peaks of the three different isotopes which occurred between counting channels.

CALCULATION OF RESULTS

Regional splanchnic blood flow (rSBF) was calculated by dividing counts per minute (cpm) per gram of tissue by counts per minute of the three minute reference blood sample, and multiplying by the reference blood sample withdrawal rate (RBWR = 3.88 ml/min).

$$\text{ml/min/gm rSBF} = \frac{\text{cpm/gm tissue}}{\text{cpm reference blood}} \times \text{RBWR}$$

Regional blood flows were calculated for each tissue sample in the normotensive and hypertensive state. The regional blood flows of duplicate tissue samples were then averaged into regional blood flows (ml/min/100 gm). Regional splanchnic vascular resistance (rSVR) was calculated by dividing the mean systemic arterial pressure (Pa) at the time of microsphere injection by the average regional blood flow (rSBF), (rSVR = Pa/rSBF).

An average blood flow was calculated for each portion of the wall and total wall blood flow was calculated as the weighted average of the three layers. The weight distribution of the three layers is taken from the work of Yu *et al*. (1975). Total wall vascular resistance was

calculated by dividing total wall blood flow by systemic arterial blood pressure.

SERIES II. THE EFFECT OF ANGIOTENSIN II ON REGIONAL SPLANCHNIC BLOOD FLOW

SURGICAL PROCEDURE

Male mongrel dogs (n=8), weighing 22 $\pm$ 2 Kg were fasted for 24 hours prior to the experiment. The animals were anesthetized with sodium pentobarbital (25 mg/Kg IV) and a cuffed endothachial tube was inserted. Artifical ventilation was maintained with a Harvard positive pressure respirator. Respiratory rate was set at 15 per minute and the tidal volume was adjusted according to body weight. The animals were positioned in a right lateral recumbency. A polyethylene cannula (PE 240) was inserted into the abdominal aorta via the right femoral artery for the withdrawal of reference blood samples (Harvard withdrawal pump, 3.88 ml/min) and to obtain arterial blood for analysis of pO_2, pCO_2, and pH (Radiometer blood gas analyzer). A similar cannula was inserted into the left common carotid artery for the measurement of mean arterial blood pressure. Pressures were measured with Stratham pressure transducers (Model 23 Gb) and a Sanborn direct writing recorder (Model 7700). A similar cannula connected to a Stratham pressure transducer (Model 23 Gb) and equipped with a 3-way stopcock and a 13 gauge needle was prepared for the documentation of left ventricular placement via puncture would of thoracic wall and myocardium and for injection of microspheres. A fourth similar cannula was placed into the right femoral vein for drug infusions. The animals were allowed to stabilize, and arterial blood gases (pO_2, pCO_2) and pH were measured and recorded. The pCO_2 and room temperature were held constant throughout the experiment.

DESCRIPTION AND PREPARATION OF STOCK MICROSPHERES

The microspheres used in Series II were again labeled with ^{85}Sr, ^{51}Cr and ^{141}Ce and were suspended in a 10% soluation of dextran (3M Company, St. Paul, Minn.). The microspheres had diameters of 13.7 $\pm$ 1.0, 13.6 $\pm$ 0.7, 14.1 $\pm$ 0.8 respectively and specific activities of 11.89 mCi/gm, 40.76 mCi/gm, and 8.57 mCi/gm respecitively. One drop of Tween 80 was added to each stock solution to prevent aggregation. One milligram of each stock solution contained approximately 440,000 microspheres. Each animal received an injection of 0.9 ml of each stock solution which represented 3.3 X 10^6 microspheres labeled with ^{85}Sr, 9.9 X 10^5 microspheres labeled with ^{51} Cr label and 4.6 X 10^6 microspheres with the ^{141}Ce label.

EXPERIMENTAL PROCEDURE

The experimental procedure for Series II consisted of three microsphere injections to measure regional splanchnic blood flow changes that resulted from the administration of angiotensin II amide (microsphere partical dispersion technique). The first micorsphere injection measured control regional splanchnic blood flow at normal (anesthetized) blood pressure (approximately 130 mmHg). The control microsphere injection was randomized between ^{85}Sr and ^{141}Ce. The procedures used in Series II for microsphere preparation, injection and reference blood sample withdrawal were identical to the procedures used in Series I.

After the first microsphere injection was completed a low pharmacological dose of angiotensin II amide (10 µg/ml) was infused into the femoral vein (Harvard infusion pump at a rate of 0.5 ml/min for approximately 5 minutes to achieve a mean systemic arterial pressure in the

approximate range of 170-180 mmHg. This low pharmacological dose of angiotensin II was approximately 0.05 µg/Kg/min. When this pressure range was achieved, a second microsphere (^{51}Cr) was inected and a reference blood sample was collected.

The ^{51}Cr labeled was used consistently as the second microsphere injection because this isotope had a specific activity which was much higher than the ^{85}Sr and ^{141}Ce isotopes. Therefore, each 0.9 ml of stock microspheres contained a smaller number of microspheres (990,000). This reduced number of injected microspheres is a possible source of error in blood flow measurement, so this isotope was used to measure blood flow that was felt to be a lesser importance.

Following the completion of the second microsphere injection, the infusion rate of angiotensin II amide was increased to 2.0 ml/min for approximately 5 minutes to obtain a mean systemic arterial pressure of 200 + mmHg. This high pharmacological dose of angiotensin was approximately 1.0 µg/Kg/min. When this pressure was reached, a third microsphere injection was made and a reference blood sample was collected.

The animals were then sacrificed and duplicated tissue samples were taken from the adrenal gland, head of the pancreas, tail of the pancreas, fundus of the stomach, duodenum at the level of the pancreatic duct, proximal jejunum, terminal ileum and descending colon as before. The samples were prepared weighted and the radioactivity measured in the same manner as described in Series I.

CALCULATION OF RESULTS

Average regional splanchnic blood flow and regional vascular resistance was calculated in the same manner described in Series I and

in the following equations.

$$rSBF = \frac{\text{cpm/gm tissue}}{\text{cpm reference blood}} \times RBWR$$

$$rSVR = \frac{Pa}{rCBF}$$

COMPARISONS MADE AND STATISTICAL ANALYSIS OF THE RESULTS

The present study consists of Series I and Series II. Series I measured the effect of chronic perinephritic hypertension on regional splanchnic hemodynamics. Values obtained from the microsphere injection at time zero which measured normotensive control blood flow will be referred to as Chronic Control values since they remained within the animals for an eight-week period during the development of chronic hypertension. Values obtained from the microsphere injection after the eight-week period during the chronic hypertensive state will be referred to as Chronic Hypertension values. Series II of the present study measured the effect of low and high pharmacological doses of intravenously infused angiotensin II on regional splanchnic hemodynamics. Values obtained from the initial microsphere injection which measured control blood flow prior to the administration of angiotensin will be referred to as Acute Control values. The second and third microsphere injection measured regional splanchnic blood during low and high doses of angiotensin respectively.

1. Chronic Control values of Series I were compared to Chronic Hypertension values for Series I using a Student's t-test modified for paired replicates. A "p" value of less than 0.05 was considered significant.

2. Acute Control values of Series II were compared to Chronic Control values of Series I using a Student's t-test. A "p" value less than 0.05 was considered significant.

3. Acute Control values of Series II were compared to Chronic Hypertension values of Series I using a Student's t-test. A "p" value less than 0.05 was considered significant.

4. Acute Control values of Series II were compared to values obtained during low and high doses of angiotensin in Series II using a Student's t-test modified for paired replicates. A "p" value of less than 0.05 was considered significant.

RESULTS

SERIES I. CHRONIC PERINEPHRITIC HYPERTENSION

Average values for unanesthetized mean systemic arterial blood pressure in the normotensive control and at each week following surgical induction of hypertension are shown in Figure 1. The average unanesthetized mean arterial blood pressures were significantly greater than control (192 $\pm$ 4 mmHg), at 2 weeks (166 $\pm$ 5 mmHg), 3 weeks (177 $\pm$ 7 mmHg), 4 week (181 $\pm$ 10 mmHg), 6 weeks (185 $\pm$ 12 mmHg), and 8 weeks (176 $\pm$ 9 mmHg), following induction of hypertension by 29%, 37%, 40%, 43% and 36%, respectively ($p < 0.05$).

CHRONIC CONTROL VALUES (SERIES I) VS. CHRONIC HYPERTENSION VALUES (SERIES I)

Average values for regional splanchnic blood flow before and after the development of chronic perinephritic hypertension are shown in Table 1. During chronic hypertension blood flow was significantly increased ($p < 0.05$) in the duodenum mucosa by 970%, duodenum submucosa by 161%, jejunum mucosa by 1080%, jejunum submucosa by 96%, ileum mucosa by 154%, ileum muscularis by 234%, colon submucosa by 236% and colon muscularis by 204% and decreased significantly ($p < 0.05$) in the liver by 108%.

Average values for regional splanchnic vascular resistance before and after the development of chronic perinephritic hypertension are shown in Table 2. During chronic hypertension resistance was significantly decreased ($p < 0.05$) in the duodenum mucosa by 1040%, ileum mucosa by 156%, ileum submucosa by 141% and colon muscularis by 218% and significantly increased ($p < 0.05$) in the stomach submucosa by 264% and in the stomach muscularis by 218%.

Abnormally low mucosal blood flows values (Table 1) and abnormally

high mucosal vascular resistance values (Table 2) of the chronic control dogs suggested that the validity of these data must be questioned since the ability of microspheres to remain within the splanchnic circulation for an eight-week period has not been documented. This necessitated the comparison of acute control values (Series II) to the chronic control data of Series).

ACUTE CONTROL VALUES (SERIES II) VS. CHRONIC CONTROL VALUES (SERIES I)

Average values for regional splanchnic blood flow of the acute control dogs and chronic control dogs were shown in Table 1. Average blood flow values of the chronic control dogs were significantly lower ($p < 0.05$) in the duodenum mucosa by 823%, jejunum mucosa by 1062% and ileum mucosa by 210% and significantly higher ($p < 0.05$) in the pancreas head by 66%, pancreas tail by 84%, liver by 70%, stomach muscularis by 1297% and duodenum muscularis by 137%.

Average values of regional splanchnic vascular resistance of the acute control dogs and chronic control dogs are shown in Table 2. Average resistance values of the chronic control dogs were significantly higher ($p < 0.05$) in the duodenum mucosa by 1246%, jejunum mucosa by 6958% and ileum mucosa by 220% and significantly lower ($p < 0.05$) in the stomach submucosa by 1080%, stomach muscularis by 93%, and duodenum muscularis by 120%.

Since possible technical error or unknown phenomena was thought to be present in blood flow and resistance values of the chronic control dogs, the decision was made to compare chronic hypertensive values to the seemingly more reliable acute control values. The values of the acute control dogs were in better agreement with values reported by Chou and Grassmick(1978).

ACUTE CONTROL VALUES (SERIES II) VS. CHRONIC HYPERTENSIVE VALUES (SERIES I)

Chronic hypertensive values were compared to data of the more reliable acute control dogs in all of the following comparisons concerned with regional splanchnic hemodynamic changes that occur during chronic one-kidney perinephritic hypertension. In Figures 2A, 2B, 3 and 4, open bars denote values of the Acute Control dogs, the cross hatched bars denote values of the Chronic Hypertensive dogs.

Average mean arterial blood pressure was significantly greater ($p < 0.05$) in the chronic hypertensive dogs (164 $\pm$ 10 mmHg) than the acute control dogs (137 $\pm$ 5 mmHg) by 20%.

TOTAL WALL BLOOD FLOW AND TOTAL WALL VASCULAR RESISTANCE DURING CHRONIC HYPERTENSION

Average values for total wall blood flow in the stomach, duodenum, jejunum, ileum and colon and total wall vascular resistance in the same regions are shown in Figures 2A, and 2B respectively. There was no significant difference in average total wall blood flow or vascular resistance between the values of the six week hypertensive group and the acute normotensive control group in any region ($p < 0.05$).

REGIONAL SPLANCHNIC BLOOD FLOW AND VASCULAR RESISTANCE DURING CHRONIC HYPERTENSION

Average values for the blood flow of various abdominal organs of the acute control dogs of Series II and the six week chronic hypertensive dogs are expressed in Table 2. Blood flows of the chronic hypertensive dogs ($p < 0.05$) in any region studied (adrenal gland, head of the pancreas, tail of the pancreas, spleen and liver).

Average values for regional blood flows within the gastrointestinal

tract are shown in Figure 3. Average blood flows of the hypertensive dogs increased significantly ($p < 0.05$) in the stomach submucosa by 320%, duodenum submucosa by 309%, duodenum muscularis by 130%, jejunum submucosa by 184%, jejunum muscularis by 212%. Regional blood flows were not significantly different ($p < 0.05$) from control in the stomach mucosa, stomach muscularis, duodenum mucosa, jejunum mucosa, ileum mucosa, ileum muscularis, colon mucosa and colon submucosa.

Average values for the resistance of various abdominal organs of the acute control dogs of Series II and the chronic hypertensive dogs are expressed in Table 3. Resistance values of the chronic hypertensive dogs were not significantly different from the acute control dogs ($p < 0.05$) in any region studied (adrenal gland, head of the pancreas, tail of the pancreas, spleen and liver).

Average values for regional vascular resistance within the gastrointestinal tract are shown in Figure 4. Regional splanchnic vascular resistance values of the hypertensive dogs were significantly lower ($p < 0.05$) than the values of the acute control dogs in the duodenum muscularis, jejunum submucosa, jejunum muscularis and colon submucosa by 106%, 199%, 136%, and 177% respectively. Regional vascular resistance values of chronic hypertensive dogs were not significantly different ($p < 0.05$) from values of acute control dogs in the stomach mucosa, stomach submucosa, stomach muscularis, duodenum mucosa, duodenum submucosa, jejunum mucosa, ileum mucosa, ileum submucosa, ileum muscularis, colon mucosa, and colon muscularis.

SERIES II: SPLANCHNIC VASCULAR RESPONSES TO ANGIOTENSIN II

The intravenous infusion of angiotensin II caused mean aortic blood pressure to rise significantly ($p < 0.05$) from control 136 $\pm$ 5 mmHg) during the infusion of a low pharmacological dose (1976 $\pm$ mmHg) and during the infusion of a high pharmacological dose (202 $\pm$ 5 mmHg) by 29% and 49% respectively.

In Figures 5, 6, 7, 8A, 8B and 8C open bars denote values of the acute control dogs before the infusion of angiotensin, cross hatched bars denote values during the infusion of a low dose of angiotensin and dotted bars denote values during the infusion of a high dose of angiotensin.

TOTAL WALL BLOOD FLOW AND VASCULAR RESISTANCE DURING ANGIOTENSIN II INFUSION

Average values for total wall blood flows of the stomach, duodenum, jejunum, ileum and colon are shown in Figure 5. When a low dose of angiotensin was infused total wall blood flows were decreased significantly ($p < 0.05$) from control in the stomach by 406%, duodenum by 177%, jejunum by 153%, ileum by 135% and colon by 60%. When the infusion rate of angiotensin was increased such that a high pharmacological dose was administered, total wall blood flows were decreased significantly ($p < 0.05$) from control in the stomach by 534%, duodenum by 198%, jejunum by 170%, ileum by 134% and colon by 46%. Total wall blood flows during the infusion of a low dose of angiotensin were not significantly different ($p < 0.05$) from total wall blood flows during the infusion of a high dose of angiotensin in any region of the gastrointestinal tract.

Average values for total wall vascular resistances of the stomach,

duodenum, jejunum, ileum and colon are shown in Figure 6. When a low dose of angiotensin was infused, total wall vascular resistances were increased significantly ($p < 0.05$) from control in the stomach by 338%, duodenum by 238%, jejunum by 273%, ileum by 237% and colon by 120%. When the infusion rate of angiotensin was increased such that a high pharmacological dose was administered, total wall vascular resistances were increased significantly ($p < 0.05$) from control in the stomach by 650%, duodenum by 360%, jejunum by 334%, ileum by 318% and colon by 170%. Total wall vascular resistances during the high dose of angiotensin were not significantly different ($p < 0.05$) from total wall vascular resistances during the low lose of angiotensin in the duodenum, jejunum ileum, and colon. However in the stomach, total wall vascular resistance during the high dose was significantly greater ($p < 0.05$) than total wall vascular resistance during the low dose of 71%.

REGIONAL SPLANCHNIC BLOOD FLOW AND VASCULAR RESISTANCE DURING ANGIOTENSIN II INFUSION

Average values for the blood flow of various abdominal organs during control and during low and high pharmacological doses of angiotensin II are shown in Table 4. Blood flow was decreased significantly ($p < 0.05$) from control during the intravenous infusion of a low dose of angiotensin in the adrenal gland by 86%, head of the pancreas by 157%, tail of the pancreas by 140%, and spleen by 75%. During the infusion of a low dose of angiotensin blood flow was not significantly different from control ($p < 0.05$) in the liver. When the infusion rate was increased such that a high pharmacological dose of angiotensin was administered, blood flow decreased significantly from control ($p < 0.05$) in the head of the pancreas by 416%, and tail of the pancreas by 318%.

During the infusion of a high dose of angiotensin blood flow was not significantly different from control ($p < 0.05$) in the adrenal gland, spleen and liver. Blood flow measured during the infusion of a high dose of angiotensin decreased significantly ($p < 0.05$) from blood flow measured during the infusion of a low dose of angiotensin in the head of the pancreas and tail of the pancreas by 101% and 74% respectively, while in the adrenal gland, spleen and liver blood flow remained unchanged ($p < 0.05$).

Average values for regional splanchnic blood flow during control and during infusions of low and high pharmacological doses of angiotensin II are shown in Figure 7. During the infusion of a low dose of angiotensin blood flow decreased significantly from control ($p < 0.05$) in the stomach mucosa by 473%, stomach submucosa by 146%, duodenum mucosa by 211%, duodenum submucosa by 44%, jejunum mucosa by 172%, jejunum submucosa by 143%, ileum mucosa by 130%, ileum submucosa by 148%, colon mucosa by 85%, and colon submucosa by 41%. During the low dose of angiotensin regional blood flow did not change significantly ($p < 0.05$) from control in the stomach muscularis, jejunum muscularis, ileum muscularis and colon muscularis. Regional splanchnic blood flow increased significantly ($p < 0.05$) from control during the infusion of a low dose of angiotensin in the duodenum muscularis by 122%. During the infusion of a high pharmacological dose of angiotensin blood flow was decreased significantly ($p < 0.05$) from control in the stomach mucosa by 625%, stomach submucosa by 89%, stomach muscularis by 107%, duodenum mucosa 250%, duodenum submucosa by 56%, jejunum mucosa by 199%, jejunum submucosa by 110%, ileum mucosa by 147% and ileum submucosa by 87%. Regional blood flows were not significantly different ($p < 0.05$) from

control during the infusion of a high dose of angiotensin in the ileum muscularis, colon mucosa, colon submucosa and colon muscularis. Regional splanchnic blood flow was increased significantly ($p < 0.05$) from control during the infusion of a high dose of angiotensin in the duodenum muscularis by 177% and jejunum muscularis by 68%. Regional blood flow during the infusion of a high dose of angiotensin decreased significantly ($p < 0.05$) from regional blood flow measured during the infusion of a low dose of angiotensin in the stomach submucosa by 44%. Regional splanchnic blood flows measured during the infusion of a high dose of angiotensin were not significantly different ($p < 0.05$) from regional blood flows measured during the infusion of a low dose of angiotensin in any of the other regions studied.

Average values for the vascular resistance of various abdominal organs during control and during the infusion of low and high pharmacological doses of angiotenin II are shown in Table 5. Vascular resistance was increased significantly ($p < 0.05$) from control during the intravenous infusion of a low dose of angiotensin in the adrenal gland by 167%, head of the pancreas by 269%, tail of the pancreas by 207%, and spleen by 105%. During the infusion of a low dose of angiotensin vascular resistance was not significantly different from control ($p < 0.05$) in the liver. When the infusion rate was increased such that a high pharmacological dose of angiotensin was administered, vascular resistance increased significantly from control ($p < 0.05$) in the adrenal gland by 198%, head of the pancreas by 734%, tail of the pancreas by 550%, spleen by 151% and liver by 146%. Vascular resistance measured during the infusion of a high dose of angiotensin increased significantly ($p < 0.05$) from vascular resistance measured

during the infusion of a low dose of angiotensin in the head of the pancreas and tail of the pancreas by 126% and 112% respectively. There were no significant differences ($p < 0.05$) between vascular resistances during the infusion of a high dose of angiotensin and during the infusion of a low dose of angiotensin in any of the other regions studied.

Average values for regional splanchnic vascular resistance during control and during infusions of low and high doses of angiotensin II are shown in Figure 8A, 8B and 8C. Regional vascular resistance was increased significantly ($p < 0.05$) from control during the infusion of a low dose of angiotensin in the stomach mucosa by 401%, stomach sbumucosa by 328%, stomach muscularis by 88%, duodenum mucosa by 339%, duodenum submucosa by 64%, jejunum mucosa by 370%, jejunum submucosa by 166%, ileum mucosa by 278%, ileum submucosa by 416%, colon mucosa by 140%, and colon submucosa by 88%. Regional splanchnic vascular resistance during the infusion of a low dose of angiotensin was significantly less than control ($p < 0.05$) in the duodenum muscularis by 31%. Regional vascular resistance was not significantly different from control ($p < 0.05$) in the jejunum muscularis, ileum muscularis, and colon muscularis during the infusion of a low dose of angiotensin.

Regional vascular resistance was increased significantly ($p < 0.05$) from control during the infusion of a high pharmacological dose of angiotensin in the stomach mucosa by 750%, stomach submucosa by 416%, stomach muscularis by 193%, duodenum mucosa by 434%, duodenum submucosa by 88%, jejunum mucosa by 382%, jejunum submucosa by 130%, ileum mucosa by 328%, ileum submucosa by 166%, ileum muscularis by 444%, colon mucosa by 100%, colon submucosa by 90%, and colon muscularis by 229%. Regional splanchnic vascular resistance during the infusion of a high dose of

angiotensin was not significantly different ($p < 0.05$) from control in the jejunum muscularis and decreased significantly ($p < 0.05$) from control in the duodenum muscularis by 58%. Regional vascular resistance during the infusion of a high dose of angiotensin was increased significantly ($p < 0.05$) from regional vascular resistance during the infusion of a low dose of angiotensin in the stomach muscularis by 56%. There were no significant differences ($p < 0.05$) between regional vascular resistances during the infusion of a high dose of angiotensin and during the infusion of a low dose of angiotensin in any of the other regions studied.

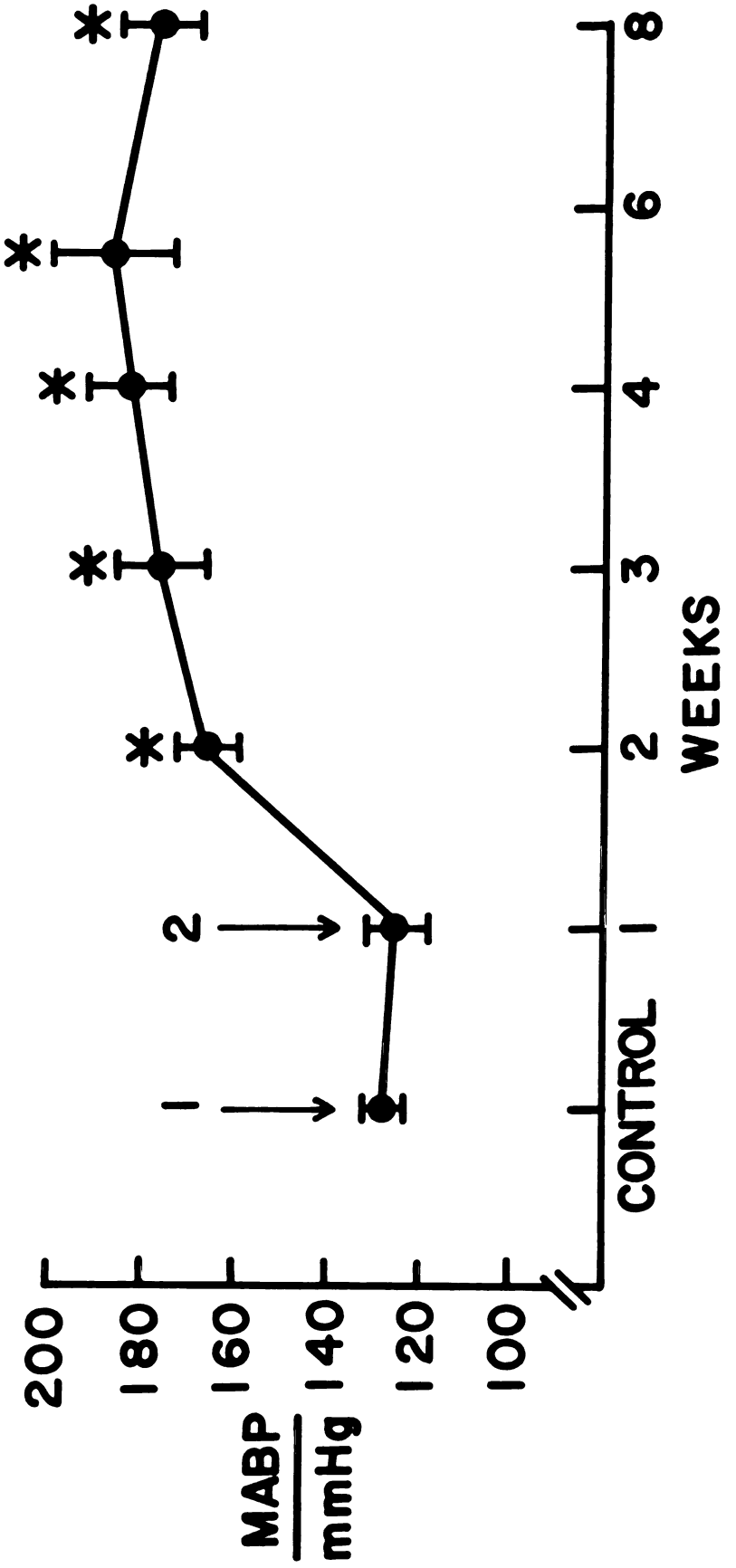
Figure 1. Changes in unanesthetized mean arterial blood pressure during six week development of chronic experimental perinephritic hypertension.

*$p < 0.05$ when compared to control using Student's t-test modified for paired replicates (N=7).

$\downarrow^{1}$ denotes surgical induction of hypertension by wrapping kidney in silk.

$\downarrow^{2}$ denotes contralateral nephrectomy.

MABP denotes mean arterial blood pressure.


MABP
mmHg
200
180
160
140
120
100
CONTROL
1
2
3
4
6
8
WEEKS
1
2
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*
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*
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Table 1. Average values for regional splanchnic vascular resistance (mmHg/ml/min/100 gm) of the acute control dogs (control) vs. the chronic control dogs (experimental). (Mean ± S.E.M.)

	(Mean ± S.E.M.)	
Tissue	N=11 Acute Control Dogs	N=11 Chronic Control Dogs
Adrenal Gland	0.05 ± 0.04	0.67 ± 0.13
Pancreas Head	4.67 ± 0.97	2.56 ± 0.52
Pancreas Tail	5.84 ± 1.03	3.37 ± 0.74
Spleen	1.35 ± 0.32	1.26 ± 0.21
Liver	10.86 ± 2.81	5.22 ± 1.06
Stomach Mucosa	2.32 ± 0.46	3.14 ± 0.70
Stomach Submucosa	44.94 ±13.21	3.81 ± 0.74*
Stomach Muscularis	29.96 ± 4.41	15.27 ± 2.31*
Duodenum Mucosa	1.22 ± 0.10	16.42 ± 3.65*
Duodenum Submucosa	33.43 ± 7.81	38.73 ± 15.43
Duodenum Muscularis	29.89 ± 4.27	13.58 ± 2.63*
Jejunum Mucosa	1.44 ± 0.04	101.63 ± 74.86*
Jejunum Submucosa	30.69 ± 5.05	49.57 ± 22.13
Jejunum Muscularis	34.36 ± 6.92	137.29 ± 106.85
Ileum Mucosa	1.27 ± 0.29	4.07 ± 0.75*
Ileum Submucosa	25.52 ± 6.87	28.42 ± 6.57
Ileum Muscularis	31.37 ± 8.53	50.49 ± 15.90
Colon Mucosa	1.14 ± 0.14	69.67 ± 68.03
Colon Submucosa	10.51 ± 1.63	11.92 ± 3.39
Colon Muscularis	11.28 ± 3.82	10.47 ± 2.74

± = S.E.M. (Standard Error Mean)

* values of the two groups are significantly different ($p < 0.05$).

Figure 2a. Average values for total-wall blood flow and mean arterial blood pressure (Pa) of the acute control dogs (open bars) vs. the chronic perinephritic hypertensive dogs (cross-hatched bars).

*$p < 0.05$ when compared to the acute control values (N=11) using a Student's t-test (N=7).

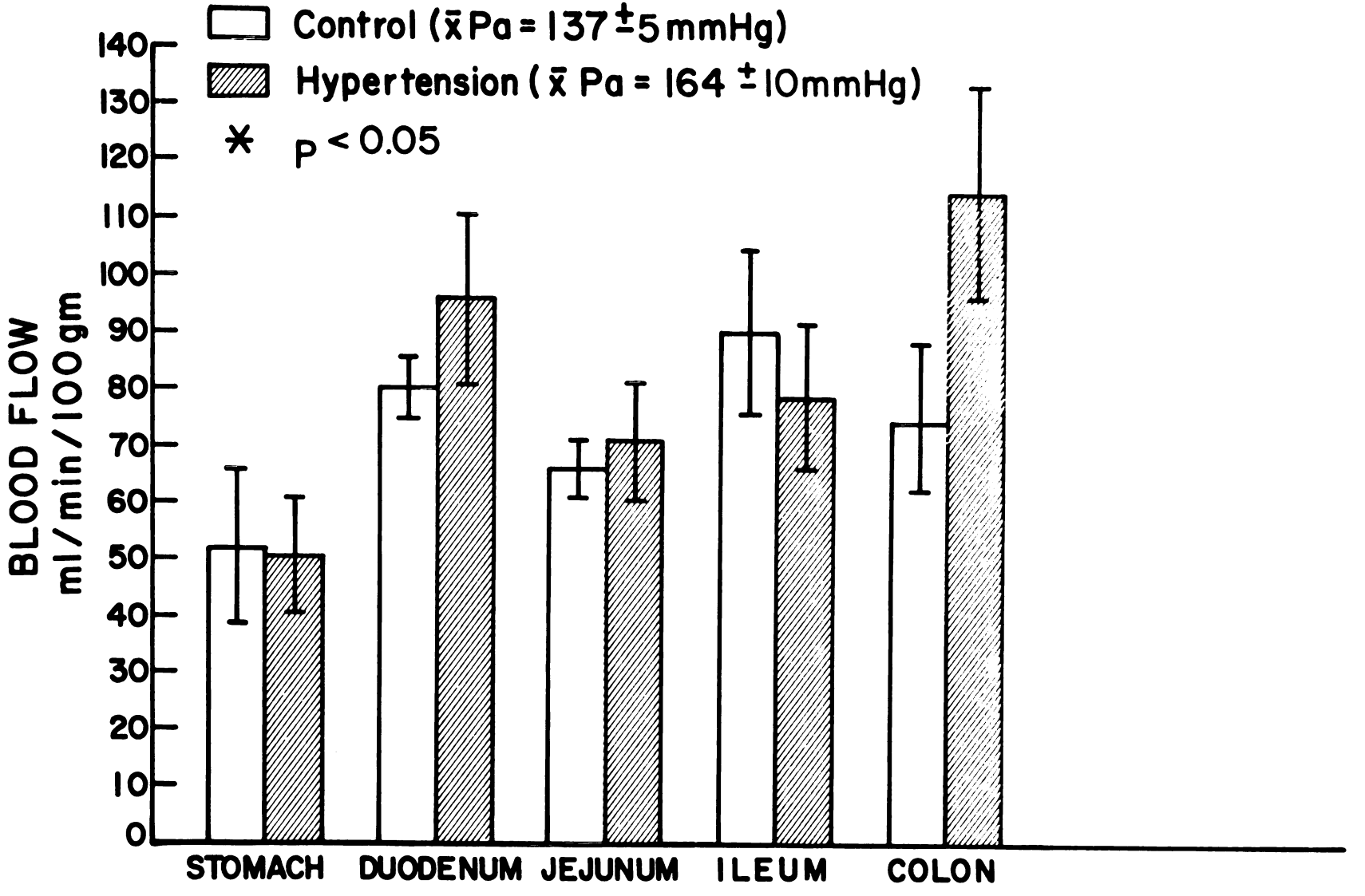

Control ($\bar{x}$ Pa = 137 ± 5 mmHg)
Hypertension ($\bar{x}$ Pa = 164 ± 10 mmHg)
* P < 0.05
BLOOD FLOW
ml/min/100gm
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
STOMACH
DUODENUM
JEJUNUM
ILEUM
COLON

Figure 2b. Average values for total-wall vascular resistance and mean arterial blood pressure (Pa) of the acute control dogs (open bars) vs. the chronic perinephritic hypertensive dogs (cross-hatched bars).

*$p < 0.05$ when compared to the acute control values (N=11) using a Student's t-test (N=7).

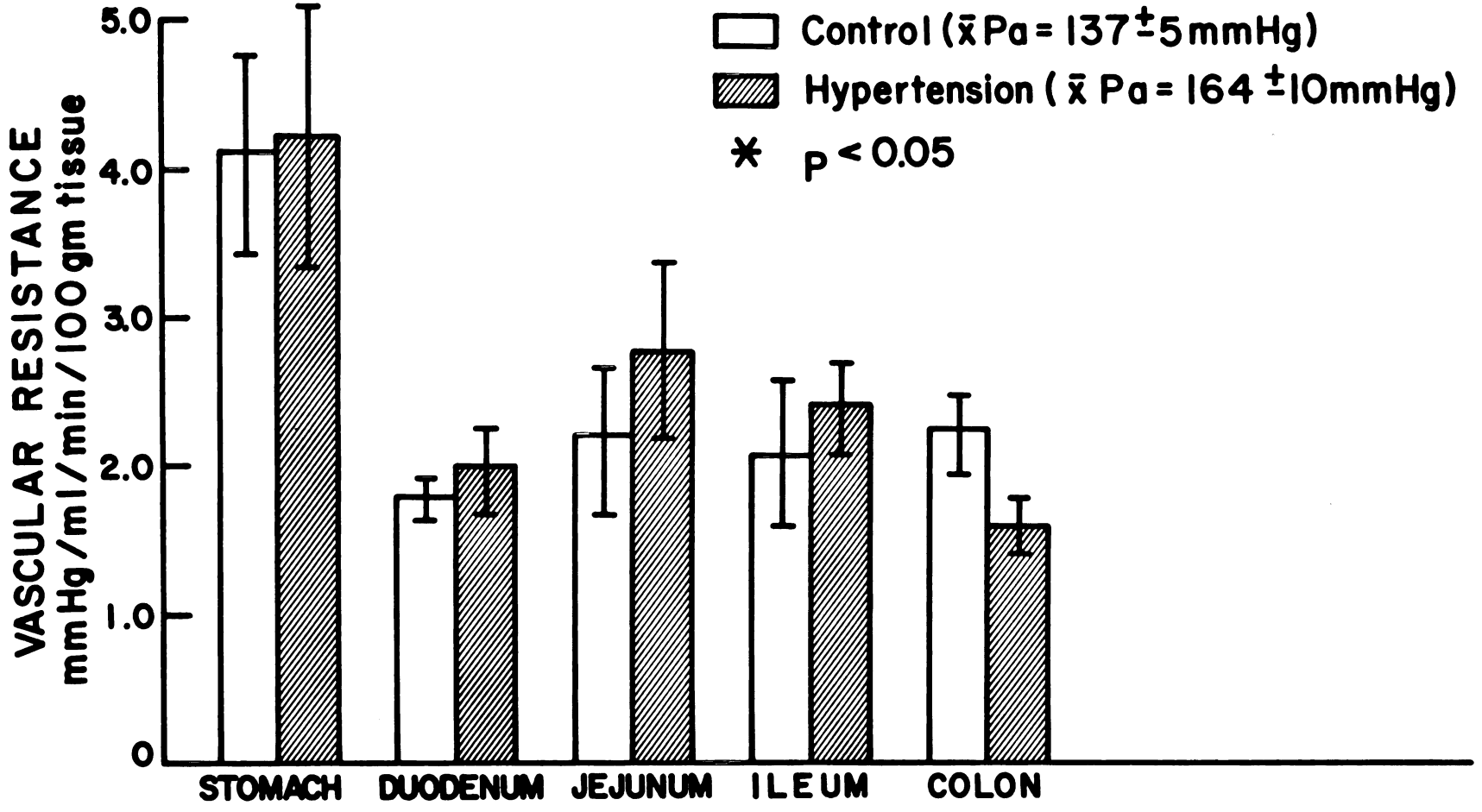

VASCULAR RESISTANCE
mmHg/ml/min/100gm tissue
5.0
4.0
3.0
2.0
1.0
0
Control ($\bar{x}$ Pa = 137 ± 5 mmHg)
Hypertension ($\bar{x}$ Pa = 164 ± 10mmHg)
* P < 0.05
STOMACH
DUODENUM
JEJUNUM
ILEUM
COLON

Table 2. Average values for blood flow (ml/min/100 gm)of the various abdominal organs of the acute control dogs vs. the chronic hypertensive dogs. (Mean ± S.E.M.)

	(Mean ± S.E.M.)	
	N=11	N=7
Organ	Acute Control Dogs	Chronic Hypertensive Dogs
Adrenal Gland	282.87 ± 14.19	295.23 ± 44.06
Pancreas Head	41.75 ± 6.80	61.26 ± 6.47
Pancreas Tail	32.50 ± 5.69	46.33 ± 7.39
Spleen	143.75 ± 27.95	99.66 ± 14.88
Liver	19.09 ± 3.34	15.62 ± 3.78

* denotes values which are significantly different ($p < 0.05$).

Figure 3. Average values for regional blood flows within the gastrointestinal tract and mean arterial blood pressure (Pa) of the acute control dogs (open bars) vs. chronic hypertensive dogs (cross-hatched bars).

*$p < 0.05$ when compared to the acute control dogs (N=11) using a Student's t-test (N=7).

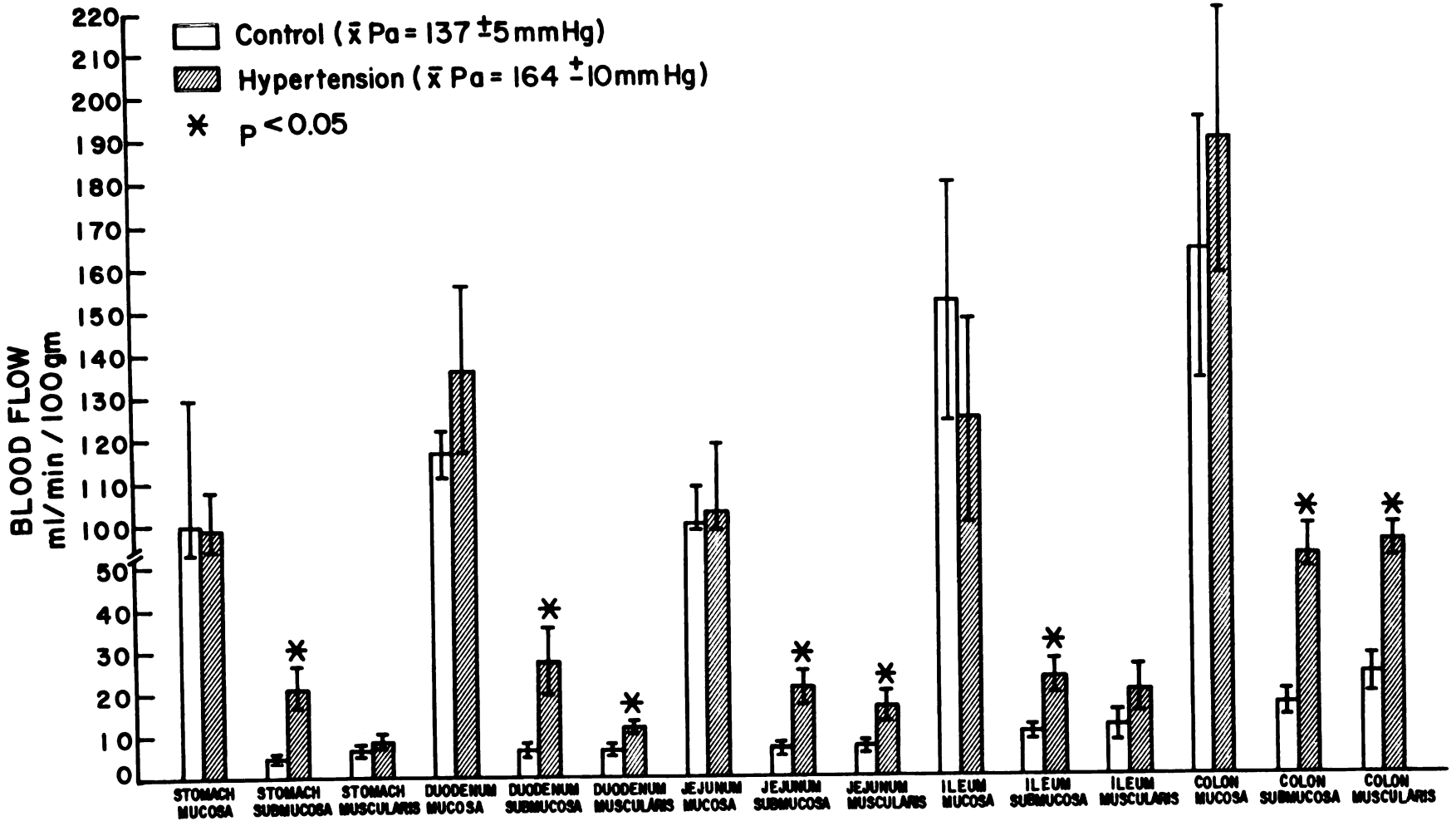

Control ($\bar{x}$ Pa = 137 ±5 mmHg)
Hypertension ($\bar{x}$ Pa = 164 ±10 mmHg)
* P < 0.05
BLOOD FLOW
ml/min/100gm
220
210
200
190
180
170
160
150
140
130
120
110
100
50
40
30
20
10
0
STOMACH MUCOSA
STOMACH SUBMUCOSA
STOMACH MUSCULARIS
DUODENUM MUCOSA
DUODENUM SUBMUCOSA
DUODENUM MUSCULARIS
JEJUNUM MUCOSA
JEJUNUM SUBMUCOSA
JEJUNUM MUSCULARIS
ILEUM MUCOSA
ILEUM SUBMUCOSA
ILEUM MUSCULARIS
COLON MUCOSA
COLON SUBMUCOSA
COLON MUSCULARIS

Table 3. Average values for vascular resistance (mmHg/ml/min/100 gm) of the various abdominal organs of the acute control dogs vs. the chronic hypertensive dogs. (Mean ± S.E.M.)

	(Mean ± S.E.M.)	
	N=11	N=7
Organ	Acute Control Dogs	Chronic Hypertensive Dogs
Adrenal Gland	0.05 ± 0.04	0.65 ± 0.12
Pancreas Head	4.67 ± 0.97	2.82 ± 0.28
Pancreas Tail	5.84 ± 1.03	4.11 ± 0.36
Spleen	1.35 ± 0.32	1.93 ± 0.36
Liver	10.86 ± 2.81	25.81 ±14.73

* denotes values which are significantly different ($p < 0.05$).

Figure 4. Average values for regional vascular resistance within the gastrointestinal tract and mean arterial blood pressure (Pa) of the acute control dogs (open bars) vs. chronic hypertensive dogs (cross-hatched bars).

*$p < 0.05$ when compared to the acute control dogs (N=11) using a Student's t-test (N=7).

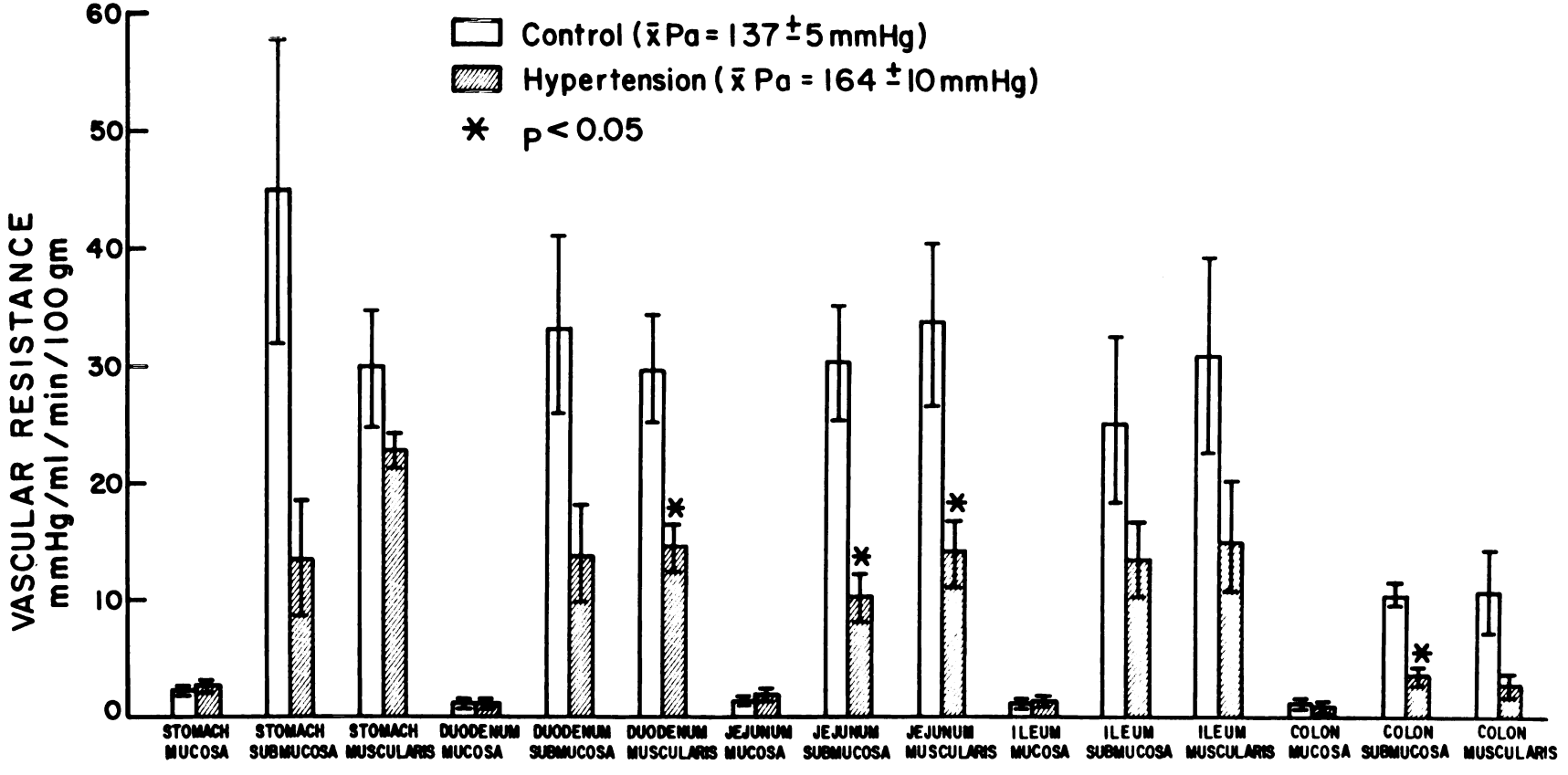

Control (x̄ Pa = 137 ± 5 mmHg)
Hypertension (x̄ Pa = 164 ± 10 mmHg)
* p < 0.05
VASCULAR RESISTANCE
mmHg/ml/min/100 gm
60
50
40
30
20
10
0
STOMACH MUCOSA
STOMACH SUBMUCOSA
STOMACH MUSCULARIS
DUODENUM MUCOSA
DUODENUM SUBMUCOSA
DUODENUM MUSCULARIS
JEJUNUM MUCOSA
JEJUNUM SUBMUCOSA
JEJUNUM MUSCULARIS
ILEUM MUCOSA
ILEUM SUBMUCOSA
ILEUM MUSCULARIS
COLON MUCOSA
COLON SUBMUCOSA
COLON MUSCULARIS

Figure 5. Average values for total-wall blood flow and mean arterial blood pressures (Pa) during control (open bars), during intravenous infusion of a low dose (0.05 μg/Kg/min) of angiotensin II (cross-hatched bars) and during intravenous infusion of a high dose (1.0 μg/Kg/min) of angiotensin II. (dotted bars).

*$p < 0.05$ when compared to control using a Student's t-test modified for paired replicates (N=8).

+$p < 0.05$ when compared to low dose using a Student's t-test modified for paired replicates (N=8).

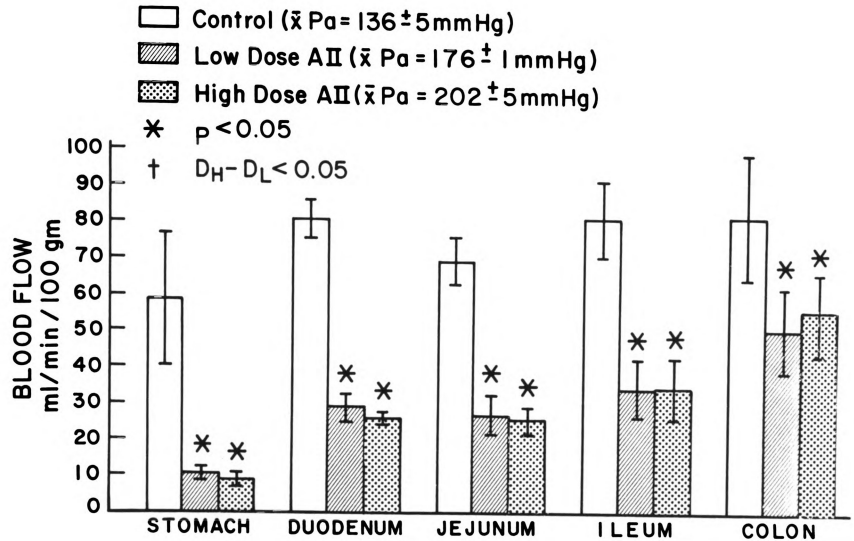

Control ($\bar{x}$ Pa = 136 ± 5 mmHg)
Low Dose AII ($\bar{x}$ Pa = 176 ± 1 mmHg)
High Dose AII ($\bar{x}$ Pa = 202 ± 5 mmHg)
* P < 0.05
† $D_H - D_L < 0.05$
BLOOD FLOW
ml/min/100 gm
100
90
80
70
60
50
40
30
20
10
0
STOMACH
DUODENUM
JEJUNUM
ILEUM
COLON

Figure 6. Average values for total-wall vascular resistance and mean arterial blood pressures (Pa) during control (open bars), during intravenous infusion of a low dose (0.05 μg/Kg/min) of angiotensin II (cross-hatched bars) and during intravenous infusion of a high dose (1.0 μg/Kg/min) of angiotentin II (dotted bars).

*$p < 0.05$ when compared to control using a Student's t-test modified for paired replicates (N=8).

+$p < 0.05$ when compared to low dose using a Student's t-test modified for paired replicates (N=8).

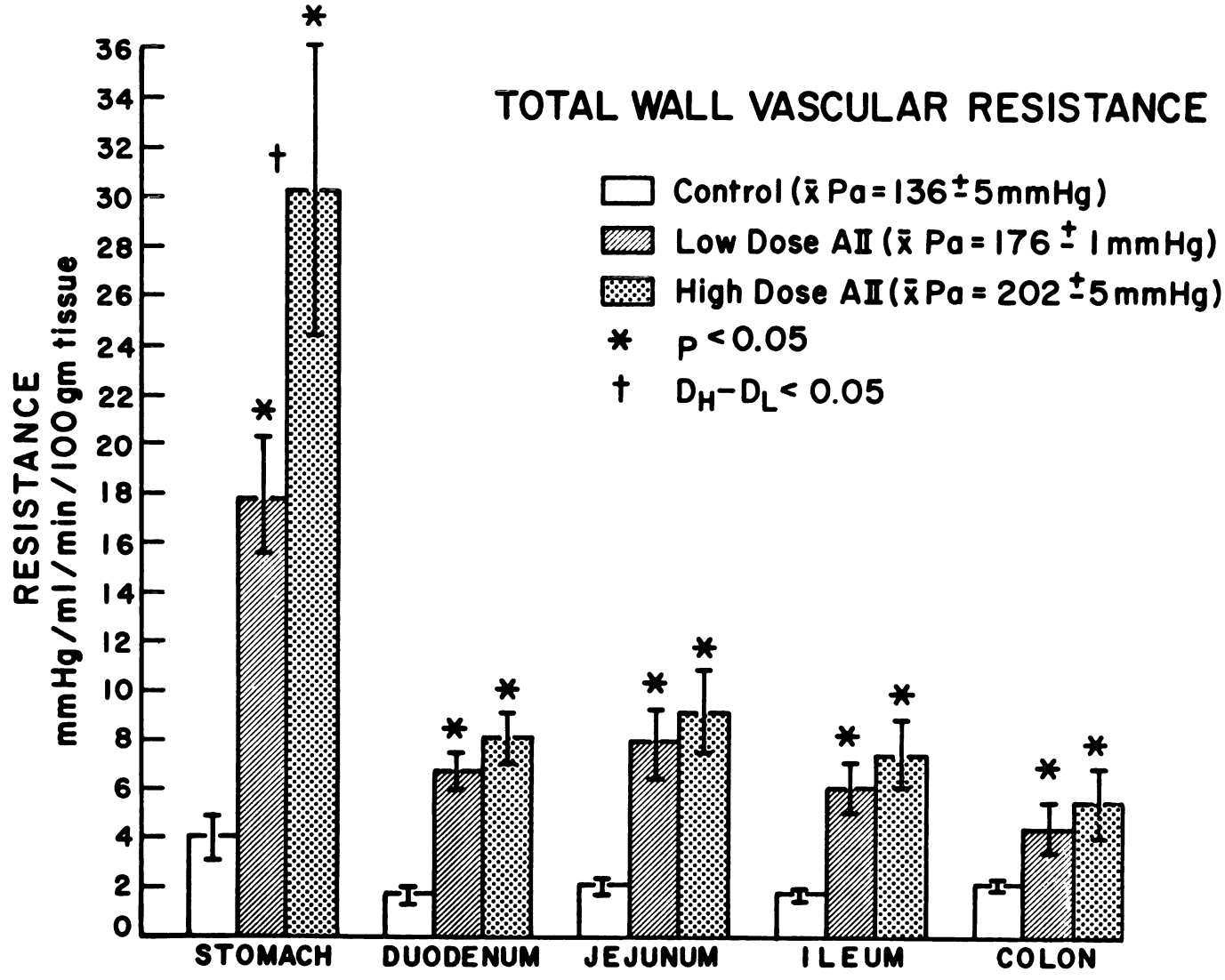

TOTAL WALL VASCULAR RESISTANCE
Control (x̄ Pa = 136 ± 5 mmHg)
Low Dose AII (x̄ Pa = 176 ± 1 mmHg)
High Dose AII (x̄ Pa = 202 ± 5 mmHg)
* p < 0.05
† $D_H - D_L < 0.05$
RESISTANCE
mmHg/ml/min/100 gm tissue
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
STOMACH
DUODENUM
JEJUNUM
ILEUM
COLON

Table 4. Average values for blood flow (ml/min/100 gm) of the various abdominal organs before (control) and after the intravenous infusion of low (0.05 μg/Kg/min) and high (1.0 μg/Kg/min) pharmacological doses of angiotensin II. (Mean ± S.E.M.)

	(Mean ± S.E.M.)		
Organ	Control	Low Dose	High Dose
Adrenal Gland	292.24 ± 16.38	157.27 ± 19.23*	225.32 ± 53.96
Pancreas Head	34.34 ± 7.02	13.34 ± 2.52*	6.65 ± 1.45*+
Pancreas Tail	27.27 ± 5.86	11.35 ± 2.21*	6.53 ± 1.43*+
Spleen	165.61 ± 34.67	94.63 ± 20.72*	94.63 ± 24.03
Liver	16.93 ± 3.60	13.69 ± 5.02	13.80 ± 5.40

* denotes values which are significantly different from control ($p < 0.05$) N=8.

+ denotes values of high dose which are significantly different from low dose ($p < 0.05$) N=8.

Figure 7. Average values for regional blood flows within the gastrointestinal tract and mean arterial blood pressures (Pa) during control (open bars), during intravenous infusion of a low dose (0.05 μg/Kg/min) of angiotensin II (cross-hatched bars) and during intravenous infusion of a high dose (1.0 μg/Kg/min) of angiotensin II (dotted bars).

*$p < 0.05$ when compared to control using a Student's t-test modified for paired replicates (N=8).

+$p < 0.05$ when compared to low dose using a Student's t-test modified for paired replicates (N=8).

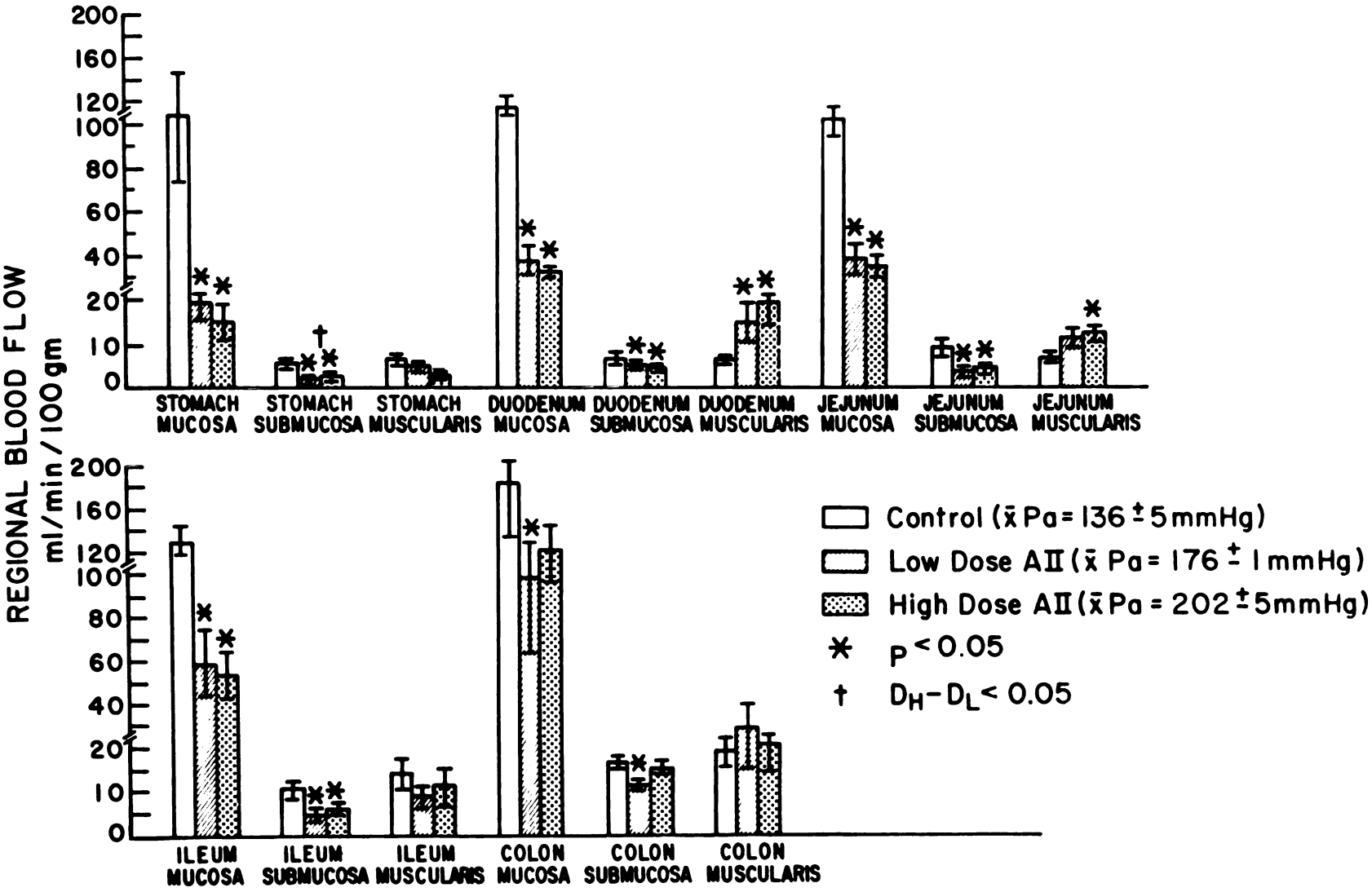

REGIONAL BLOOD FLOW
ml/min/100 gm
200
160
120
100
80
60
40
20
10
0
STOMACH MUCOSA
STOMACH SUBMUCOSA
STOMACH MUSCULARIS
DUODENUM MUCOSA
DUODENUM SUBMUCOSA
DUODENUM MUSCULARIS
JEJUNUM MUCOSA
JEJUNUM SUBMUCOSA
JEJUNUM MUSCULARIS
ILEUM MUCOSA
ILEUM SUBMUCOSA
ILEUM MUSCULARIS
COLON MUCOSA
COLON SUBMUCOSA
COLON MUSCULARIS
Control ($\bar{x}$ Pa = 136 ± 5 mmHg)
Low Dose AII ($\bar{x}$ Pa = 176 ± 1 mmHg)
High Dose AII ($\bar{x}$ Pa = 202 ± 5 mmHg)
* P < 0.05
† $D_H - D_L < 0.05$

Table 5. Average values for vascular resistance (mmHg/ml/min/100 gm) of the various abdominal organs before (control) and after the intravenous infusion of low (0.05 μg/Kg/min) and high (1.0 μg/Kg/min) pharmacological doses of angiotensin II (Mean ± S.E.M.).

	(Mean ± S.E.M.)		
Organ	Control	Low Dose	High Dose
Adrenal Gland	0.48 ± 0.04	1.28 ± 0.14*	1.43 ± 0.41*
Pancreas Head	5.56 ± 1.19	20.53 ± 6.89*	46.35 ± 11.38*+
Pancreas Tail	6.82 ± 1.24	20.92 ± 4.52*	44.32 ± 9.67*+
Spleen	1.24 ± 0.34	2.56 ± 0.49*	3.14 ± 0.69*
Liver	12.84 ± 3.63	41.05 ±22.27	31.56 ± 7.90*

* denotes values which are significantly different from control ($p < 0.05$) N=8.

+ denotes values a high dose which are significantly different from low dose ($p < 0.05$) N=8.

Figure 8a. Average values for regional vascular resistance within the gastrointestinal tract and mean arterial blood pressure (Pa) during control (open bars), during intravenous infusion of a low dose (0.05 μg/Kg/min) of angiotensin II (cross-hatched bars) and during the intravenous infusion of a high dose (1.0 μg/Kg/min) of angiotensin II (dotted bars).

*$p < 0.05$ when compared to control using a Student's t-test modified for paired replicates (N=8).

+$p < 0.05$ when compared to low dose using a Student's t-test modified for paired replicates (N=8).

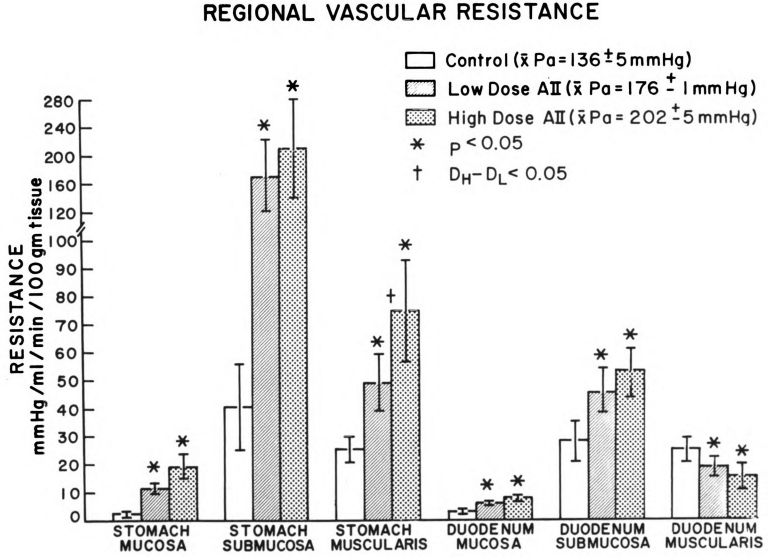

REGIONAL VASCULAR RESISTANCE
Control (x̄ Pa = 136 ± 5 mmHg)
Low Dose AII (x̄ Pa = 176 ± 1 mmHg)
High Dose AII (x̄ Pa = 202 ± 5 mmHg)
* P < 0.05
† DH − DL < 0.05
RESISTANCE
mmHg/ml/min/100 gm tissue
280
240
200
160
120
100
90
80
70
60
50
40
30
20
10
0
STOMACH MUCOSA
STOMACH SUBMUCOSA
STOMACH MUSCULARIS
DUODENUM MUCOSA
DUODENUM SUBMUCOSA
DUODENUM MUSCULARIS

Figure 8b. Average values for regional vascular resistance within the gastrointestinal tract and mean arterial blood pressure (Pa) during control (open bars), during intravenous infusion of a low dose (0.05 μg/Kg/min) of angiotensin II (cross-hatched bars) and during the intravenous infusion of a high dose (1.0 μg/Kg/min) of angiotensin II (dotted bars).

*$p < 0.05$ when compared to control using a Student's t-test modified for paired replicates (N=8).

+$p < 0.05$ when compared to low dose using a Student's t-test modified for paired replicates (N=8).

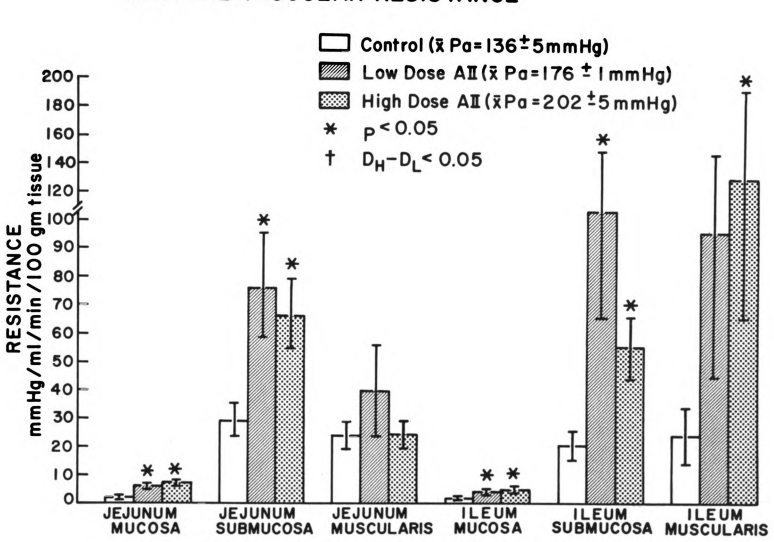
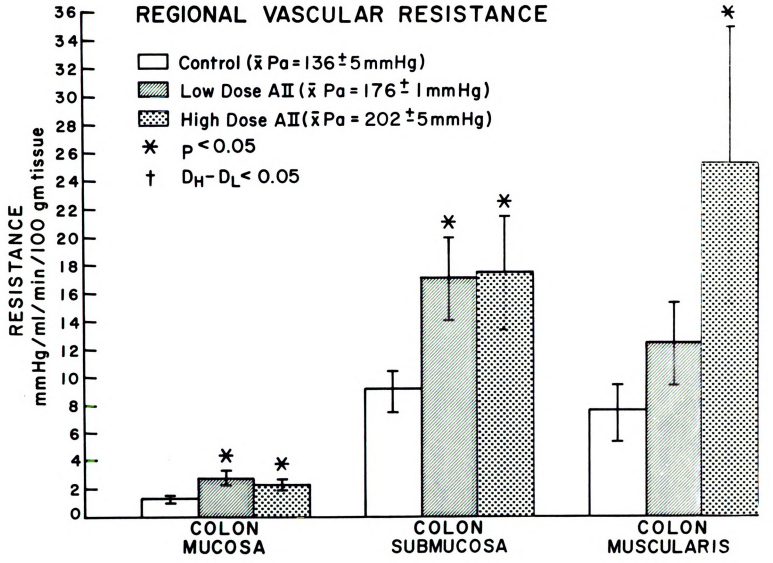

REGIONAL VASCULAR RESISTANCE
Control (x̄ Pa=136±5mmHg)
Low Dose AII (x̄ Pa=176 ± 1 mmHg)
High Dose AII (x̄Pa=202 ±5 mmHg)
* P < 0.05
† $D_H - D_L$ < 0.05
RESISTANCE
mmHg/ml/min/100 gm tissue
200
180
160
140
120
100
90
80
70
60
50
40
30
20
10
0
JEJUNUM MUCOSA
JEJUNUM SUBMUCOSA
JEJUNUM MUSCULARIS
ILEUM MUCOSA
ILEUM SUBMUCOSA
ILEUM MUSCULARIS

Figure 8c. Average values for regional vascular resistance within the gastrointestinal tract and mean arterial blood pressure (Pa) during control (open bars), during intravenous infusion of a low dose (0.05 μg/Kg/min) of angiotensin II (cross-hatched bars) and during the intravenous infusion of a high dose (1.0 μg/Kg/min) of angiotensin II (dotted bars).

*$p < 0.05$ when compared to control using a Student's t-test modified for paired replicates (N=8).

+$p < 0.05$ when compared to low dose using a Student's t-test modified for paired replicates (N=8).


REGIONAL VASCULAR RESISTANCE
Control (x̄ Pa = 136 ± 5 mmHg)
Low Dose AII (x̄ Pa = 176 ± 1 mmHg)
High Dose AII (x̄ Pa = 202 ± 5 mmHg)
* P < 0.05
† DH - DL < 0.05
RESISTANCE
mmHg/ml/min/100 gm tissue
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
COLON MUCOSA
COLON SUBMUCOSA
COLON MUSCULARIS

DISCUSSION

This study is unique in that it is one of the first investigations which utilizes radioactive microspheres in a chronic manner to measure possible regional hemodynamic responses resulting from one-kidney perinephritic hypertension. The use of radioactive labeled microspheres for acute determination of blood flow to discrete regions of the body is an accepted technique provided prescribed procedural criteria are adhered to strictly and microspheres of appropriate size are used (Wagner et al. 1969). The use of the radioactive microsphere partical dispersion technique for acute determination of blood flow assumes that: 1) The microspheres are uniformely mixed within the left ventricle upon injection; 2) the microspheres are sufficiently large to be lodged within vascular beds; 3) the microspheres have the same rheology as red blood cells; 4) the microspheres do not themselves alter the distribution of blood flow; 5) the microspheres are not metabolized so rapidly that the measured distribution is significantly altered (Wagner, et al. 1969). These assumptions have been proved to be accurate by Buckberg et al. (1971) who also reported that errors in this technique are kept to a minimum if each sample (tissue or blood) contains at least 400 microspheres.

While criteria for acute studies involving microspheres can be readily met, additional considerations need to be made when chronic studies are attempted. Basically, the microspheres must not disappear from their site of initial placement during the time period studied by: 1) free movement within the vascular system (e.g. during periods of vasodilation); 2) movement via cell mediated phenomena (e.g. macrophage

activity); 3) loss from the body via excretory and/or secretory pathways (e.g. loss from the gastrointestinal tract during normal mucosal turnover).

Comparing blood flow values of the acute control dogs of Series II of the present study (Tables 1 and 2) to similar studies using 15 μ microspheres shows a favorable correlation. Chou and Grassmick (1978) reported regional splanchnic blood flows in pentobarbital anesthetized dogs to be 1.02 ml/min/gm in the spleen, 0.65 ml/min/gm in the liver, 2.87 ml/min/gm in the pancreas and 0.50 ml/min/gm in the adrenal gland. Total wall blood flows were 0.20 ml/min/100 gm in the stomach, 1.0 ml/min/gm in the duodenum, 0.92 ml/min/gm in the jejunum, 0.49 ml/min/gm in the ileum and 0.73 ml/min/gm in the colon. Splanchnic blood flows measured in similar regions of the acute control group in Series II of the present study are found to be 144 ml/min/100 gm in the spleen, 19 ml/min/100 gm in the liver, 42 ml/min/100 gm in the pancreas and 283 ml/min/100 gm in the adrenal gland. Total wall blood flow control values of the present study are 59 ml/min/100 gm in the stomach, 81 ml/min/100 gm in the duodenum, 69 ml/min/100 gm in the jejunum, 82 ml/min/100 gm in the ileum and 82 ml/min/100 gm in the colon. Compared to Chou and Grassmick, these flows were slightly higher in the regions of the spleen, stomach, and ileum and slightly lower in the liver, duodenum and jejunum.

In comparing values of the acute control dogs in Series II to values of chronic hypertensive dogs of Series I it is important to consider that the vascular beds of the acute control dogs, which contained the microspheres injected to measure control blood flow, were leater subjected to low and high pharmacological doses of angiotensin II.

While angiotensin II causes generalized systemic vasoconstriction (except in the brain) and elevation in systemic arterial blood pressure, its effect on the stability of microspheres lodged within vascular beds has not been assessed. However, Greenway and Murthy (1972) measured the distribution of blood flow (15 μ microspheres) between the mucosal, submucosal and muscularis layers of the gut wall in cats during a period of vasoconstriction (by vasopressin) followed by a period of vasodilation (with isoprenaline). Microspheres injected into vasopressin constricted vascular beds moved from the submucosa into the mucosa along the entire length of the gastrointestinal tract upon subsequent vasodilation with isoprenaline. These findings suggest that the submucosa and mucosa are in series with each other and that microspheres have the capability of movement within this vasculature during vasodilation. They did not measure portal venous blood for microsphere content in excess of that expected due to normal A-V shunting within the gastrointestinal gract (i.e. 2-3%; Delaney 1969). Therefore, the degree of possible movement of microspheres out of the vascular bed of the gastrointestinal tract was not assessed.

As seen in Tables 1 and 2, the results of the comparison of the acute control values of Series II to the chronic control values of Series I suggest that some radioactive labeled microspheres are displaced from their initial sites of lodging after eight weeks. For example, the acute control dogs exhibited average mucosa blood flow values of 117.47 ml/min/100 gm, 101.37 ml/min/100 gm and 152.03 ml/min/100 gm in the duodenum, jejunum and ileum respectively. In comparison, the chronic control dogs exhibited average mucosal blood flow values of 12.73 ml/min/100 gm, 8.72 ml/min/100 gm and 49.05 ml/min/100 gm in the duodenum,

jejunum and ileum respectively. Therefore, the chronic control group of Series I is probably invalid and the acute control group of Series II served as the control group in all latter comparisons.

As seen in Table 1 and Table 2, the data suggests that with time, microspheres were displaced from the mucosal layers of the duodenum, jejunum and ileum while microspheres within the mucosal layers of the stomach and colon remained stable. Several hypothetical explanations might explain these findings. Since the mucosa lining of the gut has a very high rate of turnover (i.e. 4-6 days, Lipkin et. al. 1963) and is subjected to direct contact with food material, it is possible that microspheres were lost due to normal mucosal turnover and hence would be present in fecal material. During the separation of the mucosa from the submucosa and muscularis it was noted that the mucosal layers of the duodenum, jejunum, and ileum were more delicate and easier to remove than the mucosal layers of the stomach and colon. In the present study the possible presence of microspheres in fecal material was not investigated but Kaihara et. al. (1968) reported no change in total body radioactivity and negligible fecal microsphere content in dogs injection with 50 μ microspheres during a chronic period of two weeks duration. However, these microspheres were much larger than those used in the present study and external detectors lacking in sensitivity were used to measure parameters. The observation period of the present study was much longer in duration.

Microspheres may also have been displaced from mucosal regions by cell-mediated phenomena. The peritoneal cavity contains an abundance of highly mobile macrophages which have the ability to phagocytize a B. bacillus bacterium with dimensions of 15 μ by 3 μ (Roberts, 1972).

Two or more macorphages can combine to form a Giant Cell which also has phagocytic potential. It would therefore, seem possible that cell-mediated phenomena could potentially displace microspheres from regions of initial lodging to regions such as the mesenteric lymph nodes, lymphatic ducts, and lungs. However, in this study these tissues were not analyzed for possible exaggerated microsphere content and thus, no conclusions can be made.

These findings are not in agreement with Hales (1974) who reported that 15 μ microspheres lodged within the vasculature of the rabbit ear were not phagocytized and/or removed from the circulation during an eight week chronic period. Urine and feces were also devoid of microspheres during the observation period and no change in thoracic radioactivity was observed. In contrast, results of the present study suggest that microsphere displacement is present in some mucosal vascular beds. In comparison to the vascular bed of the rabbit ear, mucosal regions of the splanchnic circulation are in frequent contact with chyme (containing cellulose etc.), have a much greater degree of macrophage activity, and exhibit a much higher rate of cell turnover.

As seen in Table 1, blood flow values of the chronic control dogs were significantly higher than blood flow values of the acute control dogs in the stomach submucosa and duodenum muscularis. This result can not be explained in terms of biological phenomena, and they are probably due to technical error. During physical separation of these layers of the gut wall of the chronic control dogs, contamination of these tissue samples with protions of their respective mucosae could result in an abnormally high blood flow because the mucosa receives a much higher blood flow per gram of tissue.

As seen in Table 1 and Table 2, the data of the present study suggests that radioactive labeled microspheres remain for an eight week period after lodging within the splanchnic vascular bed in the regions of the adrenal gland, head of the pancreas, tail of the pancreas, spleen, stomach mucosa, duodenum submucosa, jejunum submucosa, jejunum muscularis, ileum submucosa, ileum muscularis, colon mucosa, colon submucosa and colon muscularis. These results agree with the findings of Hales (1974) mentioned eariler. It should be noted that in the chronic control values there was a high degree of variability within these regions of the splanchnic vascular bed. This produced a very large standard error of the means and made actual differences difficult to prove statistically.

Prior to considering the results of the comparison of the acute control values to the chronic hypertensive values, the limitations of the acute control dogs of the present study must be discussed. Firstly, all animals should receive the same conditioning prior to experimentation to assure that all animals are free of parasites and healthy. The proper treatment of the animals used as the control of chronic hypertensive dogs should also involve sham-wrapping and contralateral nephrectomy in addition to post surgical prophylactic treatment with penicillin. Chronic, normotensive control animals should also be housed under the same environmental conditions and for the same period in time as the hypertensive experimental group. Both control and experimental groups should also receive the same drugs at essentially the same doses to maintain a proper level of anesthesia and carry out experimental protocol. Unfortunately, the present economic situation warranted the use of acute (unconditioned) animals to serve as the normotensive control

dogs. The acute control dogs did not meet any of the requirements of a good control group previously mentioned. The acute animals also received low and high pharmacological doses of angiotensin II following the measurement of control blood flow by the initial microsphere injection.

The stability of the microspheres within regional vascular beds of the acute control dogs (Series II) which measured the normotensive control blood flow must be questioned since the vascular beds under study were later subjected to low and high pharmacological doses of angiotensin II. While angiotensin produces a general vasoconstriction of splanchnic vascular beds tending perhaps to hold microspheres in their initial position of lodging; this drug also raises systemic arterial blood pressure which would perhpas tend to force the microspheres beyond the initial site of lodging. Greenway and Murthy (1972) found that microspheres lodged within some vasoconstricted vascular beds move upon vasodilation. However, regional vascular beds in the present study were not subjected to vasodilatory drugs. Thus, even though movement of microspheres that measured control blood flow is remotely possible, angiotensin produced vasoconstriction in nearly every regional vascular bed, theoretically maintaining the stability of the microspheres that measured control blood flow. The animals were sacrificed immediately following the administration of a high pharmacological dose of angiotensin in hopes that a possible reactive hyperemia would play little or no role in microspheres stability.

HYPERTENSION DATA

The original protocol of Series I of the present study involved comparing blood flow and vascular resistance before and during chronic

one-kidney perinephritic hypertension in the same animal, thus eliminating inter-animal variance. However, the comparison of the acute control values of Series II to the chronic control values of Series I suggested that the microspheres of Series I which originally measured control blood flow, were displaced from some vascular beds during the eight week period for the development of chronic hypertension. Therefore, the acutely injected normotensive control values of Series II served as the control for all hypertension comparisons and inter-animal variance could not be avoided. The presence of inter-animal variance in addition to the relatively small number of dogs made significant changes in blood flow and resistance difficult to show even though systemic arterial blood pressure was significantly elevated by 27 mmHg in the hypertensive state ($p < 0.05$). These conditions necessitate the discussion of this data in terms of trends toward regional hemodynamic changes during the hypertensive state.

As seen in Table 2 and Table 3 of the present study, it was not possible to show significant differences in blood flow or vascular resistance within various abdominal organs during one-kidney chronic perinephritic hypertension. However, regional vascular beds of the pancreas head and tail tended to exhibit increases in blood flow and non-significant decreases in vascular resistance during the hypertensive state. In contrast, blood flow within the adrenal gland, spleen and liver appeared to remain at normotensive control levels. Since systemic arterial blood pressure was elevated by only 27 mmHg and there was considerable variation among the measured values, significant differences in vascular resistances were difficult to show, although they tended to be elevated in all regions except the head and tail of the pancreas.

Thus the results suggest that one kidney perinephritic hypertension is probably associated with no change in blood flows and elevated vascular resistances within the adrenal gland, spleen, and liver.

This conclusion, if correct, agrees in part with the findings of Bralet et al. (1973), and Flohr et al. (1976), who measured fractional distribution of cardiac output (^{86}Rb and radioactive microspheres respectively) to abdominal organs in one-kidney Goldblatt hypertensive rats. Compared to normotensive controls, no significant differences were found in the fractional distribution of cardiac output to the spleen and liver (Bralet et al. 1973), or adrenal galnd, pancreas, spleen and liver (Flohr et al. 1976). Resistance units were not reported, but the authors interpreted the findings to imply that these vascular beds share equally in the increase in total peripheral resistance that occurs in chronic one-kidney Goldblatt hypertension.

As seen in Figure 2A and Figure 2B of the present study, it was not possible to show significant differences in total-wall blood flow or total-wall vascular resistance within the regions of the stomach, duodenum, jejunum, ileum and colon during one-kidney perinephritic hypertension. However, on the average, total-wall blood flow tended to remain at control levels within all regions except the colon. If the data are correct, this suggest that blood flow tended to remain normal in the wall of the stomach, duodenum, jejunum, and ileum during the hypertensive state and if total peripheral resistance is in fact elevated, that these regions tend to share equally in the general rise in total peripheral resistance that occurs in the chronic hypertensive

state. In contrast, the region of the colon tended to exhibit an increase in total-wall blood flow and a decrease in total-wall vascular resistance which were of borderline statistical significance. This interpretation, if correct, implies a redistribution of cardiac output in favor to the colon during one-kidney perinephritic hypertension.

The interpretations of these data in partial agreement with the findings of other investigators. Simon et al. (1975) measured ileal blood flow directly in early (4 week) one-kidney perinephritic hypertensive dogs. When compared to sham-wrapped normotensive dogs, hypertensive animals exhibited a 20% increase in blood flow while vascular resistance remained unchanged. While they did not measure cardiac output, Ferrario et al. (1970), found that cardiac output was elevated by maximum of 18% during early renal hypertension. If cardiac output was elevated to this extent, the results of Simon et. al. would suggest that the ileal vascular bed receives an increased blood flow which is proportionate to the increased cardiac output. Hence, no redistribution of cardiac output would be present in the ileum during early hypertension. While in the present study, ileal blood flow was measured during the chronic hypertensive state when cardiac output is reportedly normal (Ferrario et al. 1974), the results tend to suggest that the ileal vascular resistance rises uniformly with total peripheral vascular resistance during chronic hypertension. Bralet et al. (1973) found that the fractional distribution of cardiac output (^{86}Rb) was increased in the stomach and colon, but remained unchanged in the small intestine of chronic one-kidney Goldblatt hypertensive rats. In contrast, Flohr et al. (1976), found that the fractional distribution of cardiac output (radioactive microspheres) was increased in the small

intestine and colon of chronic one-kidney Goldblatt hypertensive rats. When the data of the present study are considered in terms of total wall blood flow and vascualr resistance, it appears that the vascular beds within the regions of the stomach, duodenum, jejunum and ileum tend to participate uniformly in the rise in total peripheral resistance during chronic hypertension. In contrast, there appears to be a redistribution of cardiac output to the colon during chronic hypertension.

As seen in Figures 3 and 4, when compared to acute control values (Series II), it was not possible to show significant differences in blood flow or vascular resistance within the mucosal layers in any region of the gastrointestinal tract during chronic one-kidney perinephritic hypertension. However, avearge mucosal blood flow tended to remain at control levels in all regions of the gastrointestinal tract studied. If the data are correct, this suggests that there is no change in blood flow to the mucosal layers of the stomach, duodenum, jejunum, ileum or colon during the hypertensive state. The mucosal layers of these regions tend to share equally in the general rise in total peripheral vascular resistance that occurs in the chronic hypertensive states.

As seen in Figures 3 and 4, blood flow within the submucosal layer of the hypertensive dogs is significantly greater than the control dogs in all regions of the gastrointestinal tract studied. Submucosal vascular resistance of the hypertensive group was significantly less than the control group in the jejunum and colon and tended to also decrease in the stomach, duodenum and ileum. These results suggest that chronic one-kidney perinephritic hypertension is associated with an increase in blood flow from unknown vascular beds to the vascular bed of the submucosal layer within the gastrointestinal tract. Since

submucosal vascular resistance is apparently decreased in the presence of increased blood flow, passive forces may be present in this region during the hypertensitve state.

As seen in Figures 3 and 4 in the present study, blood flow within the muscularis layer of the hypertensive dogs was significantly greater than the control dogs in the regions of the duodenum, jejunum and colon and tended to also be elevated within the stomach and ileum. Muscularis vascular resistance of the hypertensive dogs was significantly less than the control group in the duodenum and jejunum and tended to also decrease within the stomach, ileum and colon. These results suggest that chronic one-kidney perinephritic hypertension is associated with an increase in blood flow from unknown vascular beds to the vascular bed of the muscularis layer within the gastrointestinal tract. Since muscularis vascular resistance is apparently decreased in the presence of increased blood flow, passive forces may be present in this region during the hypertensive state.

In brief summary, chronic one-kidney perinephritic tends to be associated with normal blood flow and elevated vascular resistance within the mucosal layer of the gastrointestinal tract. Assuming total peripheral resistance is elevated in the presence of a normal cardiac output this interpretation suggests that the mucosal layer tends to share equally in the elevation of total peripheral vascular resistance during chronic hypertension and that no redistribution of cardiac output occurs within this vascular compartment. In contrast, submucosal and muscularis layers tend to exhibit increased blood flows and decreased vascular resistances during chronic hypertension suggesting that a

redistribution of cardiac output might be occurring from unknown vascular beds to these layers of the gastrointestinal tract if cardiac output is in fact normal. Unfortunately no other studies are currently available to compare to this hemodynamic analysis of the layers of gastrointestinal tract wall during chronic hypertension. Compartmental hemodynamic data of the present study might prove valuable in that previously, other investigators have measured hemodynamic changes only within the total-wall of various regions of the gastrointestinal tract during the hypertensive state. In the present study, the data tended to suggest that total-wall blood flow reamined unchanged during the hypertensive state in all regions except the colon. However, since the mucosal layer receives a major portion of total-wall blood flow (i.e. 72%, Delaney and Grim 1964) and, in the present study mucosal blood flow appears to remain unchanged during hypertension, it is possible that the increased blood flow in the submucosa and muscularis was not large enough to have a significant effect on blood flow to the entire gut wall. As a result, in the present study total blood flow within the wall of the stomach, duodenum, jejunum, and ileum remained at normotensive levels during chronic hypertension.

ANGIOTENSIN II

As seen in Tables 4 and 5, results of the intravenous infusion of low (0.05 μg/Kg/min) and high (1.0 μg/Kg/min) pharmacological doses of angiotensin II suggest that various abdominal organs exhibit variable degrees of responsiveness to this vasoconstrictor. Expressing results in terms of decreasing responsiveness, a low dose of angiotensin decreased blood flow and increased vascular resistance in the head of the pancreas,

tail of the pancreas, adrenal gland and spleen while the liver remained apparently unresponsive to angiotensin. When the infusion rate of angiotensin was increased, such that a high pharmacological dose was administered, differential hemodynamic responses were again noted within various abdominal organs. The vascular beds of the pancreas head and pancreas tail continued to exhibit decreased blood flow and increased vascular resistance which were significantly different from both control and low dose values. In contrast, during the infusion of the high dose of angiotensin, blood flow returned to control levels in the adrenal gland, spleen and liver while vascular resistance was significantly greater than control in all regions ($p < 0.05$).

Differential responsiveness of vascular beds to angiotensin II may result from differences in the number of receptor sites for angiotensin (Bohr and Uchida 1967); the ability of the vascular bed to autoregulate its blood flow (Coleman et al. 1971); and the rate and degreee of development of tachyphylaxis to angiotensin (Khairallah et al. 1966). Results of the present study suggest taht the vasculature of the pancreas contains an abundance of receptor sites which must have a low level of refractoriness to angiotensin. Even though the pancreas is subjected to a high perfusion pressure and, since blood flow is decreased, regional vascular beds are probably subjected to a high build up of vasodilator metabolites, the vasoconstrictor action of angiotensin predominates at both low and high doses. In contrast, the vascular beds of the adrenal gland and spleen respond to a low dose of angiotensin with an increase in resistance but when the dose of angiotensin was increased blood flow returned to control values while calculated vascular resistance remained elevated. The results suggest that these vascular beds are quite

sensitive to the build up of vasodilator metabolites since blood flow returns to control levels during the infusion of a high dose of angiotensin. Passive forces might also be responsible for this response. Development of tachyphylaxis to any significant degree was not suspected to this (or any other) vascular bed since the development of acute tolerance in the presence of elevated perfusion pressures should result in blood flows and vascular resistances which are higher and lower than control respectively. In the present study, the hepatic circulation responded differently from other abdominal organs. The results suggest that the hepatic arterial circulation is comparatively unresponsive to a low dose of angiotensin and mildly responsive to a high dose.

In general, regional hemodynamic responses to angiotensin II have been shown to be both tissue and species specific (Page and Bumpus, 1974). Results of the present study are in conflict with Scholtholt and Shiraishi (1968) who reported decreased blood flow in the hepatic artery with increased portal vein pressure in dogs following the intravenous infusion of angiotensin at a dose of 0.1 μg/Kg/min. In consideration of the effect of angiotensin on regional hemodynamics in other species, Mandel and Sapirstein (1962) measured the fractional distribution of cardiac output (^{86}Rb) in rats following the intravenous infusion of low (0.05 μg/Kg/min) and high (0.5 μg/Kg/min) doses of angiotensin. Low and high doses of angiotensin slightly increased splenic and adrenal blood flow but hepatic blood flow was unchanged due to an increase in vascular resistance. Forsyth et al. (1971) measured the distribution of cardiac output (50 μ microspheres) in the unanesthetized rhesus monkey during the intravenous infusion of low (0.074 μg/Kg/min) and high (.2 μg/Kg/min) doses of angiotensin II. Infusion of a low dose

produced decreased blood flow and increased vascular resistance in the pancreas and liver (hepatic artery) while blood flow was unchanged and vascular resistance elevated in the adrenal gland and spleen. In contrast, during the infusion of a high dose of angiotensin, blood flow in the pancreas returned to control levels while vascular resistance remained increased. Blood flows remained at control levels in the adrenal gland and spleen while vascular resistances remained elevated. Thus, the regional vascular beds of the pancreas and liver exhibited a greater response to angiotensin than vascular beds of the spleen and adrenal gland. Doses of angiotensin II administered in the present study are comparable to doses used by other investigators (Mandel and Sapirstein, 1962; Shiraishi, 1968; Forsyth, 1971). However, results of the present study are in conflict with the reports of these investigators in nearly every abdominal organ studied. This conflict may be due to species differences (Page and Bumpus, 1974), differences in experimental methodology or differences in the period of measurements following the administration of angiotensin II.

As seen in Figure 5 and Figure 6 results of the present study suggest that the total wall vascular beds of different regions of the gastrointestinal tract exhibit differential degress of vasoconstriction in response to angiotensin II. The vascular response of the stomach was the largest, due perhaps to a greater abundance of angiotensin receptors. Total wall vascular beds of the duodenum, jejunum and ileum all exhibited decreased blood flow and increased vascular resistance of similar magnitude. The colon responded similarly, but at a magnitude lesser than any other region of the gastrointestinal tract. These results are in conflict with the report of Forsyth et al. (1971) who measured

the fractional distribution of cardiac output (50 μ microspheres) in the unesthetized rhesus monkey during the intravenous infusion of low and high doses of angiotensin II. It was reported that the vascular bed of the stomach failed to respond to angiotensin at both low and high doses as blood flow and vascular resistance remained at control levels. The small intestine failed to respond significantly at the low dose but normal blood flow with an elevated vascular resistance was noted at the high dose. In this report, the colonic vascular bed responded in a magnitude greater than any other region of the gastrointestinal tract. During the low dose, colonic blood flow remained at control levels while vascular resistance increased. When a high dose of angiotensin was adminstered colonic blood flow decreased and vascular resistance increased. Thus the results of this report are completely opposite of the results of the present study even though the doses of angiotensin used are comparable. Again, differences in angiotensin doses and species of experimental animal may play a role in this conflict (Page and Bumpus, 1974).

As seen in Figures 7, 8a, 8b and 8c, results of the present study suggest that the mucosal and submucosal layers of the gastrointestinal tract respond in a similar manner to both low and high doses of angiotensin II, exhibiting decreased blood flows and increased vascular resistances in the regions of the stomach, duodenum, jejunum, ileum and colon.

In contrast, as seen in Figures 7, 8a, 8b, and 8c, the muscularis of the gastrointestinal exhibited differential responses to low and high doses of angiotensin II. In the stomach muscularis blood flow decreased and vascular resistance increased. However, in the muscularis

layer of the duodenum and jejunum blood flow increased while vascular resistance decreased and remained unchanged respectively. In the muscularis layer of the ileum and colon blood flow remained unchanged while vascular resistance increased.

Thus, the constrictor effect of angiotensin appeared to dominate within the vascular compartments of the mucosal and submucosal layers in all regions of the gastrointestinal tract studied. In contrast to the vascular response of the mucosal and submucosal layers, the degree of vasoconstriction within the muscularis layer was considerably lesser. While the stomach muscularis exhibited an increased resistance to both low and high doses, the muscularis layers of the ileum and colon responded only to the high dose and the duodenum exhibited a decrease in resistance to both low and high doses of angiotensin. It is possible that the apparent lack of responsiveness of the muscularis layer in most regions of the gastrointestinal tract is due to passive forces acting upon blood vessels in the presence of an elevated perfusion pressure. While a compartmental analysis of gastrointestinal hemodynamics in response to angiotensin has not been undertaken, decreased mesenteric blood flow with increased vascular resistance has been reported (Gomori et al. 1962). A possible hypothesis explaining the apparent lack of sensitivity of the muscularis layer to angiotensin is found in the work of Shehadeh et al. (1969). In this study, injection of low (0.05 μg/Kg/min) and high (1.0 μg/Kg/min) doses of angiotensin into the canine superior mesenteric artery resulted in vasoconstriction of the total mesenteric vascular bed and an increase in jenunal motility. While gastrointestinal motility was not documented in the present study, an increases in motility would tend to produce an active hyperemic state

and thus increase the production of vasoactive metabolites within the vascular bed of the muscularis compartment disproportionately to other tissues. Autoregulation of blood flow in response to an exaggerated presence of vasoactive metabolites could explain this apparent lack of sensitivity to angiotensin within the muscularis layer of the gut wall. Thus, the results of the present study suggest that during the intravenous infusion of angiotensin, blood flow is decreased within the mucosal and submucosal layers of all regions of the gastrointestinal tract while the muscularis layers of the duodenum and jejunum exhibit a much lesser constrictor response.

SUMMARY AND CONCLUSIONS

The present study consists of two series of animals and utilizes the radioactive microsphere dispersion technique. In each series, three types of 15 $\pm$ 5 μ diameter microspheres, labeled with ^{85}Sr, ^{141}Ce and ^{51}Cr were injected into the left ventricle for splanchnic blood flow measurements.

Series I was originally designed to investigate the effect of chronic (6 week) perinephritic hypertension on regional splanchnic hemodynamics in dogs. Each animal was to serve as its won control thus eliminating inter-animal variance. Abnormal control blood flows measured by the initial microsphere injection (chronic control values) suggested that these microspheres had been displaced from some vascular beds during the 8 week experimental period. The questionable validity of the chronic control values necessitated Series II in the present study.

Series II in the present study was designed to investigate the effects of low and high pharmacological doses of angiotensin II on regional splanchnic hemodynamics in dogs. In this series, the blood flow values measured before the infusions of angiotensin II (acute control values) was also used to compare the chronic control values of Series I to determine the feasibility of using radioactive microspheres in chronic vascular research. The acute control values were also used as the control for the flows determined in Series I after 6 weeks of perinephritic hypertension (chronic hpertensive values) to determine the hemodynamic effect of 6 week chronic perinephritic hypertension. The results are as follows:

1. The radioactive microspheres dispersion technique is not a valid technique for measuring vascular parameters over an extended period of time within the splanchnic circulation. During the 8 week experimental period, microspheres are lost from the mucosal layer of the duodenum, jejunum and ileum. In contrast, microspheres are gained in the stomach submucosa and muscularis layers of the stomach and duodenum.

2. Six weeks of chronic perinephritic hypertension tends to increase blood flow in the pancreas head and pancreas tail while their vascular resistance remain unchanged. In the adrenal gland, spleen and liver blood flow remains unchanged while vascular resistance tends to be elevated.

3. Six week perinephritic hypertension tends to be associated with normal blood flow and increased vascular resistance in the wall of the stomach, duodenum, jejunum and ileum. In the colon blood flow tends to be elevated with no change in vascular resistance.

4. Six week chronic perinephritic hypertension tends to be associated with no change in blood flow and elevated vascular resistance in the mucosa of the stomach, duodenum, jejunum, ileum and colon.

5. Six week chronic perinephritic hypertension is associated with increased blood flow in the submucosal layer of the stomach, duodeunum, jejunum, ileum and colon. Submucosal vascular resistance is significantly decreased in the jeunum and colon and tends to decrease in the stomach, duodenum and ileum.

6. Six week chronic perinephritic hypertension produces significantly increased blood flow in the muscularis layer of the duodenum, jejunum and colon and tends to produce increased blood flow in the

stomach and ileum muscularis layer.

7. The intravenous infusion of low (0.05 μg/Kg/min) and high (1.0 μg/Kg/min) pharmacological doses of angiotensin II produces differential hemodynamic responses within various abdominal organs. In terms of decreasing responsiveness, a low dose produces decreased blood flow and increased vascular resistance in the pancreas head, pancreas tail, adrenal gland, and spleen, but does not affect the "vasculature perfused by the hepatic artery." When a high dose is infused the pancreas head and pancreas tail exhibit further decreased blood flow and increased vascular resistance. In contrast, during the high dose blood flow returns to control in the adrenal gland, spleen and hepatic artery while vascular resistance remains elevated.

8. The intravenous infusion of low and high doses of angiotensin II produces different degress of vasoconstriction within various regions of the gastrointestinal tract. The stomach exhibits the largest decrease in total-wall blood flow and increase in vascular resistance. The duodenum, jejunum and ileum exhibit decreased total-wall blood flow and increased vascular resistance of similar magnitude. The colon responds similarly but at a magnitude less than any other region.

9. The intravenous infusion of low and high pharmacological doses of angiotensin II produces decreased blood flow and increased vascular resistance in the mucosal and submucosal layers of the stomach, duodenum, jejunum, ileum and colon.

10. The intravenous infusion of low and high pharmacological doses of angiotensin II produced differential hemodynamic responses within the muscularis layer of the gastrointestinal tract. In the stomach

muscularis blood flow decreases and vascular resistance increases. The muscularis layer of the duodenum and jejunum exhibit increased blood flow while vascular resistance decreased and remained unchanged respectively. In the muscularis layer of the ileum and colon blood flow remains unchanged while vascular resistance increases.

In conclusion, the present study indicates that:

1. Radioactive microspheres are displaced from vascular beds with time and hence, are not feasible for measuring vascular parameters over an extended period of time.

2. Chronic one-kidney perinephritic hypertension is associated with blood flow changes within the submucosal and muscularis layers of the gastrointestinal tract.

3. Regional vascular beds exhibit differential responses to the intravenous infusion of low and high pharmacological doses of angiotensin II.

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