MESENTERIC HEMODYNAMICS OF PERINEPHRITIC HYPERTENSION IN DOGS

Dissertation for the Degree of Ph. D.
MICHIGAN STATE UNIVERSITY
GEZA SIMON
1974

This is to certify that the

thesis entitled

MESENTERIC HEMODYNAMICS OF PERINEPHRITIC HYPERTENSION IN DOGS

presented by

Geza Simon

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Physiology

Francis J. Haddy
Major professor

Date 7/18/74

O-169

DR D182

ABSTRACT

MESENTERIC HEMODYNAMICS OF PERINEPHRITIC HYPERTENSION IN DOGS

By

Geza Simon

To extend the investigation of the regional hemodynamics of experimental renal hypertension, mesenteric (ileum) blood flow and pressure relationships and mesenteric venous pressure-volume relationships were measured in fifty dogs. In addition, femoral vein pressure-volume relationships were studied in twenty-two dogs. In ten dogs (group H-1), one kidney was wrapped in silk eleven days before study; in fifteen dogs (H-2), one kidney was wrapped four weeks, and the other kidney was removed two weeks before study; in eight dogs (H-3), one kidney was wrapped and the other kidney was removed four to twenty-four weeks before study; thirty-three dogs were prepared as normotensive controls (C-1, C-2 and C-3). A significant rise ($P < 0.05$) in mean arterial blood pressure occurred in groups H-1, H-2 and H-3 in the unanesthetized state.

Under pentobarbital anesthesia (35 mg/kg, iv), blood flow and intravascular pressures were measured in the collateral-free, innervated, naturally perfused loop of ileum. Venous pressure-volume relationships were measured in isolated segments of mesenteric vein *in vivo* and in excised segments of the superior mesenteric and femoral veins *in vitro*.

G80797

Geza Simon

Veins from hypertensive and normotensive dogs were examined histologically and analyzed for their water, Na and K content.

In the combined group of hypertensive dogs (H-1 plus H-2), mesenteric (ileum) blood flow and intravascular pressures were increased ($P < 0.05$) and total and segmental vascular resistances were normal ($P > 0.05$), compared to controls (C-1 plus C-2). The venous pressure-volume curves of early, one-kidney (H-2) and chronic, one-kidney (H-3), but not of early two-kidney (H-1), hypertensive dogs were shifted in the direction of the pressure axis ($P < 0.05$). Calculated compliances were also decreased ($P < 0.05$) in groups H-2 and H-3. While there were no histological differences, the veins of hypertensive (H-2 plus H-3) dogs had an increased water ($P < 0.05$), Na ($P < 0.01$) and K ($P < 0.05$) content.

This study is the first report of increased blood flow, accompanied by normal vascular resistances, to a regional vascular bed in early experimental hypertension. Normal mesenteric vascular resistances, despite elevated intravascular pressures, suggest decreased vascular distensibility in hypertension. Vascular distensibility is decreased on both the arterial and the venous side of the circulation. Decreased venous compliance in early, one-kidney (H-2) and chronic, one-kidney (H-3) hypertensive dogs appears to be due to factors other than veno-constriction. This impression is based on the analysis of venous pressure-volume curves and the findings of increased water and electrolyte content of veins from hypertensive dogs.

MESENTERIC HEMODYNAMICS OF PERINEPHRITIC HYPERTENSION IN DOGS

By

Geza Simon

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Physiology

1974

To Janka

ACKNOWLEDGMENTS

I thank Dr. H. W. Overbeck for giving me the opportunity to come to Michigan State University and for suggesting the idea for this thesis. I also thank the members of my guidance committee: Dr. F. J. Haddy for his generosity and wisdom, Dr. C. C. Chou for his friendship, Dr. S. R. Heisey for his rigor, Dr. J. B. Hook for his skepticism and Dr. J. B. Scott for his realism.

* * * * *

TABLE OF CONTENTS

	Page
LIST OF TABLES	vi
LIST OF FIGURES	viii
CHAPTER	
I. SURVEY OF LITERATURE	1
Introduction	1
Human Essential Hypertension	2
Cardiac Output	2
Blood Volume	3
Regional Hemodynamics	3
Vascular Compliance	14
Summary	25
Experimental Renovascular Hypertension	26
Cardiac Output	27
Blood Volume	30
Regional Hemodynamics	32
Vascular Compliance	34
Summary	38
Human Renovascular Hypertension	38
Systemic Hemodynamics	39
Blood Volume	40
Regional Hemodynamics	40
Vascular Compliance	42
Summary	43
Spontaneously Hypertensive Rats	43
Systemic Hemodynamics	44
Blood Volume	45
Regional Hemodynamics	46
Vascular Compliance	47
Summary	47
II. PURPOSE OF THE INVESTIGATION	48
III. METHODS	49
Induction of Hypertension and the Preparation of Controls	49

CHAPTER Page

Mesenteric (Ileum) Blood Flow and Pressure Relationships 51
Mesenteric (Ileum) Blood Flow and Perfusion Pressure Relationships 56
Mesenteric Vein Pressure-Volume (Compliance) Relationships *In Vivo* 57
Superior Mesenteric Vein Pressure-Volume (Compliance) Relationships *In Vitro* 62
Femoral Vein Pressure-Volume (Compliance) Relationships *In Vitro* 66
Venous Wall Water, Sodium and Potassium Content 67
Histological Examination of the Mesenteric Vascular Arcade and the Femoral Vein 68
Additional Studies 68

IV. RESULTS 69

Mesenteric (Ileum) Blood Flow and Pressure Relationships 71
Mesenteric Vein Pressure-Volume (Compliance) Relationships *In Vivo* 75
Superior Mesenteric Vein Pressure-Volume Relationships *In Vitro* 89
Femoral Vein Pressure-Volume Relationships *In Vitro* . . 105
Venous Wall Water, Na and K Content 107
Histological Examination of the Mesenteric Vascular Arcade and the Femoral Vein 111

V. DISCUSSION 117

Mesenteric (Ileum) Blood Flow and Pressure Relationships 119
Venous Pressure-Volume (Compliance) Relationships . . . 125

VI. SUMMARY AND CONCLUSIONS 133

APPENDIX 135

BIBLIOGRAPHY 138

LIST OF TABLES

TABLE		Page
1.	General observations in control (C-1, C-2 and C-3) and in hypertensive (H-1, H-2 and H-3) dogs. Group means ± SEM of awake blood pressures, body weights, blood urea nitrogen, urine specific gravity and number of days (range) of hypertension and qualitative urinary albumin (range)	70
2.	Mesenteric (ileum) blood flow and pressure relationships under pentobarbital anesthesia. Group means ± SEM of weight of ileum, blood flow, pressures and resistances . .	72
3.	Group mean ± SEM of in vivo mesenteric vein pressure-volume relationships and compliance ($\Delta V/\Delta P$) in control (C-1 and C-2) and in hypertensive (H-1 and H-2) dogs, during Injection Phase	80
4.	Group mean ± SEM of in vivo mesenteric vein pressure-volume relationships and compliance ($\Delta V/\Delta P$) in control (C-1 and C-2) and in hypertensive (H-1 and H-2) dogs, during Withdrawal Phase	81
5.	Body weights and vein weights (mean ± SEM) in groups subjected to the study of in vitro superior mesenteric vein pressure-volume relationships	90
6.	Group mean ± SEM of in vitro superior mesenteric vein pressure-volume relationships and compliance ($\Delta V/\Delta P$) in control (C-1 and C-2) and hypertensive (H-1 and H-2) dogs, during Injection Phase	91
7.	Group mean ± SEM of in vitro superior mesenteric vein pressure-volume relationships and compliance ($\Delta V/\Delta P$) in control (C-1 and C-2) and hypertensive (H-1 and H-2) dogs, during Withdrawal Phase	92
8.	Group mean ± SEM of in vitro superior mesenteric vein pressure-volume relationships and compliance ($\Delta V/\Delta P$) in control (C-2) and in hypertensive (H-2) dogs, during infusion at constant rate of 9.88 ml/min	100

TABLE Page

9. Correlation between weight of superior mesenteric vein (mean ± SEM) and total volume (mean ± SEM) injected to reach 40 mm Hg intravenous pressure in groups H-2 and C-2 102

10. Correlation between weight of superior mesenteric vein (mean ± SEM) and compliance (mean ± SEM) in pressure range of 5-15 mm Hg, during injection phase, in groups H-2 and C-2 102

11. Body weights and vein weights (mean ± SEM) in groups subjected to the study of *in vitro* femoral vein pressure-volume relationships 105

12. Group mean ± SEM of *in vitro* femoral vein pressure-volume relationships and compliance ($\Delta V/\Delta P$) in control (C-2, C-3) and in hypertensive (H-2, H-3) dogs, during infusion at constant rate of 3.88 ml/min 106

13. Mean ± SEM of venous wall water, Na and K content in early, *one*-kidney (H-2), chronic, *one*-kidney (H-3) hypertensive and control (C-2, C-3) dogs 110

14. Group mean ± SEM of *in vitro* superior mesenteric vein pressure-volume relationships and compliance ($\Delta V/\Delta P$) in control (C-1) and in hypertensive (H-1) dogs, during infusion at constant rate of 9.88 ml/min 135

LIST OF FIGURES

FIGURE		Page
1.	The characteristic constricted (sigmoid) and dilated (convex toward the volume axis) venous distensibility pattern	16
2.	Venous distensibility pattern obtained during rapid continuous infusion (upper dashed line) and during stepwise injections at ten second intervals (lower dashed line). The solid line represents the continuous record of pressure-volume relationships in the vein during stepwise injections	17
3.	Schematic drawing of the innervated, collateral-free, naturally perfused loop of small intestine (ileum) preparation	54
4.	Schematic drawing of the Y-shaped (4-4-1 1/2 cm) segment of mesenteric vein used to study venous pressure-volume relationships *in vivo*	59
5.	Schematic drawing of apparatus used to study venous pressure-volume relationships *in vitro*	64
6.	Blood flow-pressure relationships in the pump-perfused vascular bed of ileum. Mean ± SEM perfusion pressure in control (C-1, C-2) and hypertensive (H-1, H-2) dogs	77
7.	Blood flow-resistance relationships in the pump-perfused vascular bed of ileum. Mean ± SEM resistance in control (C-1, C-2) and hypertensive (H-1, H-2) dogs . .	79
8.	Mean ± SEM *in vivo* mesenteric vein pressure-volume relationships (injection phase) in sham-operated control (C-1), ____ , and early, *two*-kidney hypertensive (H-1), ---- , dogs	84
9.	*In vivo* mesenteric vein pressure-volume relationships (injection phase) in 15 unilaterally nephrectomized, sham-operated control (C-2) and 15 early, *one*-kidney hypertensive (H-2) dogs. Each curve represents the average of 2 or 3 separate measurements in one animal	86

FIGURE Page

10. Mean ± SEM *in vivo* mesenteric vein pressure-volume relationships (injection phase) in unilaterally nephrectomized, sham-operated control (C-2) and early, one-kidney hypertensive (H-2) dogs. Withdrawal curve, —·—·, for controls and hypertensives is also shown. *P < 0.05; #P < 0.02 88

11. Mean ± SEM *in vitro* superior mesenteric vein pressure-volume relationships (injection phase) in sham-operated control (C-1) and early, two-kidney hypertensive (H-1) dogs 95

12. Mean ± SEM *in vitro* superior mesenteric vein pressure-volume relationships (injection phase) in unilaterally-nephrectomized, sham-operated control (C-1) and early, one-kidney hypertensive (H-2) dogs. Withdrawal curve for controls and hypertensives is also shown. *P < 0.05; #P < 0.02 97

13. Mean ± SEM in vitro superior mesenteric vein pressure-volume relationships during infusion at constant rate of 9.88 ml/min in unilaterally-nephrectomized, sham-operated control (C-2) and early, one-kidney hypertensive (H-2) dogs. *P < 0.05 99

14. Scatter diagram for the weight (gm) of superior mesenteric vein and the total volume (ml) injected to reach 40 mm Hg intravenous pressure in 11 control (C-2) and 10 hypertensive (H-2) dogs 104

15. Mean ± SEM *in vitro* femoral vein pressure-volume relationships during infusion at constant rate of 3.88 ml/min in unilaterally nephrectomized, sham-operated control (C-2, C-3) and early (H-2) and chronic (H-3) one-kidney hypertensive dogs. *P < 0.05 109

16. Cross section through portion of a small artery (left) and its accompanying vein from the mesentery. Trichrome stain. x 80 113

17. Cross section through portion of a small mesenteric vein. Trichrome stain. x 160 115

FIGURE Page

18. Analysis of venous pressure-volume data. A. Actual record of superior mesenteric vein pressure-volume relationships, injection and withdrawal phase, *in vitro*. Stepwise injection and withdrawal of 0.2 ml aliquots of Krebs-Ringer solution, horizontal axis, vs. intravenous pressure (mm Hg), vertical axis. Paper speed at 1 mm/sec. B. Plot of pressure-volume measurements, injection phase. Points were taken at 10 seconds following each injection. The calculation of venous compliance in the pressure ranges of 5-15, 15-25 and 25-35 mm Hg is also shown 136

CHAPTER I

SURVEY OF LITERATURE

Introduction

According to present concepts, the elevated blood pressure in most established forms of arterial hypertension is attributable primarily to an increase in total peripheral vascular resistance. It is not known with certainty whether or not the peripheral resistance increases uniformly in all vascular areas or whether the pattern of the early distribution of the abnormal peripheral resistance is the same or similar to that seen in chronic arterial hyptertension. Both of these considerations are important in understanding the pathogenesis of hypertension.

In this review, four types of hypertensive disease are considered: human essential hypertension, experimental renovascular hypertension, human renovascular hypertension and genetic hypertension in rats. The review of each type is subdivided to consider: cardiac output, blood volume, regional blood flows and resistances (total, parallel- and series-coupled) and autoregulatory phenomena, with special attention to the vascular bed of the mesentery.

Human Essential Hypertension

Cardiac Output

Human essential hypertension is elevated arterial blood pressure occurring in man without an evident cause. Over 90% of cases of human hypertension fall in this category. In its established, uncomplicated form, human essential hypertension is characterized by a normal cardiac output and an elevated total peripheral vascular resistance (Pickering, 1972; Varnauskas, 1955; Frohlich et al., 1967).

Relatively recent findings, however, seem to indicate that cardiac output, accompanied by normal or even decreased total peripheral vascular resistance, may be increased in the early, so-called borderline stage of human essential hypertension. According to Julius and Schork (1971), hemodynamic data on over 400 subjects with borderline hypertension are available. A substantial portion of these subjects has an increased cardiac output, which is a fairly reproducible finding. A group of patients with borderline hypertension and increased cardiac output continued after 50 months to maintain a significant elevation, although there was a tendency toward a decrease of cardiac output and an increase in total peripheral vascular resistance (Eich et al., 1966). There is some controversy as to whether the output is increased by an elevated heart rate, or a high stroke volume.

The mechanism for the elevation of the cardiac output in borderline hypertension is unexplained. In this regard, the relative role of intravascular volume and its distribution and the contribution of venous return should be explored. An increase in intravascular

volume, in the absence of heart failure or increased vascular capacitance, leads to an increase in cardiac output. Similarly, decreased venous distensibility (capacitance function), in the absence of decreased blood volume, leads to increased venous return and cardiac output in turn.

Blood Volume

Absolute blood volume in human essential hypertension seems to depend on the severity of the hypertension. Plasma volume, measured from the volume of distribution of ^{131}I- or ^{125}I-labeled human serum albumin, was found to be normal in essential hypertensive men with supine diastolic blood pressure less than 105 mm Hg. In hypertensive subjects with a diastolic blood pressure greater than 105 mm Hg, plasma volume was found to be reduced and inversely related to the diastolic blood pressure (Bello et al., 1965; Tibblin et al., 1966; Dustan et al., 1973). The reasons for the reduction of plasma volume are not apparent. It has been suggested that in human essential hypertension the reduction of plasma volume may reflect increased capillary hydrostatic pressure, because total extracellular fluid volume, estimated with either ^{82}Br or ^{24}Na, was found to be normal, while the ratio of plasma volume to interstitial fluid volume was significantly reduced (Dustan et al., 1973).

Regional Hemodynamics

Indirect measurements of regional blood flow in human subjects with established, uncomplicated human essential hypertension suggest

that the increased vascular resistance is uniformly distributed in the systemic circuit, except perhaps in skeletal muscle and kidneys. There is evidence that vascular resistance may be decreased and blood flow increased in the skeletal muscle vascular beds. There is also evidence that total blood flow and blood flow per functional tubular tissue usually decrease in the renal vascular bed, the result of disproportionately great increase in renal vascular resistance.

Brod et al. (1960, 1962) measured vascular resistance simultaneously in several vascular beds of men with essential hypertension. They estimated cardiac output by the congo-red and rose-bengal dye-dilution method and found it to be similar in hypertensives and in normotensives. They measured renal, splanchnic, skin and muscle blood flow by the p-amino-hippurate clearance, the rose-bengal disappearance, the heated thermocouple and the occlusion plethysmographic methods, respectively. Their results indicate that, compared to normals, essential hypertensives at rest have higher resistances in the renal, splanchnic and cutaneous vascular beds, while their muscle vascular resistance is lower. Thus, in hypertensives, blood flow appears to be shunted from the viscera and skin to muscle. Interestingly, the same distribution of cardiac output occurs in normal individuals during exercise and stress. The authors suggested that a disturbance of the autonomic nervous system may be responsible for the observed hemodynamic changes in human essential hypertension.

Other studies of individual regional vascular beds support the findings of Brod et al. Abramson and Fierst (1942) studied resting

blood flow, by the venous occlusion plethysmographic technique, in the forearm (hand excluded) and leg (foot excluded) of hypertensive and normotensive subjects. They found that in hypertensives, the resting blood flow in the forearm and leg was significantly greater than that in normals. In addition, they noted a tendency toward a linear relationship between systolic blood pressure and average blood flow to extremity in hypertension, implying a normal or near normal muscle vascular resistance. They, however, failed to analyze their data in terms of vascular resistance. Their reported data are insufficient to make such calculations in retrospect.

Conway (1963), using water plethysmography, measured resting blood flow in the forearm (hand excluded) of essential hypertensive and normotensive subjects. He found resting blood flow to be increased and forearm vascular resistance to be normal in established human essential hypertension.

Overbeck et al. (1969), using an indicator dilution technique, studied blood flow and pressure relationships in the entire forearm, with the hand included, of essential hypertensive and normotensive subjects. The authors found the blood flow to the forearm to be similar in the two groups. Mean forearm vascular resistance, on the other hand, was significantly greater in hypertensives. The discrepancy between the findings of Overbeck et al., on the one hand, and Abramson, Fierst and Conway, on the other, can be explained on the basis of the relative composition of the forearm with the hand excluded and the forearm with the hand included. The forearm with the hand excluded is made up

primarily of muscle and bone. The hand is made up principally of skin and bone. The findings of Overbeck et al., therefore, suggest that, while the vascular resistance to muscle is normal or only slightly increased, skin vascular resistance is significantly increased in established hypertension.

Amery et al. (1969) studied blood flow to a single muscle, the tibialis anterior, using the ^{133}Xe local clearance method in hypertensive and normal male subjects, both at rest and after ischemic exercise. Their findings show that at rest in hypertension, both muscle blood flow and resistance are increased, implying that the muscle vessels share in the increase of total peripheral vascular resistance, but to a lesser extent than the total circulation.

Reduction in renal blood flow has been a consistent finding in human essential hypertension, as attested to by both the older clearance studies and the more recent radioactive inert gas washout or desaturation methods. What is more, a direct relationship between the severity of the hypertension and the degree of reduction in renal blood flow per unit mass of tissue can be discerned. In view of the arterial hypertension, the reduced renal blood flow is indicative of a considerably elevated renal vascular resistance, which is in excess of that seen in other regional vascular beds (Goldring et al., 1941; Ladefoged et al., 1969; Hollenberg et al., 1969).

In contrast to the elevated muscle blood flow and the reduced renal blood flow in human essential hypertension, investigators have found normal blood flow and increased vascular resistance in the brain

(Kety et al., 1948; Mallett et al., 1963), the splanchnic bed (Culbertson et al., 1951; Wilkins et al., 1952; Cohn et al., 1962), the coronary bed (Rowe et al., 1961), the hand (Stead et al., 1940), the foot (Stead et al., 1940), the digit (Caliva et al., 1963) and the skin (Brod et al, 1962).

In comparison to the other regional vascular beds, few data are available concerning the splanchnic circulation in human essential hypertension. The splanchnic circulation is defined here as the vascular system that is perfused by the celiac, the superior mesenteric, and the inferior mesenteric arteries, and is drained by the hepatic veins. The reason for the scarcity of data concerning the splanchnic circulation is the relative inaccessibility of these vascular beds.

Wilkins et al. (1951, 1952) measured hepatic blood flow in hypertensive patients and in normal subjects, utilizing the BSP extraction method, first developed in their laboratory. The method is based on the ability of the liver to take up the dye rapidly. Although it was once considered to be a simple index of liver blood flow, the clearance of BSP from the blood is also influenced by the rate of transmembrane transport of the dye, the hepatic storage capacity and the blood-to-bile transfer maximum. Furthermore, the method requires catheterization of a branch of the hepatic vein, a process which introduces a venous sampling error, in that blood withdrawn from the catheter may not truly represent the concentration of the dye in the hepatic venous effluent. The average estimated hepatic blood flow, as measured by Wilkins et al., was 1303 ± 50 ml/min in a group of 41

hypertensives and 1381 ± 78 ml/min in a group of 21 normotensives. The difference in blood flow was not significantly different in the two groups. Unfortunately, only a small fraction of the two groups of subjects is characterized as to age, body weight, severity of hypertension and hepatic function. It is, therefore, difficult to determine how well the two groups were matched.

Cohn et al. (1962) measured hepatic blood flow in hypertensives, without comparison to normotensives, using both the BSP clearance and the radioactive colloidal chromic phosphate uptake method. In a group of 8 hypertensives, the estimated hepatic blood flow averaged 1576 ml/min by the BSP and 1825 ml/min by the radioactive colloidal chromic phosphate method. The latter method is, however, based on the ability of the reticuloendothelial system of not only the liver, but also the spleen and the mesenteric lymph nodes to take up the colloidal material. The results obtained by the two methods are, therefore, not comparable, but they emphasize the difficulty that is inherent in the interpretation of this type of data. As far as the discrepancy between the mean estimated hepatic blood flow of 1303 ml/min in hypertensive patients, obtained by Wilkins, and that of 1576 ml/min, obtained by Cohn, is concerned, there is no apparent explanation. The calculated hepatoportal resistance, on the other hand, is invariably increased in human essential hypertension, but the extent of this increase in proportion to the other regional vascular resistances is uncertain.

The estimation of hepatic blood flow is a crude measure of splanchnic blood flow for it lumps together blood flow through two regional vascular beds: the hepatic and the mesenteric-portal. The arteries supplying the two vascular beds are in parallel with respect to each other, but they share the same venous outflow (hepatic veins). Furthermore, the mesenteric-portal bed itself is composed of two vascular beds in series. To date, no method applicable to the study of human subjects has been devised that would allow us to study these three vascular beds separately from each other. Their relative participation in the increase of the total peripheral vascular resistance in human essential hypertension remains to be defined. Finally, blood flow to the spleen, although of minor importance in man, should be considered, too.

Parallel-coupled resistances.--Few studies have been designed to explore the status of parallel-coupled resistances within an organ or tissue in established human essential hypertension, probably because of the technical difficulties involved. However, an alteration in parallel resistances in organs concerned with blood pressure regulation, such as the brain and the kidney, might well induce or modify the hypertension. To date, indicator-dilution techniques have been used to study the distribution of blood flow in the brain and in the kidney of hypertensive subjects. The distribution of blood flow in the brain appears to be normal to the white and gray matter of the cerebrum (Mallett et al., 1963). Dickinson et al. (1960), on the other hand, raised the possibility that blood flow through the vertebral artery system to the

brain stem may be impaired early in the course of the hypertension, leading to an increased basal vasomotor tone and the perpetuation of the hypertension in turn. In post-mortem studies, they were able to demonstrate reduced flow and increased resistance of the cerebral arteries of hypertensive patients, with preferential and early involvement of the vertebral arteries. Unfortunately, there is no method at the present time that would allow one to measure blood flow to the brain stem selectively *in vivo* in human subjects, a necessary requirement for testing Dickinson's hypothesis.

Recent investigators (Logan *et al.*, 1973) applied the inert gas-washout and the constant infusion, indicator-dilution techniques to the study of renal hemodynamics in hypertensive patients. The results indicate that the reduction of renal blood flow in human essential hypertension is due to a selective fall in renal cortical blood flow. In view of the arterial hypertension, the reduced cortical blood flow is indicative of a considerably elevated renal cortical vascular resistance. Medullary blood flow is preserved and medullary vascular resistance rises to a lesser degree than cortical vascular resistance. An increased pressure in the vasa recta because of transmission of elevated arterial pressure through a relatively nonvasoconstricted medullary vascular bed could inhibit sodium transport in the loop and account for the concentrating defect and exaggerated natriuresis observed in hypertensive subjects (Baldwin *et al.*, 1965).

With regard to the splanchnic circulation, there is no report in the literature concerning compartmental blood flow and parallel-coupled resistances of the vascular bed of the gastrointestinal wall in human essential hypertension. The gastrointestinal wall consists of four layers: the mucosa, the submucosa, the muscularis and the serosa. The blood flow through these layers is not uniform. Certain stimuli, such as hypertension, may influence blood flow through one of these layers without altering blood flow through the others. Other stimuli, including hypertension, may increase mucosal flow and decrease muscle flow, the total flow being unchanged. An alteration of mucosal blood flow may bring about important changes in the absorptive and secretory function of the small intestine, possibly affecting the overall body water and electrolyte metabolism.

Series-coupled resistances.--Series-coupled resistances have been more extensively studied in hypertension. The consideration of series-coupled resistances within any given organ is just as important from the pathogenetic point of view of hypertension as that of parallel-coupled resistances, especially if series-coupled resistances are altered early in the course of the hypertension. Normal blood flow and pressure relationships on the venous or low pressure side of the circulation, throughout the course of the hypertension, would suggest stimuli which act solely on the arterial side of the circulation. An early and selective alteration of the flow and pressure relationships of the venous side of the circulation would suggest pathogenetic stimuli which act primarily on the veins.

Nailfold and skin capillary pressure have been studied indirectly, by the color blanching (Ellis et al., 1929), and directly, by the microinjection method (Eichna et al., 1942), in hypertension and have been reported as normal. The actual mean values in the two studies, however, differ greatly, not to mention the wide range of readings in both normals and hypertensives. In view of the normal blood flow to these areas, the similarity of the cutaneous capillary blood pressure of normals and hypertensives suggests that the increased vascular resistance of hypertensive subjects is precapillary and presumably arteriolar.

A possible exception to the finding of normal capillary pressure in hypertension is the renal vascular bed where an elevated filtration fraction, as measured by the clearance ratios of inulin and p-aminohippurate, is an early finding in chronic diastolic hypertension. Elevated filtration fraction may possibly reflect glomerular capillary hypertension, with relatively greater constriction of the efferent arteriole than of the afferent arteriole (Goldring et al., 1941). However, this conclusion about the distribution of resistance between the efferent and afferent arterioles has been disputed (Gomez et al., 1951).

What is the contribution of the larger arteries to the increased precapillary resistance in human essential hypertension? Oppenheimer and Prinzmetal (1937) attempted to answer this question by measuring the pressure gradient from the brachial to the digital artery of hypertensive subjects, assuming that the total forearm and hand blood flow is

normal. The authors reasoned that if the pressure gradient from large to small artery should become steeper with the rise of blood pressure in hypertension, it would point to an increased resistance in the larger arteries. They measured the brachial pressure by sphingomanometry and the digital artery pressure by Gartner capsule. The authors found that there is no increase in the arterial pressure gradient. They concluded that the arteries do not play an important role in the production of high peripheral resistance in human essential hypertension.

Kettel, Overbeck et al. (1969) measured intravascular pressures directly, through the insertion of catheters, in the brachial artery (large artery), the radial artery (small artery), a vein on the dorsum of the hand (small vein), and an antecubital vein (large vein) in hypertensive and normotensive subjects. The authors found the pressure gradient from small artery to small vein to be increased in hypertensives. The pressure gradient from large artery to small artery and from small vein to large vein was similar in the two groups. Assuming that blood flow to the whole arm is also similar in the two groups, their findings suggest that not only the large artery resistance but also the venous resistance in the arm of hypertensives is normal. Therefore, the elevated upper extremity vascular resistance in hypertension must result from constriction of the smaller vessels. However, Caliva et al. (1963), using a venous occlusion plethysmographic technique to measure indirectly venous pressure in the digits of patients with essential hypertension, found an elevated digitial venous pressure with normal digital blood flow and concluded that venous resistance is

elevated in hypertension, although to a lesser extent than small vessel resistance. As a result of the relative inaccessibility of the splanchnic circulation in human subjects, there is a complete lack of data concerning series-coupled resistances in this vascular bed. Specifically, little or nothing is known about the contribution of the portal and hepatic pre- and postsinusoidal and of the mesenteric pre- and postcapillary resistances to the overall increase of splanchnic vascular resistance.

It should be mentioned at this point that all the studies in this section of this review have dealt with the various regional hemodynamic features of established, uncomplicated human essential hypertension, characterized by normal cardiac output and increased total peripheral vascular resistance. The relatively recent finding of an increased cardiac output in borderline hypertension indicates the need to evaluate regional hemodynamics at the onset of hypertension, so that primary, pathogenetically important patterns may be distinguished from secondary, complicating features. To date, the distribution of the increased peripheral blood flow in subjects with borderline hypertension is essentially unexplored. Bello et al. (1967) indicate that renal blood flow may be elevated in borderline hypertension.

Vascular Compliance

General considerations (Spencer et al., 1963; Alexander et al., 1963).--Compliance is a property of the vascular wall, arising from its distensibility. Each component of the vessel wall, smooth muscle,

elastin, collagen and ground substance contribute to compliance. Compliance (C) is expressed in terms of blood volume (V) in the segment and the attending pressure difference across the vascular wall (P_c),

$$C = \frac{V}{P_c}$$

In vitro studies of excised segments of arteries and veins revealed two types of tension-length or pressure-volume (compliance) curves (Figure 1). One was described as curvilinear with considerable convexity toward the length or volume axis, the other sigmoid in character. At first, the latter was ascribed to an experimental artifact, until MacWilliam took the precaution of collecting fresh tissues and observed their behavior during the immediate post-mortem period. Shortly after the vessel was excised, it developed marked spasm. Tension-length or pressure-volume measurement at this time would reveal the characteristic sigmoid curve. When the state of contraction was eliminated by warming, the more conventional stretch curve was obtained. MacWilliam interpreted the sigmoid curve as a manifestation of the resistance to stretch of the smooth muscle. The curvilinear curve with convexity toward the length or volume axis, on the other hand, represents primarily the resistance to stretch of the connective tissue elements of the vessel wall, the smooth muscle elements being in a state of relaxation. Later, Alexander (1948, 1953, 1954, 1955), in his in vivo study of the femoral and mesenteric veins, demonstrated the same distensibility patterns. A controversy exists as to whether the sigmoid distensibility pattern of constricted veins is or is not associated with an overall reduction in total distensibility.

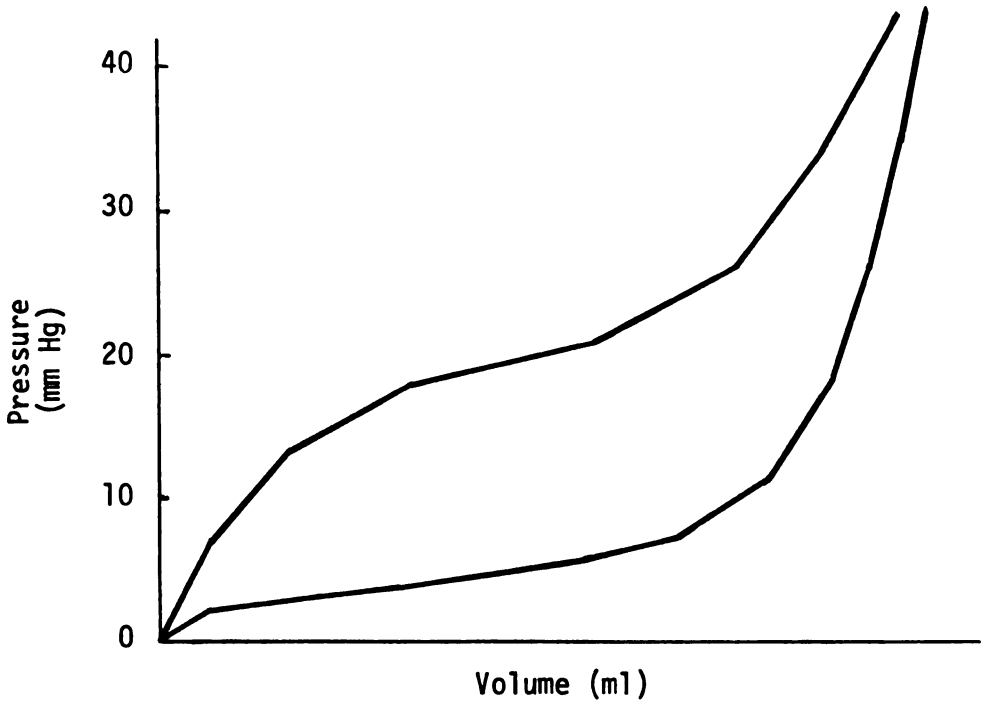


Figure 1. The characteristic constricted (sigmoid) and dilated (convex toward the volume axis) venous distensibility pattern.

Another feature of vascular distensibility or compliance is the marked time dependency in elastic behavior, sometimes referred to as "elastic hysteresis," "delayed compliance" or "stress relaxation," the latter implying that pressure dissipates following sudden distention to a constant volume (Figure 2). As a result, the pressure-volume (compliance) curve observed on injection and the pressure-volume curve found on withdrawal form a loop. Alexander pointed out that the initial state of venoconstriction or venodilation has appreciably greater influence on the pressure-volume curve observed during injection than during withdrawal. The latter curve is more reproducible than the former, being subject to fewer stimuli.

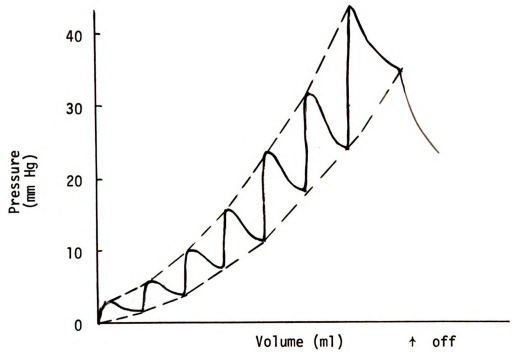


Figure 2. Venous distensibility pattern obtained during rapid continuous infusion (upper dashed line) and during stepwise injections at ten second intervals (lower dashed line). The solid line represents the continuous record of pressure-volume relationships in the vein during stepwise injections.

From the experimental point of view, especially, when one is trying to compare experimental data from one animal with those from another, these characteristics of vascular distensibility have important practical implications. First, the timing of the administration of anesthetics and of surgery should be standardized, so that the state of the vascular smooth muscle would be comparable in different animals. In the case of an in vitro study, the time elapsed between the excision of the tissue and the first in vitro determination of vascular distensibility should be similar from one experiment to another. Second, since

pressure-volume data obtained from arteries and veins are strongly influenced by the exact conditions of vascular distension, identical rates and magnitudes of distension should be used. Third, the time interval between subsequent pressure-volume determination should be set. Stress relaxation implies that a second stretch curve differs greatly from an initial stretch unless sufficient time is allowed between measurements for a complete restoration of the resting distensibility state. Studies have shown that this critical time period is between 20-30 minutes. Fourth, pressure-volume data have no absolute meaning unless related to a critical volume. Therefore, an attempt should be made to standardize the initial length and/or volume of the tissue. In the case of pressure-volume studies, the initial volume should be 0. There are obvious practical difficulties which interfere with accomplishing this objective, especially in the in vivo study of veins, where valve action may prevent complete emptying.

Inter-group comparison of vascular pressure-volume (compliance) relationships is valid only if proper attention has been paid to these considerations.

Vascular compliance in human essential hypertension.--Greene et al. (1966) studied pressure-volume (compliance) relationships directly in the isolated, temporarily occluded segment of the brachial artery of normotensive and hypertensive subjects. Following the isolation and occlusion of a 3 cm segment of the brachial artery, they emptied the segment of its blood content; 0.05 ml aliquots of normal saline at body

temperature were injected into the segment through an indwelling Cournand needle. An equilibration period of approximately ten seconds was allowed following each injection. Stepwise increments of fluid were added until intrasegmental pressure reached 150-200 mm Hg pressure. The authors found that the arterial pressure-volume curve of hypertensives is shifted in the direction of the pressure axis, implying decreased distensibility of the brachial artery in chronic human essential hypertension. This finding can be explained on the basis of structural changes, such as medial hypertrophy, elastic intimal thickening and increased water and electrolyte content, described by various investigators in both large and small arteries from hypertensive patients (Pickering, 1972). The question, then, arises as to whether these changes are primary or secondary to the increased intraluminal pressure in hypertension. The consensus of opinion at the present time appears to be that these are secondary changes.

There are no reports of direct measurements of venous compliance in essential hypertensive subjects. A number of indirect measurements are, however, available. Caliva et al. (1963) examined digital vascular compliance by rheoplethysmographic techniques (Burch, 1956), in hypertensive and normotensive subjects. Following occlusion of the venous outflow from the digit, the time course of the volume increase in the digit was measured until outflow pressure exceeded the occlusion pressure. The hypertensive pressure-volume curves showed small changes in volume associated with large pressure increases, that is, a steep pressure-volume curve. Since approximately two-thirds of systemic blood

is normally contained in veins, the authors concluded that, in addition to arterial compliance, digital venous compliance is probably also decreased in hypertensives.

More recently, Walsh et al. (1969) studied forearm venous distensibility in human essential hypertension, using the electro-capacitance plethysmographic method, and came to a conclusion similar to that of Caliva et al. The authors first determined the minimal occluding pressure that resulted in a measurable increase in forearm volume, usually in the range of 3-10 mm Hg. Then they measured the distensibility curve during emptying ("elastic hysteresis" or "delayed compliance") rather than during filling. Vascular distensibility, defined as the percent increase in forearm volume at cuff pressure of 30 mm Hg above the minimal occluding cuff pressure, was significantly less in their hypertensive than in their normotensive subjects. Whether the decreased vascular distensibility is due to decreased arterial and/or decreased venous compliance cannot be determined by this method.

Anderson (1954) studied total forearm vascular distensibility by a slightly different technique. He suddenly occluded the total circulation to the forearm, while he monitored venous pressure through a catheter inserted into one of the major superficial veins of the forearm. A period of 15-45 seconds was allowed for the intravascular pressure to come into equilibrium between the arterial and venous sides of the circulation. The highest reading in the vein, following the occlusion of the total circulation to the forearm, was defined as the intrinsic blood pressure. Intrinsic blood pressure in normals ranged

between 12-19 cm H_2O. Patients with chronic diastolic blood pressure showed a significantly elevated intrinsic blood pressure. Blood volume was not measured.

Ulrych et al. (1964) studied the cardiac and renal responsiveness of hypertensives and normotensives to acute volume expansion with 1200 ml/70 kg of iso-oncotic dextran in isosmotic normal saline. Control central venous pressure, cardiac output, glomerular filtration rate and urinary volume were similar in the two groups. Control total peripheral vascular resistance, on the other hand, was significantly higher and urinary Na excretion significantly lower in the hypertensive group. Fifty to seventy minutes after the infusion, the absolute increase in cardiac output, urinary sodium excretion and urinary flow was significantly greater in hypertensives than in normotensives, even though the absolute increase in central venous pressure was not different. Blood pressure changes, if any, were not reported. The authors suggest that the excessive response of cardiac output in hypertension may possibly reflect a deficient ability of the capacity vessels to dilate in response to the sudden expansion of intravascular volume, which leads to increased venous return. If this is true, one would have expected to see a significantly greater absolute increase in central venous pressure as well. In addition, the hypertensive subjects demonstrated a significantly greater fall in total peripheral vascular resistance than normotensives. The possibility that the greater increase in cardiac output in hypertension is due to the more pronounced vasodilatory response of the resistance vessels of hypertensives to

infusion of dextran cannot be ruled out. Although blood volume was not measured, an initially increased blood volume in hypertensives is an unlikely explanation for the reported findings in light of other studies indicating normal or even decreased volume in essential hypertensive patients. These experiments of Ulrych et al. confirm the findings of earlier studies showing an exaggerated natriuresis in human essential hypertension, following saline load (Baldwin et al., 1965).

In contrast to the above studies, there is other evidence which seems to indicate that venous compliance is not elevated in hypertension. Two groups of investigators measured vascular distensibility, using water-plethysmographic techniques, of the forearm and the calf of hypertensives subjects. Abramson and Fierst (1942) studied the vascular distensibility of both the forearm and the calf during filling. The initial 20 mm Hg occluding pressure resulted in a volume increment of only 0.16 ml/100 ml of forearm volume. The maximum volume increment at 70 mm Hg occluding pressure amounted to 0.52 ml/100 ml. When the results are plotted on a pressure-volume curve, the rapidly rising portion of a characteristic distensibility curve is never obtained. Thus, a difference in distensibility in the higher pressure ranges between hypertensives and normotensives could have been missed by the authors. The same observations applies to the experiments of Wood (1961), who studied forearm volume increments only up to 30 mm Hg occluding pressure. (An occluding pressure of 30 mm Hg applied to the surface of the arm may not represent an equivalent pressure in the deep veins of the arm). There was no demonstrable difference in the vascular

distensibility in hypertensives and in normotensives in this range of venous (occluding) pressure.

There are no reports in the literature concerning the venous distensibility of other regional vascular beds in human essential hypertension, including the liver and the intestines. This is unfortunate in view of the important blood storage function of the splanchnic circulation. Under normal physiologic conditions 14% of circulating blood volume is contained within the mesenteric veins (Texter et al., 1968). If there is a disturbance of venous capacitance function in human essential hypertension, the logical place to look for it is in the splanchnic vascular bed.

As to the mechanism underlying the suggested reduction in vascular distensibility in established, uncomplicated human essential hypertension, the consensus of opinion appears to be that it is due to increased smooth muscle tone, that is to say, to arterial and/or venous constriction (Caliva et al., 1963; Walsh et al., 1969). However, data that would bear out this suggestion are lacking. Walsh et al. (1969) repeated distensibility measurements in their hypertensive subjects after several weeks of antihypertensive therapy, but were unable to show a statistically significant increase in vascular distensibility.

Finally, while decreased arterial compliance in chronic human essential hypertension seems to be established, the evidence for decreased venous compliance is indirect and incomplete.

Venous wall anatomy and function (Alexander, 1963; Bader, 1963).--In order to understand the mechanism that may underlie the suggested reduction in venous distensibility in human essential hypertension, one has to consider the normal anatomy and function of the venous circulation. The venous bed includes veins and venules, i.e., vessels which cannot constrict against an internal pressure greater than 70-80 mm Hg (Abramson et al., 1942). The capacitance function of the venous bed is about equally shared by the venules and the larger veins.

In contrast to the arteries, the veins are very variable in their wall structures. Usually they have a larger percentage of collagen fibers, especially the large veins, but there are veins in which the muscular mass exceeds that of the collagen fibers, especially in the smaller veins and the veins of the lower extremities, which are subject to a large hydrostatic pressure. The inferior mesenteric vein of humans, for instance, is made up primarily of collagen and elastin (> 90%), while the skin vein of the foot is 50-60% smooth muscle.

Another important difference between arteries and veins is that the veins are securely embedded in the surrounding tissues. Decreased venous distensibility, therefore, could be partially due to decreased interstitial tissue compliance, as had been suggested by Lucas et al. (1973).

The elastic modulus defined as $\Delta P/\Delta V/V$, (where ΔP is pressure in dynes/cm^2 and V is volume in ml), of the various vascular wall elements are as follows: elastic modulus$_{(collagen)}$ = 300 x 10^6 dynes/cm^2; elastic modulus$_{(elastin)}$ = 6 x 10^6; elastic modulus$_{(smooth\ muscle)}$

and elastic modulus$_{(endothelium)}$ = 0.1 x 10^6 (Wiederhielm, 1965). On this basis, collagen fibers are considered some 3000 times stiffer (or less distensible) than smooth muscle fibers. Any consideration of vascular distensibility, therefore, has to take into account the contribution of collagen fibers, especially, in the higer pressure ranges, along the rapidly rising portion of the pressure-volume curve, where the connective tissue elements of the vessel wall begin to be stretched.

With regard to the proposed reduction in venous distensibility in human essential hypertension, pathologic data are completely lacking. In particular, data concerning the water and electrolyte and collagen content of the venous wall are needed. The composition of the interstitial tissue surrounding the veins should also be examined.

Summary

Chronic human essential hypertension is characterized by a normal cardiac output and an elevated total peripheral vascular resistance. Cardiac output, accompanied by a normal or even decreased total peripheral vascular resistance, may be increased in a large proportion of early human essential hypertension. Blood volume is either normal or decreased.

The study of the regional hemodynamics of human essential hypertension is extensive, but confined to a great extent to the chronic stage of the hypertension, where secondary, complicating changes may obscure primary, pathogenetically important changes. Also, by necessity the experimental techniques that have been utilized are indirect and,

therefore, the information concerning the role of parallel- and series-coupled resistances is incomplete or completely lacking, as in the case of the splanchnic circulation.

Although vascular distensibility seems to be decreased, the relative contribution of arterial vs. venous compliance has not been established.

Experimental Renovascular Hypertension

In 1934, Goldblatt et al. (1934) demonstrated that constriction of one or both renal arteries can lead to hypertension. In the dog, constriction of one renal artery, the other kidney being intact, produces either no hypertension or only a mild, transient elevation of arterial blood pressure. Constriction of both renal arteries or constriction of one renal artery plus removal of the opposite kidney, on the other hand, leads to chronic hypertension. There is, therefore, a definite difference in the severity of the hypertension produced by two-kidney and one-kidney Goldblatt hypertension.

In 1939, Page (1939) introduced an alternative method of producing renal hypertension in experimental animals. He showed that wrapping one kidney in silk or cellophane, with or without contralateral nephrectomy, induces an inflammatory reaction around the kidney which, in turn, leads to hypertension. This type of experimental hypertension is referred to as perinephritic hypertension, and it is one of the most effective ways of producing hypertension in experimental animals. Whether the hypertension is due to compression of the kidney itself

or to the compression of the renal pedicle is still uncertain. So far as is known, the hypertension produced by perinephritis behaves in every respect like that due to renal artery constriction (Pickering, 1972). The pathogenesis of both the Goldblatt and the perinephritic type of experimental renal hypertension remains uncertain despite the large body of research dedicated to this question since the introduction of these experimental models some 40 years ago.

Cardiac Output

In the animal models of experimental renovascular hypertension so far studied, cardiac output is increased in the early (less than four weeks) stage of the hypertension, followed by a gradual return of cardiac output to normal.

Ledingham et al. (1964, 1967) monitored the cardiac output of unanesthetized rats with electromagnetic flowmeters in place around the arch of the aorta, both before and after the clipping of one renal artery and the removal of the untouched kidney. Following clipping, total peripheral vascular resistance and blood pressure rose within two hours and remained elevated throughout the rest of the experiment. Cardiac output after having fallen below control values during the first five days postoperatively, began to rise on the fifth day and remained elevated for as long as 35 days, when the experiment was terminated.

Ferrario et al. (1970) monitored cardiac output with an electromagnetic flowmeter implanted around the arch of the aorta in unanesthetized dogs before and after the induction of perinephritic hypertension.

Eight to 15 days following wrapping of one kidney in cellophane, with the other kidney untouched, they found the cardiac output to be significantly elevated with slightly decreased total peripheral vascular resistance. Following removal of the untouched kidney, at two weeks, arterial blood pressure and, for the first time, total peripheral vascular resistance began to rise, while cardiac output rose further, reaching a maximum, amounting to 18% of control values, approximately two weeks postnephrectomy. By the fourth to sixth week postnephrectomy, cardiac output returned to normal, and an elevated total peripheral vascular resistance had become the predominant cause of the hypertension.

Very recently, Ferrario (1974) performed similar studies in unilaterally nephrectomized dogs with Goldblatt hypertension. Following constriction of the renal artery of the sole remaining kidney in unanesthetized dogs by an externally adjustable, chronically implanted clamp, cardiac output rose during the first week and remained elevated for a period of four weeks. During the first two weeks, the elevated cardiac output was solely responsible for the rise in mean arterial blood pressure, total peripheral vascular resistance being normal. An increase in heart rate and to a lesser extent an increase in stroke volume accounted for the increase in cardiac output. At three weeks after renal artery constriction, total peripheral vascular resistance began to rise, and by the fifth week an elevated total peripheral vascular resistance was the only cause of the hypertension. These two studies of Ferrario confirm the impression of previous investigators regarding the similarity between the hemodynamics of perinephritic and Goldblatt experimental hypertension.

Bianchi et al. (1970, 1972) noted a more transient rise in cardiac output and an earlier rise in total peripheral vascular resistance in conscious dogs with one-kidney (contralateral nephrectomy) and two-kidney (contralateral kidney intact), Goldblatt hypertension. In one-kidney hypertension, cardiac output, measured by dye dilution technique, was significantly elevated on days 4 and 7, following renal artery constriction. Total peripheral vascular resistance rose immediately and remained elevated for a period of 24 hours, thereafter, returning toward normal. In two-kidney hypertension, the rise in cardiac output was significant only on day 1 after renal artery constriction. By 6-7 days, cardiac output was normal. Total peripheral vascular resistance rose immediately and remained elevated throughout the duration of the study (7 days).

Coleman and Guyton (1969) studied hypertension caused by subtotal nephrectomy and salt loading in dogs and reported findings similar to those of Bianchi et al., namely, an early transient rise in cardiac output, with decreased total peripheral vascular resistance, followed by a return to normal of cardiac output and a rise of total peripheral vascular resistance.

With regard to an initial rise in cardiac output, followed secondarily by a rise in total peripheral vascular resistance, the "autoregulation theory" of the development of hypertension was proposed (Coleman and Guyton, 1969; Coleman et al., 1971). According to this theory, the increase in blood flow through all or some of the regional vascular beds gradually leads to an increase in total peripheral vascular resistance.

The autoregulatory function of the renal vascular bed is well known, renal blood flow being maintained at a relatively constant level in the arterial blood pressure range of 80-200 mm Hg. In the splanchnic circulation, autoregulation has been described in the liver (hepatic artery system), spleen and intestine. In the stomach, there is no autoregulation (Texter et al., 1968). The exact mechanism underlying autoregulation is not clear. Furthermore, our knowledge of autoregulation is confined to information derived from short-term animal experiments or clinical observations. Little is known about the time course and duration of autoregulatory response over the extended period of weeks or months. Therefore, it is uncertain how short-term regional autoregulation relates to the long-term total body autoregulation that has been suggested to occur in the course of the development of hypertension.

Blood Volume

Ledingham and Cohen (1964) measured extracellular fluid volume and plasma volume by the thiocyanate and Evans blue distribution method, respectively, in unilaterally nephrectomized rats following renal artery clipping. Although extracellular fluid volume and plasma volume tended to increase in both the clipped and the sham-operated control rats, the rise of extracellular fluid volume and plasma volume was significantly greater at three and seven days post-clipping of the renal artery. Extracellular fluid volume and plasma volume returned to normal by the fifteenth day following clipping.

Bianchi et al. (1970), using similar techniques, measured extracellular fluid volume and plasma volume in conscious, unilaterally nephrectomized dogs following renal artery constriction. The authors found a significant increase in extracellular fluid volume and plasma volume on days 1, 3-4 and 6-7 following renal artery constriction. By the twelfth to fourteenth day, extracellular fluid volume and plasma volume returned to normal. Therefore, a transient expansion of extracellular fluid volume and plasma volume appears to be a consistent accompaniment of the evolution of experimental renovascular hypertension in unilaterally nephrectomized animals following renal artery constriction.

Bianchi et al. (1972) repeated these same studies in conscious dogs following renal artery constriction, the contralateral kidney being left untouched. In these dogs, there was no significant change in extracellular fluid volume and plasma volume either during the first or the second week following renal artery constriction.

Ferrario et al. (1970) studied plasma and total blood volume, using the radioiodinated (^{125}I) serum albumin method, in dogs, 15 days after wrapping one kidney in cellophane, 15 days after contralateral nephrectomy (30 days post-wrapping), and after 10-17 months of chronic, one-kidney, perinephritic hypertension. There was no significant change in plasma and total blood volume at any one time investigated. Extracellular fluid volume was not measured by these authors. In contrast, very recently, Ferrario (1974) found, by the 10-minute Evans blue dye-dilution technique, a small rise in plasma and total blood volume,

accompanied by a fall in hematocrit, during the first two weeks after renal artery constriction in unanesthetized, unilaterally nephrectomized dogs.

Extracellular fluid volume was measured, using the constant infusion of mannitol method, by Grollman et al. (1953) in dogs with chronic, one-kidney, Goldblatt hypertension. Extracellular fluid volume was found to be significantly increased in comparison to that of control dogs. However, there is no information available concerning the renal and cardiac status of these animals. Uremia and/or congestive heart failure could possibly account for the extracellular volume expansion of hypertensive animals.

Regional Hemodynamics

In chronic hypertensive dogs with unilateral renal artery-stenosis and intact, contralateral kidney, blood flow per unit renal weight, measured directly, is reported normal in the non-stenotic kidney, and normal or decreased in the stenotic kidney, depending on the post-stenotic blood pressure. Renal vascular resistance, excluding the resistance offered by the stenosed artery, increases in both the stenotic and the non-stenotic kidneys, but the rise is greater in the stenotic kidney (Bounous et al., 1962).

In unilaterally nephrectomized, Goldblatt and perinephritic hypertensive dogs, in the early and chronic stages of hypertension, absolute renal blood flow, calculated from the phenol clearance and extraction percentage, and effective renal plasma flow, calculated

from the plasma diodrast clearance, are maintained at a normal level (Corcoran and Page, 1974).

More recently, Ferrario and McCubbin (1973) studied renal blood flow with the aid of chronically implanted flowmeters in unanesthetized and unilaterally nephrectomized dogs, before and after renal artery constriction. After mild stenosis (c. 20%) of the renal artery, mean renal blood flow decreased during the first 1-8 days; thereafter, mean renal blood flow returned to, or even exceeded, control values. Pressure distal to the stenosis was low compared to the systemic pressure, but in view of the developing hypertension, it was above control values. Therefore, the renal vascular resistance, excluding the resistance offered by the stenosed artery, was initially elevated, but tended to return toward normal after the first week of renal artery stenosis. More severe renal artery stenosis (c. 45%) led to sustained reduction in mean renal blood flow and sustained rise in renal vascular resistance distal to the stenosis.

Total coronary vascular resistance and coronary vascular resistance calculated on a unit myocardial weight basis have been reported as elevated in dogs with perinephritic experimental renovascular hypertension. These dogs had normal or slightly increased coronary blood flow per unit weight of myocardium (West et al., 1959). Brain blood flow, determined by the particle distribution method, has also been reported as normal in rats with experimental renovascular hypertension (Flohr et al., 1971).

More recently, hemodynamics in the vascular bed of the limb in dogs have been intensively investigated in the early (less than 4 weeks) and the chronic (more than 4 weeks) stages of perinephritic hypertension. 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. The parallel resistances of limb skin and skeletal muscle vascular beds share equally in the general increase in limb vascular resistance. The elevated limb resistance in the early stage, as well as in the chronic stage, is primarily confined to the small vessel segment of the limb vascular bed, consisting of small arteries, arterioles, capillaries and venules, although large artery resistance to skin may also be elevated. Skin and muscle venous resistances were normal in both the early and chronic stage of perinephritic hypertension (Overbeck et al., 1971; Overbeck, 1972).

There is no report in the literature to date on the status of the splanchnic circulation in either the early or the chronic stages of experimental renovascular hypertension.

Vascular Compliance

Feigl et al. (1963) studied the mechanical properties of the femoral arteries in a group of dogs before and after the induction of chronic, bilateral, perinephritic renal hypertension. The authors monitored intrafemoral arterial pressure and vessel diameter simultaneously with the help of transducers attached to the vessel wall in unanesthetized dogs. At the conclusion of the in vivo measurements,

a segment of the femoral artery was excised, and its wall thickness was determined. The authors expressed their findings in terms of the elastic modulus (E_p), defined as follows:

$$E_p = \frac{\Delta P}{\Delta \varepsilon} ,$$

ΔP representing pulse pressure, $\Delta \varepsilon$ representing change in strain. ε was, in turn, defined as: $\varepsilon = (r-r_o/r_o$, r and r_o representing radius under stress and radius at zero stress, respectively). The elastic modulus represents the distensibility of the arterial segment. The elastic modulus of the femoral artery was significantly increased following the induction of chronic perinephritic hypertension. The authors suggest that the increased elastic modulus of the femoral artery probably represents changes in the arterial wall material during hypertension. In this regard, the authors demonstrated that the water content of the hypertensive femoral artery was significantly increased over control values.

A number of indirect studies are available to suggest that venous distensibility or compliance may also be reduced in experimental renovascular hypertension. Richardson et al. (1964) measured mean circulatory pressure in ten unilaterally nephrectomized, Goldblatt hypertensive and in ten control dogs. Mean circulatory pressure was obtained by stopping the heart either by fibrillating it or by injecting acetylcholine, and quickly pumping blood from the arterial to the venous side of the circulation, until an equilibrium of pressures was effected. The equilibrium pressure is termed mean circulatory pressure. Under

conditions of unaltered blood and interstitial tissue volume, mean circulatory pressure reflects the distensibility of the entire vascular bed. The authors found the mean circulatory pressure to be increased in hypertension, but they did not measure blood or extracellular fluid volume. Ferrario et al. (1970) confirmed the findings of Richardson et al. in dogs with early one-kidney perinephritic hypertension. In addition, they measured the blood volume of these same animals and found it to be normal. Extracellular fluid volume was not estimated.

Floyer et al. (1961) studied parabiotic rats. These are rats in pairs that are surgically united at a young age by grafting their skin together so that they have a capillary bed in common. In normotensive, parabiotic rats, the authors noted that the rat with the spontaneously higher blood pressure would show a higher plasma volume. The situation reversed itself after the induction of hypertension in one member of the pair by clipping one of its renal arteries and leaving the other kidney intact. Under these circumstances, although the plasma volume rose in both animals, the rise of plasma volume was less in the clipped rat. The authors inferred that the capillary hydrostatic pressure must have risen in the clipped or hypertensive member of the pair, and this resulted in a fluid shift into the other rat. To account for the rise in capillary hydrostatic pressure, the authors further suggest that, in view of the increased precapillary resistance in hypertension, the postcapillary resistance must have risen disproportionately. The increased postcapillary resistance may possible reflect decreased distensibility of the capacitance vessels.

The only direct evidence bearing on the subject of decreased venous distensibility in experimental renovascular hypertension comes from the work of Overbeck (1972). The author studied pressure-volume (compliance) relationships in the isolated, temporarily occluded segment of the femoral and jugular vein in the early (less than 4 weeks) stage of one- and two-kidney, perinephritic hypertension in dogs. He found the femoral but not jugular vein pressure-volume curve of the hypertensive dogs to be shifted in the direction of the pressure axis, suggesting decreased distensibility of the femoral vein in experimental renovascular hypertension. Systemic intravenous administration of propranolol (a beta-blocker), diazoxide, or guanethidine (a ganglionic blocker) failed to alter the venous distensibility of hypertensive or normotensive dogs, therefore, the shift of the hypertensive femoral vein pressure-volume curve persisted. Furthermore, the shape of the pressure-volume curves tended to be convex toward the volume axis and were similar in hypertensives and normotensives. The author was never able to demonstrate the characteristic sigmoid configuration of the pressure-volume curves that would suggest venoconstriction. He, therefore, suggests that the decreased femoral venous compliance of hypertensive animals may be attributable to abnormal vascular wall water and electrolyte composition. This suggestion, however, has not been tested. Nor did the author offer an explanation for the normal pressure-volume relationships in the hypertensive jugular veins, which may reflect a lower smooth muscle content of these veins.

Summary

The earliest demonstrable hemodynamic changes in the various models of experimental renovascular hypertension are simultaneous increases of cardiac output and blood pressure, followed by the return to normal of cardiac output and the rise of total peripheral vascular resistance. A transient increase in blood volume may in part be responsible for the early increase in cardiac output, at least in one-kidney, Goldblatt hypertension. The distribution of the early rise in total peripheral blood flow and the distribution of the later rise in total peripheral vascular resistance among the various organs of the body remain, to a large extent, unexplored. With the exception of limb hemodynamics, no attempt has been made to study specific organ blood flow from the point of view of parallel- and series-coupled resistances and from that of the stage of the hypertension. In particular, there is a complete lack of information concerning the role of the splanchnic circulation in the development and maintenance of experimental renovascular hypertension. Decreased venous distensibility, among others, has been suggested to account for the initial rise in cardiac output, but confirmatory studies are needed. The pathogenetic mechanisms underlying the possibily decreased venous distensibility should be explored.

Human Renovascular Hypertension

Goldblatt's demonstration that hypertension could be produced by renal artery stenosis led to a search for renal artery lesions in human hypertensives. Goldblatt himself showed that, in some cases of

human essential hypertension, the renal artery was obstructed. In 1954, six cases of severe hypertension with renal artery lesions were presented, in which the hypertension remitted following removal of the affected kidney (Howard et al., 1954). Since then, renovascular hypertension has become an established, though uncommon, form of human hypertension that is surgically correctable.

Systemic Hemodynamics

Frohlich et al. (1967) examined the systemic hemodynamics of 15 patients with hypertension secondary to non-atherosclerotic, fibrosing, unilateral renal artery stenosis. The group comprised 12 females and 3 male patients, as this type of lesion occurs predominantly in young women. Patients with atherosclerotic renal artery stenosis were excluded, because antecedent human essential hypertension and unrecognized coronary arterial disease could not be ruled out in their case. The control group was matched for age and severity of hypertension, but its sex composition was different (13 male, 2 female patients). The results showed a significantly higher cardiac output and total peripheral vascular resistance in the hypertensive group of patients. The results remained essentially unaltered when the series was extended to 29 patients, three with atherosclerotic renal artery stenosis (Frohlich et al., 1969).

Brod et al. (1966) studied an older group of nine hypertensive patients with atherosclerotic renal artery stenosis. The authors found no difference between the cardiac output of hypertensives and of normotensive controls.

Blood Volume

The total blood volume, measured by the radioiodinated human serum albumin distribution method, of Frohlich's patients (Frohlich et al., 1967) (see above) was significantly lower than that of their controls. Therefore, the increased cardiac output, seen in patients with non-atherosclerotic renal artery stenosis, cannot be explained on the basis of increased intravascular volume.

More recently, the finding of decreased intravascular volume in patients with human renovascular hypertension was confirmed in another series of patients by the same group of investigators (Dustan et al., 1973), using similar techniques. In addition, the reduction in plasma volume was found to be inversely related to the diastolic blood pressure. The red cell mass was normal in these patients.

Regional Hemodynamics

There is little information available concerning the regional hemodynamics of human renovascular hypertension. Conway (1963), using plethysmographic techniques, was unable to demonstrate statistically significant differences in the forearm (hand excluded) blood flow and vascular resistance of renovascular hypertensives and of normals, although both measurements tended to be higher in hypertensives. The forearm vascular bed, therefore, does not seem to participate proportionately in the increase of total peripheral vascular resistance in this form of hypertension.

Brod et al. (1966), in addition to measuring cardiac output, compared the regional hemodynamics of 9 renovascular hypertensive

patients with those of control subjects, using techniques similar to the ones that they employed in the investigation of essential hypertensive patients (Brod, 1960; Brod et al., 1962) (see under Human Essential Hypertension). Renal, splanchnic and skin vascular resistances were significantly higher in hypertensives than in normotensives. Forearm (skin flow deducted) vascular resistance, on the other hand, was similar in the two groups. Since cardiac output was normal in this group of hypertensive subjects, the data indicate a redistribution of blood flow from the kidneys and the splanchnic bed to muscle.

Additional regional flow studies in human renovascular hypertension were reported for the kidney. Blood flow to the affected kidney and the ratio of clearance of p-amino-hippurate (RPF) to T_m glucose are diminished, suggesting a decrease primarily in renal cortical blood flow (Traeger et al., 1963). Stamey (1962) found an average decrease of 50 to 60% in renal plasma flow (PAH clearance) when the kidney with the renal artery stenosis was compared to the contralateral kidney. The reduction in renal plasma flow produced a proportional reduction in glomerular filtration rate (inulin clearance), i.e., the filtration fraction was nearly the same in the two kidneys. The contralateral kidney, however, was not evaluated with respect to the kidney of a normal subject. The findings of Stamey were confirmed by Kioschos et al. (1967), using the indocyanine-green dye dilution method across the kidney. The comparative study between the kidney with renal artery stenosis and its non-stenotic companion revealed a flow difference of 32%.

Somewhat different results were obtained by more recent investigators (Pederson et al., 1969; Ladefoged et al., 1969) who studied renal blood flow per unit mass of tissue. In the stenotic kidney, renal blood flow per unit mass of tissue, measured by the ^{133}Xe desaturation technique, appears to be reduced, in comparison to the mean value in normals, in all cases of human renovascular hypertension. There was a small but insignificant difference between the stenotic and the contralateral kidneys, renal blood flow being reduced in the non-stenotic kidney as well. In view of the systemic hypertension, the data indicate that renal vascular resistance was increased in both the stenotic (including the resistance offered by the stenosed artery) and the non-stenotic kidney, but the rise is greater in the stenotic kidney.

Vascular Compliance

There is only indirect evidence to suggest a change in vascular distensibility in human renovascular hypertension. Ulrych et al. (1969) calculated the cardiopulmonary blood volume of renovascular hypertensive patients from the product of the mean transit time of the indocyanine-green dye through the lungs and heart and the cardiac output per second. The authors found the cardiopulmonary blood volume of renal hypertensive patients to be significantly increased, while their total peripheral blood volume was decreased, in comparison with control values. In the absence of heart failure, the distribution of blood between the systemic and the cardiopulmonary segments of the circulation should reflect the relative capacitance function of the peripheral and pulmonary vascular beds. The shift of blood volume from the systemic into the pulmonary

vascular bed suggests decreased distensibility of the systemic vascular bed in human renovascular hypertension, due to arterial and/or venous abnormalities.

Summary

The systemic and regional hemodynamics of human renovascular hypertension are characterized by increased cardiac output, increased renal, splanchnic and skin vascular resistances and low or normal muscle vascular resistance. In contrast to human borderline essential hypertension, the increased cardiac output is accompanied by an increased total peripheral vascular resistance, and it is uncertain whether the increased cardiac output is an early, transient or a permanent feature of this type of hypertension. Blood volume is reduced and is inversely proportional to the diastolic pressure. The role of veins has not been directly evaluated.

Spontaneously Hypertensive Rats

During the past 15 years, a number of strains of genetically hypertensive rats have been developed, notably by Smirk and Hall (1958) in New Zealand, referred to as the New Zealand strain, and by Okamoto and Aoki in Japan (1963), referred to as the Okamoto-Aoki strain of hypertensive Wistar rats. Both strains develop severe and sustained hypertension spontaneously in practically 100% of the cases. When the New Zealand strain of hypertensive rats is compared to matched, normotensive, control rats, a difference in blood pressure is apparent by

two days of age (Jones et al., 1970). It is generally held that these spontaneously hypertensive rats despite minor metabolic strain-related differences constitute the best model yet developed as an experimental counterpart for essential hypertension in man. The hypertension appears to be multigenetic in origin. There is little evidence for a Goldblatt-type mechanism like in experimental renovascular hypertension (Folkow et al., 1973).

Systemic Hemodynamics

Pfeffer and Frohlich (1973) measured, under ether anesthesia and thoracotomy, the aortic blood flow, via an electromagnetic flow-meter, and carotid arterial and central venous pressures in three age groups of paired normotensive and spontaneously hypertensive Wistar rats. In the youngest (9-12 weeks) group of spontaneously hypertensive rats, the authors found a significantly elevated arterial pressure accompanied by a hyperkinetic circulation, manifested by significantly increased heart rate and cardiac output. Total peripheral vascular resistance was normal in this stage of hypertension. In the older group of spontaneously hypertensive rats (18-33 weeks and 62-97 weeks), the elevated arterial pressure was associated with an increased total peripheral vascular resistance and a normal cardiac output.

The results of Pfeffer and Frohlich were in part confirmed by Iriuchijima (1973). The author studied the systemic hemodynamics, under pentobarbital anesthesia, of spontaneously hypertensive rats and of matched controls, aged 12-23 weeks, using techniques similar to those

of Pfeffer and Frohlich. He found the cardiac output to be normal and blood pressure and total peripheral vascular resistance to be elevated in spontaneously hypertensive rats.

Blood Volume

Blood volume is reportedly normal in the Japanese strain of spontaneously hypertensive rats (Gresson et al., 1973). Other investigators, however, report different findings in other strains.

Nikodijevic et al. (1972) performed direct, simultaneous measurements of plasma volume and erythrocyte volume by means of double isotope dilution technique (albumin ^{125}I and ^{51}Cr) in spontaneously hypertensive rats and matched controls, weighing 200-250 gm. The authors found a significantly increased plasma and total blood volume in the hypertensive group of rats.

Gresson et al. (1973) performed similar studies in male, albino rats, weighing 150-300 gm, of the New Zealand colony of spontaneously hypertensive rats. They used the normotensive parent strain of rats for weight-matched controls. They measured plasma volume, extracellular fluid volume and the total erythrocyte volume by the Evans blue, the standardized inulin (with the renal pedicles ligated) and the ^{51}Cr labelled erythrocyte dilution technique, respectively. The hypertensive rats showed a significant reduction in all volumes measured, in comparison to values in controls.

There is, therefore, evidence for normal, increased and decreased blood volumes in spontaneously hypertensive rats. The

discrepancies cannot be reconciled unless the pathogenesis of the hypertension in the various strains of spontaneously hypertensive rats is different, or we are dealing with strain- and age-dependent differences that may or may not be related to the hypertension.

Regional Hemodynamics

Regional hemodynamics of hypertensive rats have been studied by various authors under constant flow conditions. Laverty and Smirk (1961) pump-perfused the intact hindlimb of 6-month-old, spontaneously hypertensive (New Zealand strain) and control rats with the rats' own blood at 1 ml/min, monitoring perfusion pressure. The mean hindlimb perfusion pressure was greater in the spontaneously hypertensive than in the control rats. Folkow et al. (1970) perfused, with an artificial solution, both hindlimbs of c. 6 month-old, spontaneously hypertensive and control Wistar rats, and monitored the resulting perfusion pressure. They found the hindlimb vascular resistance to be significantly higher in spontaneously hypertensive rats, almost in proportion to their raised blood pressure.

Folkow et al. (1971) also studied renal vascular resistance in 7-month-old spontaneously hypertensive rats and matched, normotensive controls, but at variable flow rates. At very low flow rates, they found renal vascular resistance to be similar in the two groups. At high flow rats, on the other hand, the renal vascular resistance of spontaneously hypertensive rats was significantly lower than that of controls, in contrast to findings in other major vascular beds. In

the discussion of their paper, the authors refer to some as yet unpublished data from their laboratory, indicating that, under natural flow, resting conditions, the renal vascular resistance of spontaneously hypertensive rats is similar or slightly higher than that of controls.

McGregor et al. (1968) perfused the superior mesenteric artery system of spontaneously hypertensive (New Zealand strain) and control rats, weighing 260-340 gm, at 1 ml/min constant flow, using the blood of donor rats or physiologic saline. They found higher perfusion pressures in the hypertensive rats.

Vascular Compliance

There is no report in the literature concerning vascular compliance in spontaneously hypertensive rats.

Summary

From the limited amount of data available, the spontaneously hypertensive rats appear to behave similarly to humans with borderline hypertension, with respect to an early, transient increase in cardiac output, followed by a sustained rise in total peripheral vascular resistance. Regional hemodynamic data suggest that in the chronic stage of spontaneous hypertension in rats, vascular resistance is increased in the limb and mesentery. The vascular resistance of the kidneys appears to be low in comparison to the rise in total peripheral vascular resistance, in contrast to other forms of hypertension.

CHAPTER II

PURPOSE OF THE INVESTIGATION

The purpose of this investigation is twofold: (1) to study mesenteric (ileum) blood flow and pressure relationships in early perinephritic hypertension in order to determine the distribution of increased cardiac output at this stage of the hypertensive process, and (2) to evaluate venous function and to analyze venous wall composition in early and chronic perinephritic hypertension.

CHAPTER III

METHODS

Healthy, conditioned, male mongrel dogs, weighing 18.1-27.2 kg were trained to lie quietly during femoral arterial punctures for blood pressure measurements. Resting arterial blood pressure less than 140 mm Hg mean pressure was documented on at least two occasions in each dog prior to surgery. Postoperatively, femoral arterial blood pressures and hematocrits were measured weekly until the time of the hemodynamic studies. Conditioning over a 2-4 week period included the examination of the stool for ova and parasites and vaccination against rabies, distemper, leptospirosis and hepatitis. During the entire study period, the dogs were maintained on a diet of standard dog chow (Wayne Dog Food, Allied Mills, Inc., Chicago, Ill. 60606) and water ad libitum.

A total of 66 dogs were used, divided into the following groups: (Hypertensive)-1, 10 dogs; H-2, 15 dogs; H-3, 8 dogs; (Control)-1, 10 dogs; C-2, 15 dogs; and C-3, 8 dogs.

Induction of Hypertension and the Preparation of Controls

Prior to surgery, the dogs were given procaine penicillin (600,000 units) and streptomycin (0.5 gm) intramuscularly, as a prophylactic measure against wound infection. A flank incision was made

under pentobarbital anesthesia (25 mg/kg, iv) and sterile conditions. In dogs of groups H-1, H-2 and H-3, I dissected one kidney free from its fat pad and wrapped it in silk to produce perinephritic hypertension. The silk-wrapped kidney, in turn, was wrapped in saran (Saran Wrap, The Dow Chemical Co., Midland, Mich. 48640), in order to minimize the amount of adhesions between the kidney and the surrounding tissues. In groups C-1, C-2 and C-3, I dissected one kidney free from its fat pad and restored the kidney to its normal position. Saran wrap was laid down along-side the kidney, and left in place in order to reproduce the experimental situation as closely as possible. In groups H-1 and C-1, the contralateral kidney was left intact. In groups H-2 and C-2, two weeks after the first operation, I performed contralateral nephrectomy under pentobarbital anesthetic (25 mg/kg, iv), following premedication with antibiotics (see above). In groups H-3 and C-3, contralateral nephrectomy was performed at the time of the first operation.

I studied mesenteric hemodynamics in dogs of groups H-1 and C-1 9-11 days after kidney wrapping and sham surgery, respectively. I studied hemodynamics in dogs of groups H-2 and C-2 two weeks after nephrectomy. Finally, groups H-3 and C-3 were studied 4-20 weeks post-nephrectomy, after four consecutive weeks of arterial hypertension (>140 mm Hg mean pressure).

The overall design of the experiments was as follows:

Group H-1: Silk bag on one kidney 9-11 days hemodynamic studies.

Group H-2: Silk bag on one kidney 2 weeks → contralateral nephrectomy 2 weeks → hemodynamic studies.

Group H-3: Silk bag on one kidney and contralateral nephrectomy 4-20 weeks → hemodynamic studies.

Group C-1: Sham surgery on one kidney 8-10 days → hemodynamic studies.

Group C-2: Sham surgery on one kidney 2 weeks → contralateral nephrectomy 2 weeks → hemodynamic studies.

Group C-3: Sham surgery on one kidney and contralateral nephrectomy 4-20 weeks → hemodynamic studies.

In the course of my discussion, I will also refer to the H-1 group of dogs as early, two-kidney hypertension, to the H-2 group as early, one-kidney hypertension and to the H-3 group as chronic (four consecutive weeks of mean arterial blood pressure greater than 140 mm Hg), one-kidney hypertension. I will refer to the control animals (C-1, C-2 and C-3) as the appropriate controls.

Mesenteric (Ileum) Blood Flow and Pressure Relationships

Dogs, fasted for 24 hours, were anesthetized with sodium pentobarbital, 35 mg/kg, iv. Supplemental doses of 50-100 mg iv were given later, as necessary, but not until after the completion of mesenteric blood flow and pressure measurements. Following the induction of anesthesia, the dogs were intubated with a cuffed endotracheal tube

and artificially ventilated with a positive pressure respirator (model #607, Harvard Apparatus Co., Inc., Harvard, Mass.). Respiratory rate was set at twenty per minute and tidal volume was adjusted so that systemic arterial blood pH was at 7.39-7.43. Heparin (10,000 UPS units) was given intravenously for systemic anticoagulation.

After an abdominal midline incision, the greater omentum was retracted, and the ileocecal junction of the intestines was identified. Starting from the ileocecal junction, the mesenteric vascular arcades were counted retrograde and numbered. The in vivo hemodynamic studies were performed in a standardized segment consisting of a mesenteric vascular arcade, numbered between 5 and 10, and a portion of the small intestine corresponding roughly to the mid portion of the ileum.

I used the innervated, collateral-free, naturally perfused loop of small intestine plus its mesentery for the study of mesenteric blood flow and pressures (Figure 3) (Scott et al., 1964). Venous outflow from the loop drained through a single vein. With the artery and the extrinsic nerves undisturbed, the vein was cannulated with polyethylene tubing (PE 240) for direct measurement of the venous outflow. The venous outflow was directed into a reservoir and continuously pumped back to the dog via an external jugular vein.

Through a T-tube arrangement, attached 2 cm distal to the insertion of the venous outflow catheter into the mesenteric vein, venous pressure was measured (large vein pressure, P_{LV}). Large vein pressure (P_{LV}) was set at 7 mm Hg, by adjusting the vertical level of the venous outflow catheter. The purpose of this maneuver was to

Figure 3. Schematic drawing of the innervated, collateral-free, naturally perfused loop of small intestine (ileum) preparation.

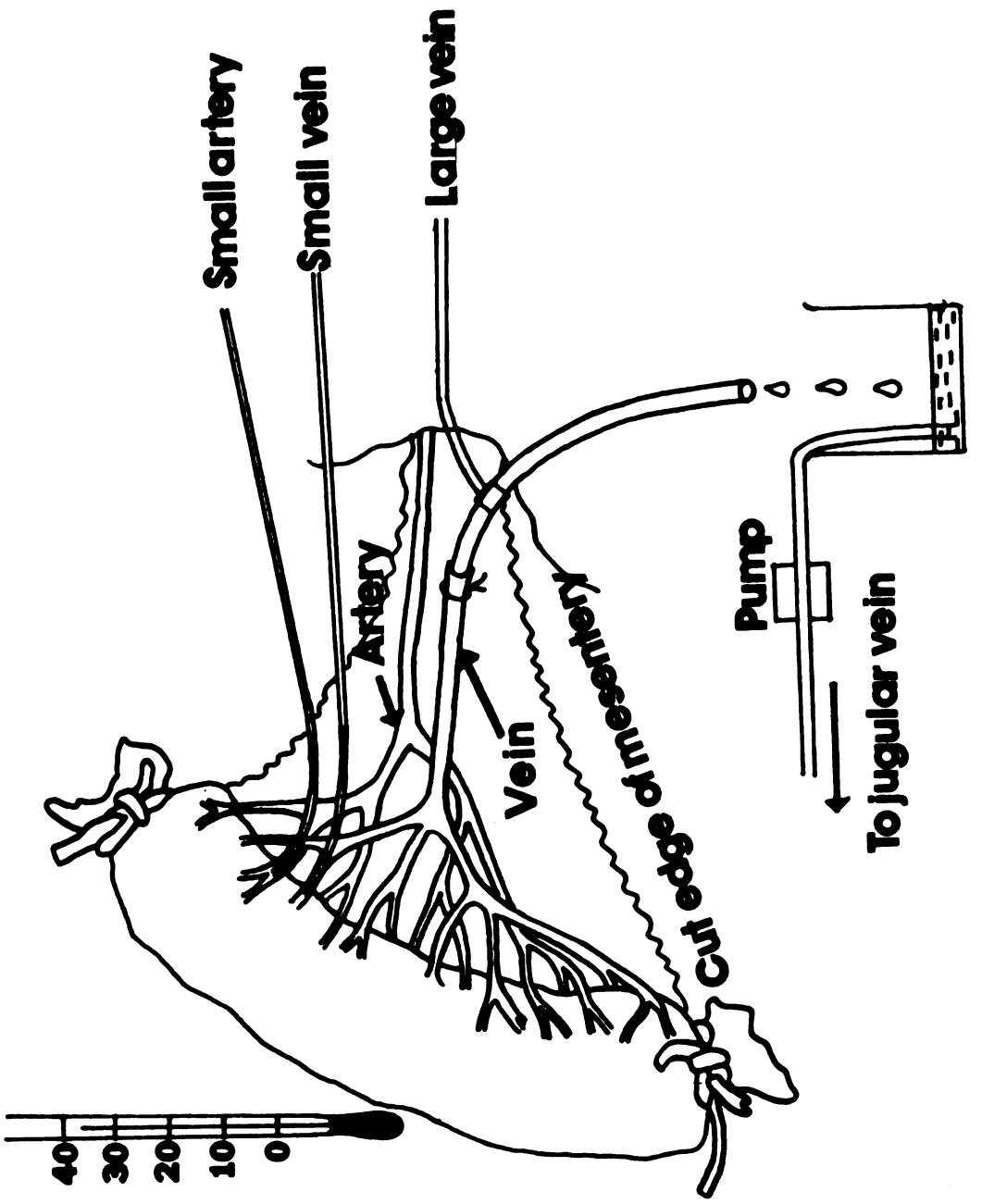

Small artery
Small vein
Large vein
Artery
Vein
Cut edge of mesentery
Pump
To jugular vein
40
30
20
10
0

Figure 3

standardize the preparation in order to allow comparison from animal to animal. I monitored small artery (P_{SA}) and small vein pressure (P_{SV}) through polyethylene catheters (PE 10) inserted into a small artery and retrograde into a small vein, near the junction of the mesenteric vascular arcade and the small intestine wall. Reflux of blood into either catheter was freely obtained. The small intestinal loop was tied at both ends and the mesentery cut to exclude collateral flow. The preparation was kept at 37°-39° by a heating lamp and moist by covering it with saran wrap. Finally, a femoral artery was cannulated (PE 240) for monitoring systemic blood pressure (large artery pressure, P_{LA}). Intravascular pressures were detected by a Statham P 23 Gb pressure tranducer (Hato Rey, Puerto Rico) and recorded on a Sanborn oscillographic recording machine.

Beginning 90 minutes after the initial anesthesia in all dogs, I made repeated measurements of intravascular pressures and of mesenteric venous outflow. Venous outflow was collected and measured in a calibrated cylinder, accurate to ± 0.2 ml. Measurements were carried out in duplicate over two consecutive one minute periods and averaged. Duplicate readings were taken every five minutes for a minimum of three collection periods or until the averaged duplicate readings were within ± 1.0 ml of each other. Venous outflow for the experiment was calculated as the average of all duplicate readings.

At the termination of the blood flow and pressure measurements, the loop of small intestine was excised and weighed on a top-loading balance, accurate to ± 50 mg (Mettler, model P 1200, Highstown, N.J.).

I expressed blood flow both as ml/min and as ml/min 100 g^{-1} of small intestine. I divided means of intravascular pressure gradients by the appropriate blood flow to calculate steady-state segmental vascular resistances as follows:

- Mesenteric large artery resistance (R_A) = ($P_{LA} - P_{SA}$)/blood flow/100 gm of small intestine.
- Mesenteric small vessel resistance (R_{SV}) = ($P_{SA} - P_{SV}$)/blood flow/100 gm of small intestine.
- Mesenteric large vein resistance (R_V) = ($P_{SV} - P_{LV}$)/blood flow/100 gm of small intestine.
- Mesenteric total resistance (R_T) = ($P_{LA} - P_{LV}$)/blood flow/100 gm of small intestine.

Finally, I compared flows, pressures and calculated resistances in dogs of the hypertensive groups (H-1 and H-2) with those in dogs of the control groups (C-1 and C-2) by Student's t-test, rejecting the null hypotheses at probability values ≤ 0.05.

Mesenteric (Ileum) Blood Flow and Perfusion Pressure Relationships

At the conclusion of the mesenteric blood flow-pressure measurements in 3 H-1, 3 H-2, 3 C-1 and 3 C-2 dogs, I prepared an additional loop of small intestine for pump perfusion of its vascular bed. The venous outflow from the collateral-free, innervated small intestinal loop was directed into a reservoir and continuously pumped back to the dog via an external jugular vein. Large vein pressure (P_{LV}) was monitored as described previously. A blood pump (Sigmamotor), pressure-independent to 300 mm Hg, was then interposed between the left femoral

artery and the single mesenteric artery supplying the loop of small intestine. A 16 gauge needle at the end of the pump tubing was carefully inserted into the mesenteric artery, adjusted, and secured to prevent inflow obstruction. Flow to the loop of small intestine was measured by the direct collection of the venous outflow and varied from 3.9 to 45.1 ml/min. Inflow pressure (IP) was recorded via a needle inserted into the pump outlet tubing. The preparation was kept moist at 37°-39°C. At the end of the measurements, the loop of small intestine was excised and weighed as described previously.

For each experiment, I plotted both the perfusion pressure ($IP-P_{LV}$) (mm Hg) and the total mesenteric vascular resistance (mm Hg/ml min^{-1} 100 g^{-1}) as a function of mesenteric blood flow (ml/min 100 g^{-1}).

Mesenteric Vein Pressure-Volume (Compliance) Relationships In Vivo

During the initial surgical preparation, a mesenteric vascular arcade, numbered between 5 to 10 and different from the ones selected for the flow and pressure studies (see above), was selected for the *in vivo* measurement of mesenteric vein pressure-volume relationships. The Y-shaped vein of the vascular arcade was standardized by measuring a 4-4-1 1/2 cm segment of its length in each dog (Figure 4).

After the completion of the mesenteric blood flow and pressure studies the vein selected for mesenteric venous pressure-volume measurements was cannulated with polyethylene tubing (PE 200) at its downstream end and allowed to drain into a reservoir. The rest of the vein was left

Figure 4. Schematic drawing of the Y-shaped (4-4-1 1/2 cm) segment of mesenteric vein used to study venous pressure-volume relationships *in vivo*.

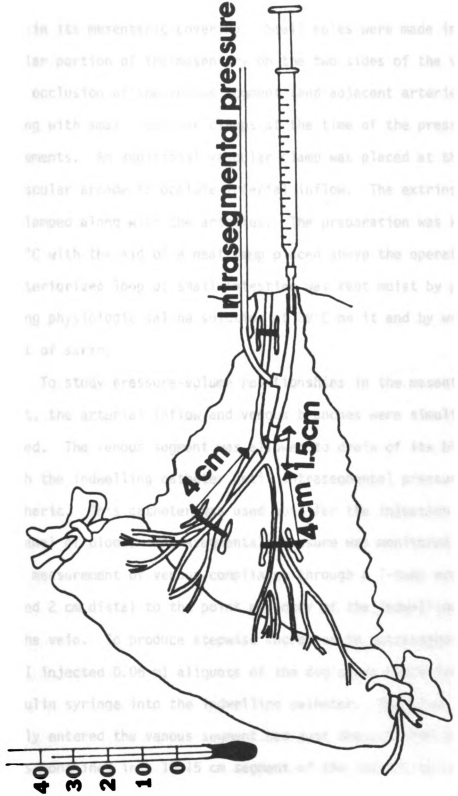


Figure 4

intact in its mesenteric covering. Small holes were made in the avascular portion of the mesentery on the two sides of the vein to permit occlusion of the venous segment (and adjacent arteries) by clamping with small vascular clamps at the time of the pressure-volume measurements. An additional vascular clamp was placed at the root of the vascular arcade to occlude arterial inflow. The extrinsic nerves were clamped along with the arteries. The preparation was kept at 37°-39°C with the aid of a heat lamp placed above the operating table. The exteriorized loop of small intestine was kept moist by periodically dripping physiologic saline solution at 39°C on it and by wrapping it in a sheet of saran.

To study pressure-volume relationships in the mesenteric vein segment, the arterial inflow and venous branches were simultaneously occluded. The venous segment was allowed to drain of its blood content through the indwelling catheter until intrasegmental pressure was atmospheric. This catheter was used both for the injection and the withdrawal of blood. Intrasegmental pressure was monitored during the entire measurement of venous compliance through a T-tube arrangement attached 2 cm distal to the point of entry of the indwelling catheter into the vein. To produce stepwise increases in intrasegmental pressure, I injected 0.05 ml aliquots of the dog's own blood from a glass tuberculin syringe into the indwelling catheter. The blood that actually entered the venous segment had just drained from the vein and was contained in a 10-15 cm segment of the indwelling catheter overlying the abdomen, which was kept at 37°-39°C. Six to 19 0.05 ml

blood aliquots were injected, producing intrasegmental pressures of up to 50 mm Hg (injection phase). A ten-second pause after each injection was allowed to establish steady-state pressures. These steady-state intrasegmental pressures were detected with a Statham P 23 Gb pressure transducer and recorded on a Sanborn oscillographic recording machine. I then withdrew 0.05 ml samples of blood at similar time intervals, again measuring the resulting pressures (withdrawal phase). The time required for each pressure-volume study, injection and withdrawal phase, was less than 5 minutes. Circulation through the venous segment was then restored by removing clamps. I repeated the same measurements after a waiting period of at least 25 minutes. Data were accepted if all injected blood was recovered from the segment, and intrasegmental pressure returned to atmospheric level ± 2 mm Hg. Additionally, the total number of injections required to reach an intraluminal pressure of 40-50 mm Hg had to be the same during repeat measurements.

Using the means of two or three series of measurements, a pressure-volume curve representing the injection phase and the withdrawal phase, respectively, was constructed for each dog. Total volumes, during injection and withdrawal, producing intrasegmental pressure of 5, 15, 25 and 35 mm Hg in hypertensive dogs were compared by Student's t-test with volumes in control normotensive dogs. Null hypotheses were rejected at a probability value of ≤ 0.05. In addition, venous compliance, $\Delta V/\Delta P$, in the pressure ranges of 5-15, 15-25 and 25-35 mm Hg, was calculated for the averaged injection and withdrawal curve of each dog. Venous compliances of hypertensive dogs were compared by Student's t-test

with venous compliances of controls. Again, null hypotheses were rejected at a probability value of ≤ 0.05. The analysis of pressure-volume data is illustrated in the Appendix (Figure 18).

Superior Mesenteric Vein Pressure-Volume (Compliance) Relationships In Vitro

At the conclusion of the *in vivo* hemodynamic studies, I removed a segment of the superior mesenteric vein. The vein was exposed, and its caudal pancreatico-duodenal branch was identified. This branch of the vein serving as mid-point, a 5 cm-long segment of the superior mesenteric vein was dissected in situ, with the collaterals tied off and cut near their origin. The superior mesenteric vein segment was removed and transferred immediately to a chamber, containing Krebs-Ringer bicarbonate solution (NaCl, 118.3 mM; KCl, 4.7 mM; $MgSO_4$, 1.2 mM; KH_2PO_4, 1.2 mM; Ca gluconate, 2.5 mM; $NaHCO_3$, 25.0 mM; and glucose, 11.1 mM) aerated with 95% O_2 and 5% CO_2 gas mixture (Matheson Gas Products, Joliet, Ill.). The pH of the tissue bath was adjusted to 7.40-7.43, if necessary, by the addition of small aliquots (0.1-0.5 ml) of 0.1 N HCl. The temperature of the tissue bath was kept constant at 38°-39°C by circulating water through its double wall.

Each end of the cut segment was secured to the tip of a thin-walled glass cannula with an outside diameter similar to the inside diameter of the vein. The preparation was placed horizontal in the chamber, and the *in vitro* length of the venous segment was adjusted to 4 cm in each experiment. The vein was perfused in the direction of flow in the intact animal, at constant flow (25 ml/min) with the

same Krebs-Ringer solution as used in the chamber (Figure 5) (Vanhoutte et al., 1970).

Pressure-volume measurements were made after an equilibration period of 10 minutes, as follows: perfusion was stopped and the inflow and the outflow tubes were clamped at their point of attachment to the glass cannulae. The intrasegmental pressure was adjusted to atmospheric pressure through the side arm of one of the glass cannulae. Two-tenths ml aliquots of Krebs-Ringer solution were injected through the side-arm of the other glass cannula. Pressure-volume measurements were repeated once after 25 minutes. Pressure-volume curves were constructed in a manner that is analogous to my in vivo technique.

In addition, I also measured venous compliance by rapid continuous infusion of Krebs-Ringer solution (Infusion-Withdrawal Pump, Harvard Apparatus, Model 600-000, Dover, Mass.). A 9.88 ml/min infusion rate was chosen so that 40-50 mm Hg intrasegmental pressure would be reached within 5-15 seconds. A rate of infusion of this kind was shown by others (Alexander, 1948 and 1963) to give rise to pressure-volume curves that are most sensitive to changes in vascular smooth muscle tone.

In 3 H-2 and 3 C-2 dogs, I repeated the measurement of superior mesenteric vein compliance by rapid continuous infusion, following the perfusion of the segment with NaCN in saline (500 mg/liter) at 37°C, for 20 minutes.

At the end of the experiment, the venous segment was removed, cleared of the suture ligatures, blotted dry and weighed on an analytical balance (Mettler, Type H 16, Highstown, N.J.) to within ± 0.001 gm.

Figure 5. Schematic drawing of apparatus used to study venous pressure-volume relationships *in vitro*.

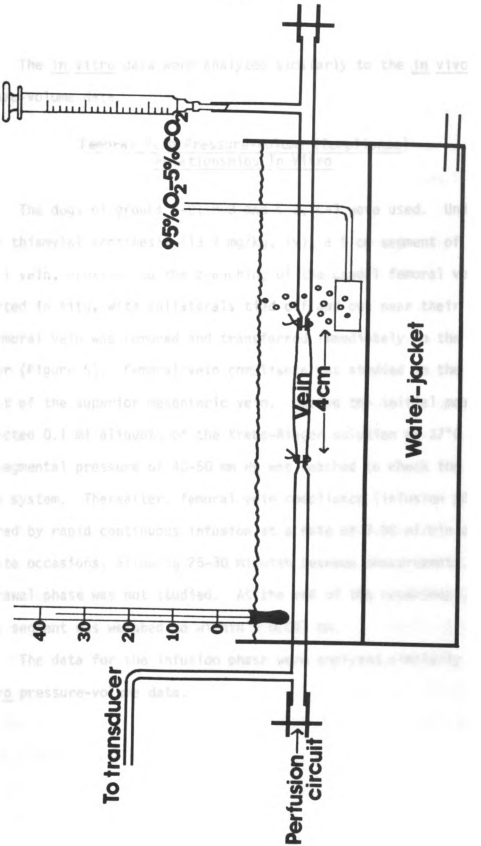

95%O2-5%CO2
Vein
4cm
Water-jacket
40
30
20
10
0
To transducer
Perfusion circuit

Figure 5

The *in vitro* data were analyzed similarly to the *in vivo* pressure-volume data.

Femoral Vein Pressure-Volume (Compliance) Relationships In Vitro

The dogs of groups H-2, H-3 and C-2, C-3 were used. Under sodium thiamylal anesthesia (13.2 mg/kg, iv), a 5 cm segment of the femoral vein, proximal to the branching of the caudal femoral vein, was dissected in situ, with collaterals tied off and cut near their origin. The femoral vein was removed and transferred immediately to the *in vitro* chamber (Figure 5). Femoral vein compliance was studied in the same way as that of the superior mesenteric vein. During the initial measurement, I injected 0.1 ml aliquots of the Krebs-Ringer solution at 37°C until an intrasegmental pressure of 40-50 mm Hg was reached to check the patency of the system. Thereafter, femoral vein compliance (infusion phase) was measured by rapid continuous infusion at a rate of 3.88 ml/min on two separate occasions, allowing 25-30 minutes between measurements. The withdrawal phase was not studied. At the end of the experiment, the venous segment was weighed to within ± 0.001 gm.

The data for the infusion phase were analyzed similarly to the *in vivo* pressure-volume data.

Venous Wall Water, Sodium and Potassium Content

In a number of animals from groups H-2, H-3, C-2 and C-3, I removed segments of mesenteric and femoral veins and of vena cava. The segments of vein were immediately dissected clean, opened longitudinally, blotted once with filter paper to remove surface blood, placed in preweighed bottles and weighed on an analytical balance (Mettler, Type H 16, Highstown, N.J.) to the nearest 0.01 mg. Then the open bottles were placed in an oven at 100°C for 24 hours. Two hours following removal from the oven, the capped bottles were reweighed. The difference between the two weights represented water content, which was expressed as percent wet weight. The water contents of veins from hypertensive animals were compared to those from normotensive dogs by Student's t-test, rejecting the null hypothesis at a probability value of ≤ 0.05.

For measurement of Na and K content, 5 milliliters of 0.1 N nitric acid were added to each bottle. The venous tissue was allowed to digest for a period of 2-4 weeks, following which the tissue content of Na and K was measured by flame photometry (Beckman Model 105 Flame Photometer). Ion content was expressed as mEq/kg tissue dry weight. The Na and K content of veins from hypertensive dogs was compared to that from control dogs by Student's t-test, rejecting the null hypotheses at a probability value of ≤ 0.05.

Histological Examination of the Mesenteric Vascular Arcade and the Femoral Vein

In a number of animals from each group, a mesenteric vascular arcade and a segment of femoral vein were removed and placed in 10% buffered formalin for pathological examination, which was performed by John F. Dunkel, M.D., Asst. Prof., Dept. of Anatomy, Michigan State University. Serial sections of mesenteric vascular arcade and femoral vein were made. For each section of tissue the following stains were performed: hematoxylin and eosin, elastic, reticulum, trichrome, allochrome and AB PAS.

Additional Studies

1. Hematocrit. Arterial blood hematocrit was measured by the microhematocrit method, weekly pre- and post-operatively in each dog.

2. Blood urea nitrogen (BUN). At the time of the hemodynamic studies, immediately after the induction of anesthesia, 2-3 milliliters of blood were drawn from the cannulated jugular vein of each animal. The separated plasma was frozen and stored for the determination of BUN, expressed as mg/100 ml of plasma.

3. Urinanalysis. Prior to killing each animal, a sample of urine was obtained by direct puncture of the bladder. Urinary specific gravity was measured by hydrometer. Urinary protein was estimated by Uristix (Ames Co., Elkhart, Ind.).

CHAPTER IV

RESULTS

General data on 66 dogs, 33 control and 33 hypertensive, are presented in Table 1. The hypertensive dogs (H-1, H-2 and H-3) and their respective controls (C-1, C-2 and C-3) had similar preoperative body weights, awake mean arterial blood pressures and hematocrits.

Following sham operation and nephrectomy in control animals, there was no significant change ($P > 0.9$) in the mean arterial blood pressure. Following the wrapping of one kidney in silk, all hypertensive groups (H-1, H-2 and H-3) showed a significant rise in mean artetial blood pressure. The mean arterial blood pressure of early, two-kidney hypertensives (H-1) rose 7% ($P < 0.05$, paired Student's t-test). The rise of mean arterial blood pressure in groups H-2 and H-3 was 42% and 43% ($P < 0.001$), respectively. One to five days prior to the hemodynamic studies, the awake mean arterial blood pressure of hypertensives was significantly higher than that of controls, including group H-1, 128.3 mm Hg, and C-1, 117.8 ($P < 0.05$, unpaired Student's t-test). The average duration of hypertension, calculated from the time of induction to the time of the hemodynamic studies, in groups H-1, H-2 and H-3 was 11.2, 29.4 and 88.0 days, respectively.

Table 1. General observations in control (C-1, C-2 and C-3) and in hypertensive (H-1, H-2 and H-3) dogs. Group means ± SEM of awake blood pressures, body weights, blood urea nitrogen, urine specific gravity and number of days (range) of hypertension and qualitative urinary albumin (range)

	C-1	H-1	C-2	H-2	C-3	H-3
Preop. mean blood pressure[a] (mm Hg)	119.3 ± 1.3 N = 10	119.8 ± 2.8 N = 10	117.1 ± 2.3 N = 15	116.0 ± 2.0 N = 15	110.9 ± 2.0 N = 7	110.0 ± 4.8 N = 8
Postop. mean blood pressure[b] (mm Hg)	117.8 ± 2.7 N = 10	128.3 ± 3.5* N = 10	115.3 ± 2.1 N = 15	165.2 ± 5.0*** N = 15	115.4 ± 2.8 N = 8	157.5 ± 3.7*** N = 8
Days of hypertension		11 (8-15) N = 10		29 (25-35) N = 15		88 (28-170) N = 8
Preop. body weight[a] (kg)	21.6 ± 0.7 N = 10	22.9 ± 1.0 N = 10	24.0 ± 0.8 N = 15	24.0 ± 0.7 N = 15	26.4 ± 0.6 N = 7	26.8 ± 0.5 N = 7
Postop. body weight[a] (kg)	21.7 ± 0.7 N = 10	22.1 ± 1.0 N = 10	23.7 ± 0.8 N = 15	23.4 ± 0.8 N = 15	27.3 ± 0.8 N = 8	27.0 ± 0.7 N = 8
Preop. hematocrit[a] (%)	47.7 ± 0.9 N = 10	49.5 ± 1.0 N = 10	50.5 ± 0.6 N = 14	50.1 ± 0.6 N = 14	48.4 ± 0.9 N = 6	48.0 ± 0.4 N = 7
Postop. hematocrit[a] (%)	47.8 ± 1.2 N = 10	48.9 ± 1.0 N = 10	47.8 ± 0.6 N = 15	45.6 ± 1.1 N = 14	47.9 ± 0.9 N = 8	45.9 ± 1.0 N = 8
Blood urea nitrogen[c] (mg/100 ml)	14.1 ± 0.6 N = 7	13.1 ± 0.9 N = 7	15.2 ± 1.3 N = 10	19.4 ± 1.9 N = 12		
Urinary albumin[c]	0 (0-1+) N = 9	0 (0-2+) N = 9	0 (0-1+) N = 13	0 (0-1+) N = 12		
Urine specific gravity[c]	1.040 ± 0.002 N = 10	1.031 ± 0.002# N = 10	1.033 ± 0.003 N = 12	1.031 ± 0.003 N = 13		

*P < 0.05; #P < 0.02; ***P < 0.001, for comparison of hypertensive group with appropriate control group.

[a]Average of weekly measurements; [b]Taken 1-5 days prior to the hemodynamic studies; [c]Measured at the end of hemodynamic studies, under pentobarbital anesthesia.

The body weight of both hypertensive and control dogs remained constant throughout the observation period, up to the time of the hemodynamic studies.

There was no significant change postoperatively in the hematocrit of groups C-1, C-3, H-1 and H-3, on a paired basis. In contrast, the hematocrit of C-2 and H-2 dogs, which underwent two separate operations, fell significantly by 5% ($P < 0.001$, paired Student's t-test) and 9% ($P < 0.02$), respectively. At the time of the hemodynamic studies, however, there was no significant difference in the hematocrit of any one hypertensive and appropriate control group.

BUN, qualitative urinary albumin and urine specific gravity measured during the hemodynamic studies, under anesthesia, were similar in H-1 and H-2 hypertensive and C-1 and C-2 control groups, with one exception. In the early, two-kidney (H-1) hypertensive dogs, urinary specific gravity, 1.031, was significantly lower ($P < 0.02$) than in their controls (C-1), 1.040. BUN, urinary albumin and urine specific gravity were not measured in H-3 and C-3 groups of dogs.

Mesenteric (Ileum) Blood Flow and Pressure Relationships

Table 2 presents mesenteric (ileum) blood flow and pressure data in the early, two-kidney (H-1), the early, one-kidney (H-2) hypertensive and the appropriate control (C-1, C-2) dogs. Table 2 also shows the combined data from groups H-1 plus H-2 and C-1 plus C-2. In this and all subsequent tables, all the data obtained were included in the calculation of group means unless I state it otherwise. Mesenteric blood

Table 2. Mesenteric (ileum) blood flow and pressure relationships under pentobarbital anesthesia. Group means ± SEM of weight of ileum, blood flow, pressures and resistances.

	C-1 N = 10	H-1 N = 10	C-2 N = 14	H-2 N = 14	C-1 + C-2 N = 24	H-1 + H-2 N = 24
Weight of intestine (gm)	41.0 ± 3.5	41.1 ± 4.6	45.6 ± 4.2	40.2 ± 2.1	43.7 ± 2.8	40.6 ± 2.2
Blood flow[a]						
(ml/min)	18.8 ± 0.9	21.0 ± 1.8	20.5 ± 1.7	22.0 ± 1.1	19.8 ± 1.0	21.6 ± 1.0
ml/min 100 g^{-1}	48.2 ± 3.6	53.9 ± 5.0	46.7 ± 3.2	56.1 ± 3.5	47.3 ± 2.3	55.2 ± 2.9*
Pressure (mm Hg)						
Large artery	156.5 ± 3.2	163.4 ± 4.1	145.9 ± 3.4	183.2 ± 3.7***	150.3 ± 2.6	175.0 ± 3.4***
Small artery	122.5 ± 3.9	114.4 ± 4.9	106.8 ± 3.7	130.9 ± 3.4***	113.3 ± 3.1	124.0 ± 3.2*
Small vein	12.7 ± 0.8	12.9 ± 1.0	11.6 ± 0.5	15.0 ± 1.2#	12.1 ± 0.4	14.1 ± 0.8*
Large vein[b]	(7)	(7)	(7)	(7)	(7)	(7)
Resistance (mm Hg/ml min^{-1} 100 gm^{-1})						
Total	3.24 ± 0.23	3.13 ± 0.31	3.22 ± 0.32	3.27 ± 0.18	3.23 ± 0.21	3.21 ± 0.17
Large artery	0.73 ± 0.08	0.97 ± 0.15	0.90 ± 0.12	0.98 ± 0.10	0.83 ± 0.08	0.98 ± 0.08
Small vessel	2.38 ± 0.18	2.05 ± 0.22	2.12 ± 0.24	2.14 ± 0.11	2.28 ± 0.15	2.11 ± 0.11
Large vein	0.123 ± 0.024	0.117 ± 0.021	0.098 ± 0.010	0.145 ± 0.021	0.109 ± 0.011	0.133 ± 0.015

*P < 0.05; #P < 0.02; ***P < 0.001, for comparison of hypertensive group with appropriate control group.

[a]Obtained by direct collection of venous effluent; [b]Held constant at 7 mm Hg.

flow and pressure data were rejected from one H-2 hypertensive dog because of an unexplained drop in blood pressure during anesthesia (mean arterial blood pressure 117.5 mm Hg), prior to the blood flow and pressure measurements. By the time of the hemodynamic studies, this dog was blind, had a mean arterial blood pressure of 225 mm Hg and a hematocrit of 31%. Despite a normal BUN (19.0 mg/100 ml), the dog probably had malignant hypertension. His mesenteric (ileum) blood flow was 18.0 ml/min 100 g^{-1}. I also rejected the mesenteric blood flow and pressure data from one C-2 dog, because of atrial fibrillation during the hemodynamic measurements. This dog had a mesenteric (ileum) blood flow of 25.2 ml/min 100 g^{-1}.

The weight of small intestine (ileum) was similar in all groups. Although there was a tendency for higher blood flows to the mesentery in hypertensive dogs, mesenteric (ileum) blood flow, ml/min 100 g^{-1}, in groups H-1, 53.9, and H-2, 56.1, were not significantly different ($0.10 > P > 0.05$) from corresponding values in their controls (C-1, C-2), 48.2 and 46.7. When I combined the flow data from the hypertensive animals (H-1 plus H-2) and compared them to the combined flow data from controls (C-1 plus C-2), the mesenteric (ileum) blood flow in hypertensives, 55.2 ml/min 100 g^{-1}, became significantly higher ($P < 0.05$) than that of controls, 47.3. In terms of mean values, the increase in blood flow in hypertensives (H-1 plus H-2) was 17%. Because of minor variations in the average weight of ileum studied among groups, the actual measured blood flow, ml/min, was similar ($P > 0.2$) in hypertensives and controls, including the combined data from groups H-1 plus H-2, 21.6, and C-1 plus C-2, 19.8.

Approximately 90 minutes after induction of pentobarbital anesthesia, the mean arterial blood pressure (large artery pressure) had increased by 35-40 mm Hg in groups H-1 and C-1 and by 25-30 mm Hg in groups H-2 and C-2, compared to values in the unanesthetized state. As a result of a greater rise in mean arterial (large artery) pressure, due to pentobarbital, in C-1 dogs, their large and small artery pressure, 156.5 and 122.5 mm Hg, under anesthesia, were higher ($P < 0.05$ and $P < 0.02$) than the corresponding values, 145.9 and 106.8, in C-2 dogs.

Intravascular pressures, large artery, small artery and small vein, under anesthesia, in early, two-kidney hypertensives (H-1) were similar ($P > 0.2$) to those of their controls (C-1). The H-1 hypertensive dogs, therefore, were not hypertensive under anesthesia. On the other hand, intravascular pressures in early, one-kidney hypertensives (H-2) and in the combined group of hypertensives (H-1 plus H-2) were all significantly higher ($P < 0.05$) than the corresponding values in controls (C-2 and C-1 plus C-2). Intravascular pressure rose on the venous side of the circulation too, in that the small vein pressure in H-2 dogs, 15.0 mm Hg, was significantly higher ($P < 0.02$) than the small vein pressure in controls (C-2), 11.6. Mean large venous pressure, calculated by adding small vein pressure and large vein pressure, and dividing by two, was 11.0 ± 0.6 (mean $\pm$ SEM) mm Hg in hypertensives and 9.4 ± 0.2 in normotensives ($P < 0.05$).

As compared to groups C-1 and C-2, the mesenteric (ileum) vascular resistances, total, large artery, small vessel and large vein of H-1 and H-2 hypertensive dogs were normal ($P > 0.05$). The vascular

resistances of hypertensives remained normal, when data from groups H-1 and H-2 were pooled and compared to the combined data from C-1 and C-2 dogs. The combined total mesenteric (ileum) vascular resistance of 10 H-1 and 14 H-2 hypertensive dogs, 3.21 ± 0.17 mm Hg/ml min^{-1} 100 g^{-1} (mean ± SEM) was practically identical to the combined total vascular resistance of 24 control dogs, 3.23 ± 0.21.

Figures 6 and 7 present the blood flow-pressure and blood flow-resistance relationships in the pump-perfused vascular bed of ileum of 6 hypertensive (3 H-1 and 3 H-2) and 6 normotensive control (3 C-1 and 3 C-2) dogs. These data extend the findings of the natural flow experiments by showing, over a wide range of flows, the similarity of perfusion pressure and total resistance in the mesenteric vascular bed of hypertensives and normotensives. No discernible shift or change of shape of the hypertensive flow-pressure and flow-resistance curve is apparent.

Mesenteric Vein Pressure-Volume (Compliance) Relationships In Vivo

The study of mesenteric vein pressure-volume relationships was successful in every dog in which it was attempted. Tables 3 and 4 present the *in vivo* mesenteric vein pressure-volume data in early, *two*-kidney (H-1) and early, *one*-kidney (H-2) hypertensives and the appropriate controls (C-1 and C-2). (See Figure 18 in the Appendix for the analysis of pressure-volume data, including the illustration of an actual recording.) Both the means and standard errors of total volume (ml) which produced intravenous pressures of 5, 15, 24 and 35 mm Hg,

Figure 6. Blood flow-pressure relationships in the pump-perfused vascular bed of ileum. Mean ± SEM perfusion pressure in control (C-1, C-2) and hypertensive (H-1, H-2) dogs.

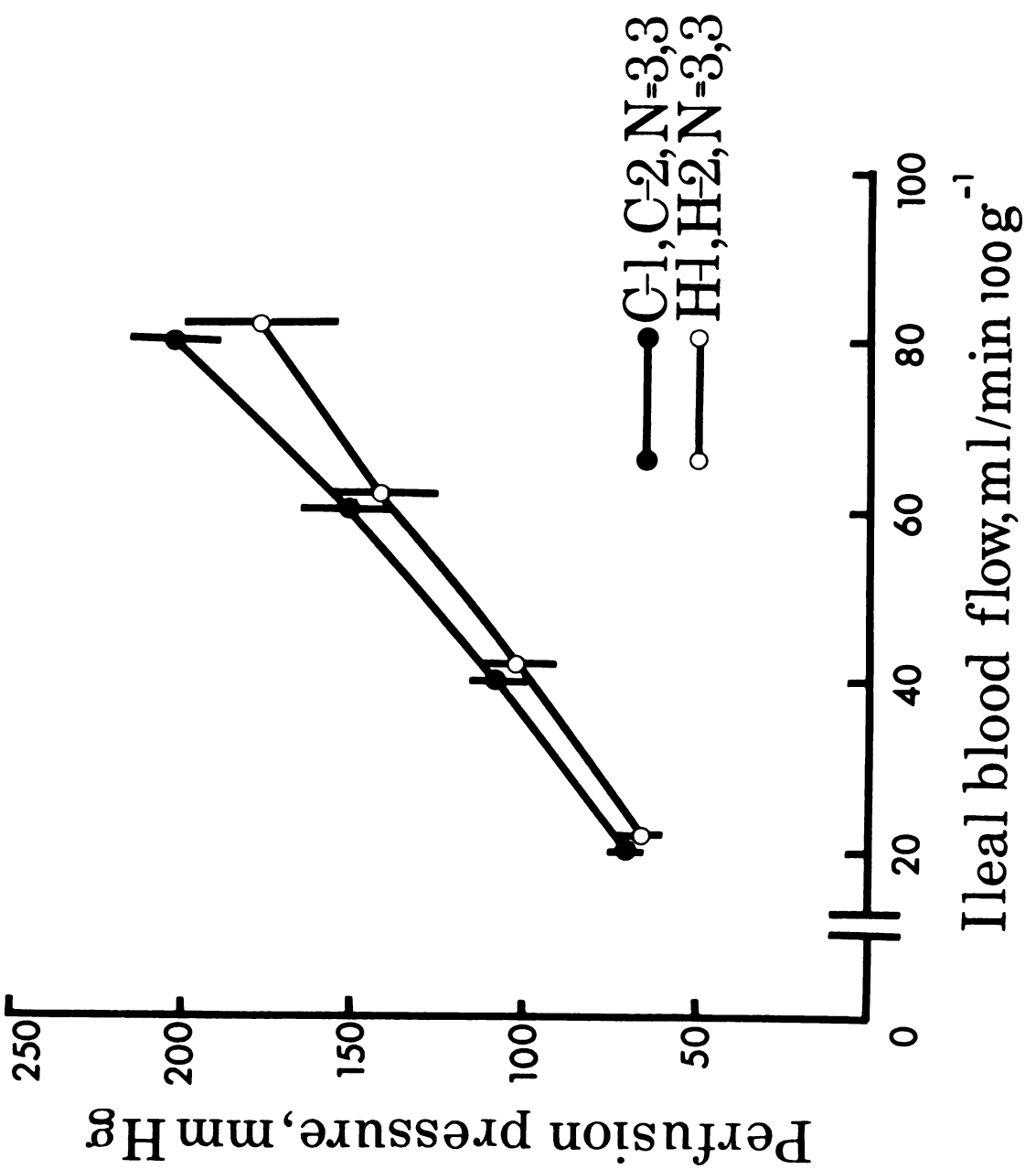

Perfusion pressure, mm Hg
250
200
150
100
50
0
20
40
60
80
100
Ileal blood flow, ml/min 100 g^{-1}
C-1, C-2, N=3,3
H-1, H-2, N=3,3

Figure 6

Figure 7. Blood flow-resistance relationships in the pump-perfused vascular bed of ileum. Mean ± SEM resistance in control (C-1, C-2) and hypertensive (H-1, H-2) dogs.

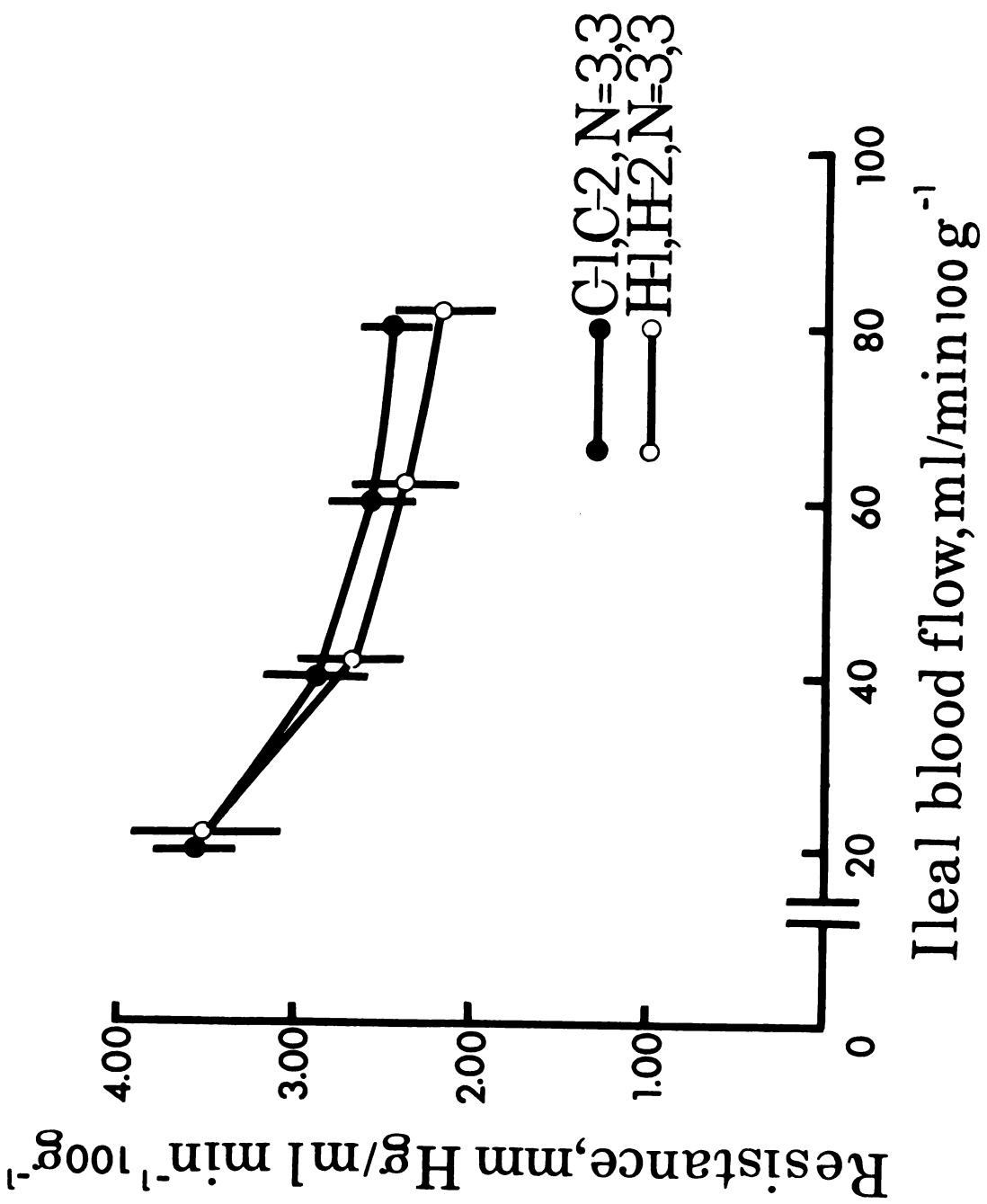

Resistance,mm Hg/ml min⁻¹ 100g⁻¹
4.00
3.00
2.00
1.00
0
20
40
60
80
100
Ileal blood flow,ml/min 100 g⁻¹
C-1,C-2,N=3,3
H-1,H-2,N=3,3

Figure 7

Table 3. Group mean ± SEM of *in vivo* mesenteric vein pressure-volume relationships and compliance ($\Delta V/\Delta P$) in control (C-1 and C-2) and in hypertensive (H-1 and H-2) dogs, during Injection Phase

Intravenous pressures	C-1 N = 10	H-1 N = 10	C-2 N = 15	H-2 N = 15
		Volume (ml)		
5 mm Hg	0.185 ± 0.021	0.174 ± 0.021	0.238 ± 0.029	0.157 ± 0.017*
15 mm Hg	0.340 ± 0.024	0.370 ± 0.040	0.426 ± 0.038	0.305 ± 0.031*
25 mm Hg	0.443 ± 0.032	0.484 ± 0.042	0.534 ± 0.038	0.393 ± 0.036#
35 mm Hg	0.495 ± 0.041	0.532 ± 0.045	0.584 ± 0.040	0.431 ± 0.036#
Pressure range	C-1 N=10	H-1 N = 10	C-2 N = 15	H-2 N = 15
		Compliance, $\Delta V/\Delta P$, (ml/mm Hg)		
5-15 mm Hg	0.0186 ± 0.0016	0.0166 ± 0.0018	0.0202 ± 0.0015	0.0149 ± 0.0018*
15-25 mm Hg	0.0112 ± 0.0013	0.0102 ± 0.0022	0.0104 ± 0.0011	0.0086 ± 0.0013
25-35 mm Hg	0.0047 ± 0.0007	0.0052 ± 0.0011	0.0051 ± 0.0007	0.0038 ± 0.0003

*$P < 0.05$; #$P < 0.02$, for comparison of hypertensive group with appropriate control group.

Table 4. Group mean ± SEM of *in vivo* mesenteric vein pressure-volume relationships and compliance ($\Delta V/\Delta P$) in control (C-1 and C-2) and in hypertensive (H-1 and H-2) dogs, during Withdrawal Phase

Intravenous pressures	C-1 N = 10	H-1 N = 10	C-2 N = 15	H-2 N = 15
		Volume (ml)		
5 mm Hg	0.286 ± 0.042	0.278 ± 0.028	0.341 ± 0.045	0.253 ± 0.030
15 mm Hg	0.483 ± 0.044	0.455 ± 0.036	0.544 ± 0.040	0.411 ± 0.035*
25 mm Hg	0.526 ± 0.045	0.487 ± 0.040	0.587 ± 0.042	0.438 ± 0.034#
35 mm Hg	0.544 ± 0.046	0.507 ± 0.042	0.608 ± 0.043	0.455 ± 0.034*
Pressure range	C-1 N = 10	H-1 N = 10	C-2 N = 15	H-3 N = 15
		Compliance, $\Delta V/\Delta P$, ml/mm Hg		
5-15 mm Hg	0.0198 ± 0.0019	0.0178 ± 0.0027	0.0204 ± 0.0016	0.0158 ± 0.0013#
15-25 mm Hg	0.0043 ± 0.0006	0.0032 ± 0.0006	0.0042 ± 0.0006	0.0026 ± 0.0003*
25-35 mm Hg	0.0018 ± 0.0001	0.0020 ± 0.0003	0.0021 ± 0.0004	0.0017 ± 0.0001

*$P < 0.05$; #$P < 0.02$, for comparison of hypertensive group with appropriate control group.

and the means and standard errors of compliance, $\Delta V/\Delta P$, in the pressure ranges of 5-15, 15-25 and 25-35 mm Hg, during the injection and withdrawal phase, are tabulated. To produce intravenous pressures of 5, 15, 25 and 35 mm Hg, during injection and withdrawal, total volumes were similar ($P > 0.5$) in H-1 and C-1 dogs. Similarly, the calculated compliances in all pressure ranges were comparable and, as would be expected, compliance decreased as pressure increased in the two groups. In contrast, the total volumes required to produce intravenous pressures of 5, 15, 25 and 35 mm Hg during injection, and 15, 25 and 35 mm Hg during withdrawal, were significantly lower ($P < 0.05$ at 5 and 15 mm Hg; $P < 0.02$ at 25 and 35 mm Hg) in H-2 than in C-2 dogs. Calculated compliances were also lower in hypertensives (H-2) in the pressure ranges of 5-15 mm Hg ($P < 0.02$), that is over the operating range, during injection, and in the pressure ranges of 5-15 ($P < 0.02$) and 15-25 ($P < 0.05$) mm Hg during withdrawal. Calculated compliances were similar in H-2 and C-2 dogs in the pressure ranges of 15-25 and 25-35 mm Hg during injection and in the pressure range of 25-35 mm Hg during withdrawal.

Figures 8, 9 and 10 illustrate the pressure-volume data in graphic form. Figure 8 illustrates the mesenteric vein pressure-volume relationships in vivo for early, two-kidney hypertensive (H-1) dogs and their controls (C-1). The two pressure-volume curves are practically identical. Mesenteric vein pressure-volume curves, injection phase, for individual early, one-kidney (H-2) hypertensive dogs and their controls (C-2) are shown in Figure 9. Overall, curves in hypertensive

Figure 8. Mean ± SEM in vivo mesenteric vein pressure-volume relationships (injection phase) in sham-operated control (C-1), ____ , and early, two-kidney hypertensive (H-1), ---- , dogs.

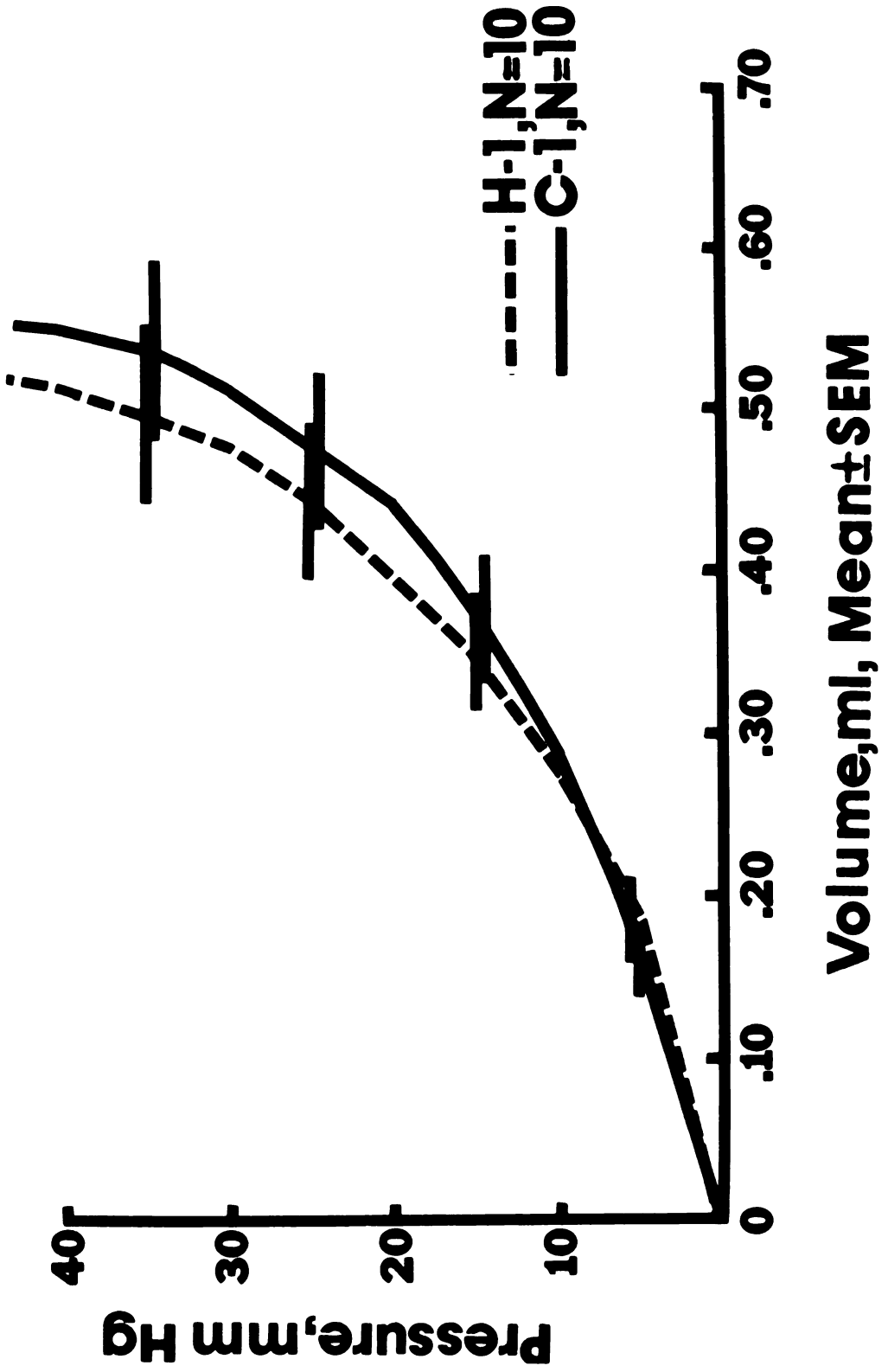

H-1,N=10
C-1,N=10
Pressure,mm Hg
40
30
20
10
0
.10
.20
.30
.40
.50
.60
.70
Volume,ml, Mean±SEM

Figure 8

Figure 9. In vivo mesenteric vein pressure-volume relationships (injection phase) in 15 unilaterally nephrectomized, sham-operated control (C-2) and 15 early, one-kidney hypertensive (H-2) dogs. Each curve represents the average of 2 or 3 separate measurements in one animal.

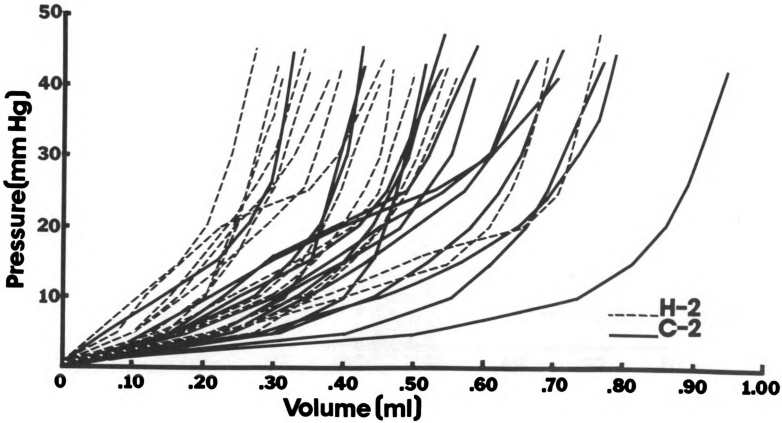

50
40
30
20
10
Pressure(mm Hg)
H-2
C-2
0
.10
.20
.30
.40
.50
.60
.70
.80
.90
1.00
Volume (ml)

Figure 9

Figure 10. Mean ± SEM *in vivo* mesenteric vein pressure-volume relationships (injection phase) in unilaterally nephrectomized, sham-operated control (C-2) and early *one*-kidney hypertensive (H-2) dogs. Withdrawal curve, —·—·, for controls and hypertensives is also shown. *P < 0.05; #P < 0.02.

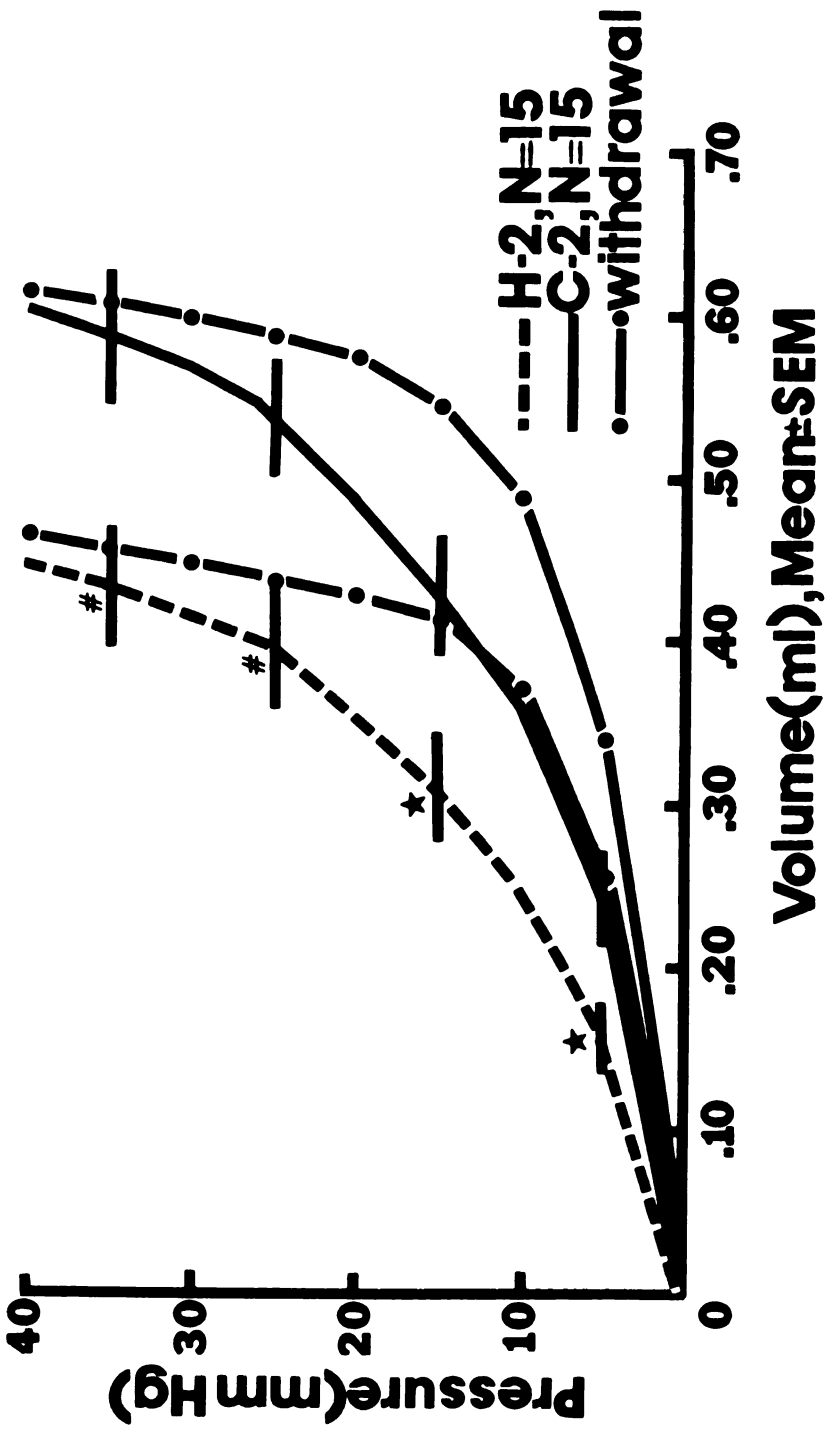

H-2, N=15
C-2, N=15
withdrawal
Pressure(mm Hg)
Volume(ml), Mean±SEM
0
10
20
30
40
.10
.20
.30
.40
.50
.60
.70
#
#
★
★

Figure 10

dogs are shifted in the direction of the pressure axis and are steeper over the low pressure range (0-15 mm Hg). Finally, Figure 10 illustrates the mean ± SEM mesenteric vein pressure-volume relationships, during injection and withdrawal phase, for H-2 and C-2 dogs. Compared to the control curves, the shift toward the pressure axis of the hypertensive injection and withdrawal curve is statistically significant ($P < 0.05$). For the sake of clarity, the standard error of mean volumes and the statistical analysis of the hypertensive and normotensive withdrawal curve are not shown.

Superior Mesenteric Vein Pressure-Volume Relationships In Vitro

I successfully completed the study of the superior mesenteric vein in 20 hypertensive (9 H-1 and 11 H-2) and in 20 control (9 C-1 and 11 C-2 dogs. Pressure-volume data were rejected in 3 hypertensive (1 H-1 and 2 H-2) and in 2 control (1 C-1 and 1 C-2) dogs because of venous leakage. Table 5 presents the body and vein weights of dogs in which the study of the superior mesenteric vein was successfully completed. The body weights of hypertensives were similar to those of controls. Although there was a tendency for the hypertensive veins to weigh less than their controls, this difference was not statistically significant ($P > 0.10$).

Tables 6 and 7 present the in vitro superior mesenteric vein pressure-volume data in early, two-kidney (H-1), early, one-kidney (H-2) hypertensive and the appropriate control (C-1 and C-2) dogs.

Table 5. Body weights and vein weights (mean ± SEM) in groups subjected to the study of *in vitro* superior mesenteric vein pressure-volume relationships

	C-1 N = 9	H-1 N = 9	C-2 N = 11	H-2 N = 11
Body weight (kg)	22.4 ± 0.9	22.4 ± 1.0	23.0 ± 0.8	24.4 ± 0.8
Weight of vein (gm)	0.270 ± 0.024	0.230 ± 0.015	0.284 ± 0.019	0.266 ± 0.018[a]

[a] N = 10.

These tables are organized similarly to Tables 3 and 4. The total volumes to produce intravenous pressures of 5, 15, 25 and 35 mm Hg and the compliances in all pressure ranges, during injection and withdrawal, were similar in groups H-1 and C-1. In contrast, the total volumes required to produce intravenous pressures of 5, 15, 25 and 35 mm Hg, during injection and withdrawal, were significantly lower ($P < 0.05$) in H-2 than in C-2 dogs. In H-2 dogs, calculated compliance in the pressure range of 5-15 mm Hg, during injection, but not during withdrawal, was also lower ($P < 0.05$) than the corresponding value in controls (C-2). Calculated compliances in the higher pressure ranges, 15-25 and 25-35 mm Hg, during injection and withdrawal, were similar in groups H-2 and C-2, with one exception. During the injection phase, in the pressure range of 25-35 mm Hg, the calculated venous compliance of controls (C-2) was actually lower ($P < 0.05$) than that of H-2 hypertensives.

Table 6. Group mean ± SEM of in vitro superior mesenteric vein pressure-volume relationships and compliance ($\overline{\Delta V/\Delta P}$) in control (C-1 and C-2) and hypertensive (H-1 and H-2) dogs, during Injection Phase

Intravenous pressures	C-1 N = 9	H-1 N = 9	C-2 N = 11	H-2 N = 11
			Volume (ml)	
5 mm Hg	1.211 ± 0.138	0.960 ± 0.123	1.009 ± 0.145	0.513 ± 0.086#
15 mm Hg	2.014 ± 0.168	1.632 ± 0.123	1.815 ± 0.200	1.160 ± 0.106#
25 mm Hg	2.281 ± 0.175	1.872 ± 0.125	2.073 ± 0.202	1.444 ± 0.095#
35 mm Hg	2.449 ± 0.184	2.020 ± 0.135	2.233 ± 0.201	1.645 ± 0.083*
Pressure range	C-1 N = 9	H-1 N = 9	C-2 N = 11	H-2 N = 11
			Compliance, $\Delta V/\Delta P$, (ml/mm Hg)	
5-15 mm Hg	0.0803 ± 0.0098	0.0672 ± 0.0066	0.0821 ± 0.0066	0.0629 ± 0.0046*
15-25 mm Hg	0.0267 ± 0.0026	0.0240 ± 0.0017	0.0257 ± 0.0014	0.0284 ± 0.0020
25-35 mm Hg	0.0168 ± 0.0014	0.0152 ± 0.0010	0.0160 ± 0.0010*	0.0203 ± 0.0013

*$P < 0.05$; #$P < 0.02$, for comparison of hypertensive group with appropriate control group.

Table 7. Group mean ± SEM of in vitro superior mesenteric vein pressure-volume relationships and compliance ($\Delta V/\Delta P$) in control (C-1 and C-2) and hypertensive (H-2 and H-2) dogs, during Withdrawal Phase

Intravenous pressures	C-1 N = 9	H-1 N = 9	C-2 N = 11	H-2 N = 11
		Volume (ml)		
5 mm Hg	1.573 ± 0.116	1.371 ± 0.142	1.384 ± 0.156	0.982 ± 0.073*
15 mm Hg	2.230 ± 0.168	1.863 ± 0.132	2.013 ± 0.189	1.501 ± 0.079*
25 mm Hg	2.383 ± 0.188	1.971 ± 0.140	2.188 ± 0.196	1.656 ± 0.082*
35 mm Hg	2.461 ± 0.190	2.049 ± 0.140	2.272 ± 0.199	1.729 ± 0.083*
Pressure range	C-1 N = 9	H-1 N = 9	C-2 N = 11	H-2 N = 11
		Compliance, $\Delta V/\Delta P$, (ml/mm Hg)		
5-15 mm Hg	0.0668 ± 0.0107	0.0486 ± 0.0042	0.0634 ± 0.0063	0.0534 ± 0.0036
15-25 mm Hg	0.0153 ± 0.0022	0.0108 ± 0.0012	0.0166 ± 0.0014	0.0135 ± 0.0014
25-35 mm Hg	0.0078 ± 0.0005	0.0078 ± 0.0005	0.0084 ± 0.0005	0.0071 ± 0.0003

*$P < 0.05$, for comparison of hypertensive group with appropriate control group.

Figure 11 illustrates the mean ± SEM superior mesenteric vein pressure-volume relationships, injection phase, for the early, two-kidney hypertensive (H-1) and the appropriate control (C-1) dogs. Although there is a shift of the hypertensive pressure-volume curve in the direction of the pressure axis, this shift is not statistically significant ($0.20 > P > 0.05$). Figure 12 illustrates the mean ± SEM pressure-volume relationships, during injection and withdrawal phase, for H-2 and C-2 dogs. There is a statistically significant ($P < 0.05$) shift of the hypertensive injection and withdrawal curve in the direction of the pressure axis. For the sake of clarity, the standard error of mean volumes and the statistical analysis of the hypertensive and normotensive withdrawal curve are not shown.

In addition to stepwise injection and withdrawal of Krebs-Ringer solution, I also determined pressure-volume relationships in the same superior mesenteric veins by rapid (10-15 second) infusion at a constant rate of 9.88 ml/min. Figure 13 illustrates the *in vitro* superior mesenteric vein pressure-volume relationships at constant infusion in H-2 and C-2 dogs. Data on which Figure 13 is based are shown in Table 8. The shift of the hypertensive pressure-volume curve is similar to that in Figure 12. The total volume infused to reach a given intravenous pressure was, however, lower in both hyptertensives and normotensives. For instance, it required a total volume of 1.82 ml by stepwise injection, and 1.72 ml by rapid infusion, to reach 15 mm Hg pressure in normotensive veins. A similar relationship held for the individual hypertensive veins, but it is not apparent from the

Figure 11. Mean ± SEM *in vitro* superior mesenteric vein pressure-volume relationships (injection phase) in sham-operated control (C-1) and early, *two*-kidney hypertensive (H-1) dogs.

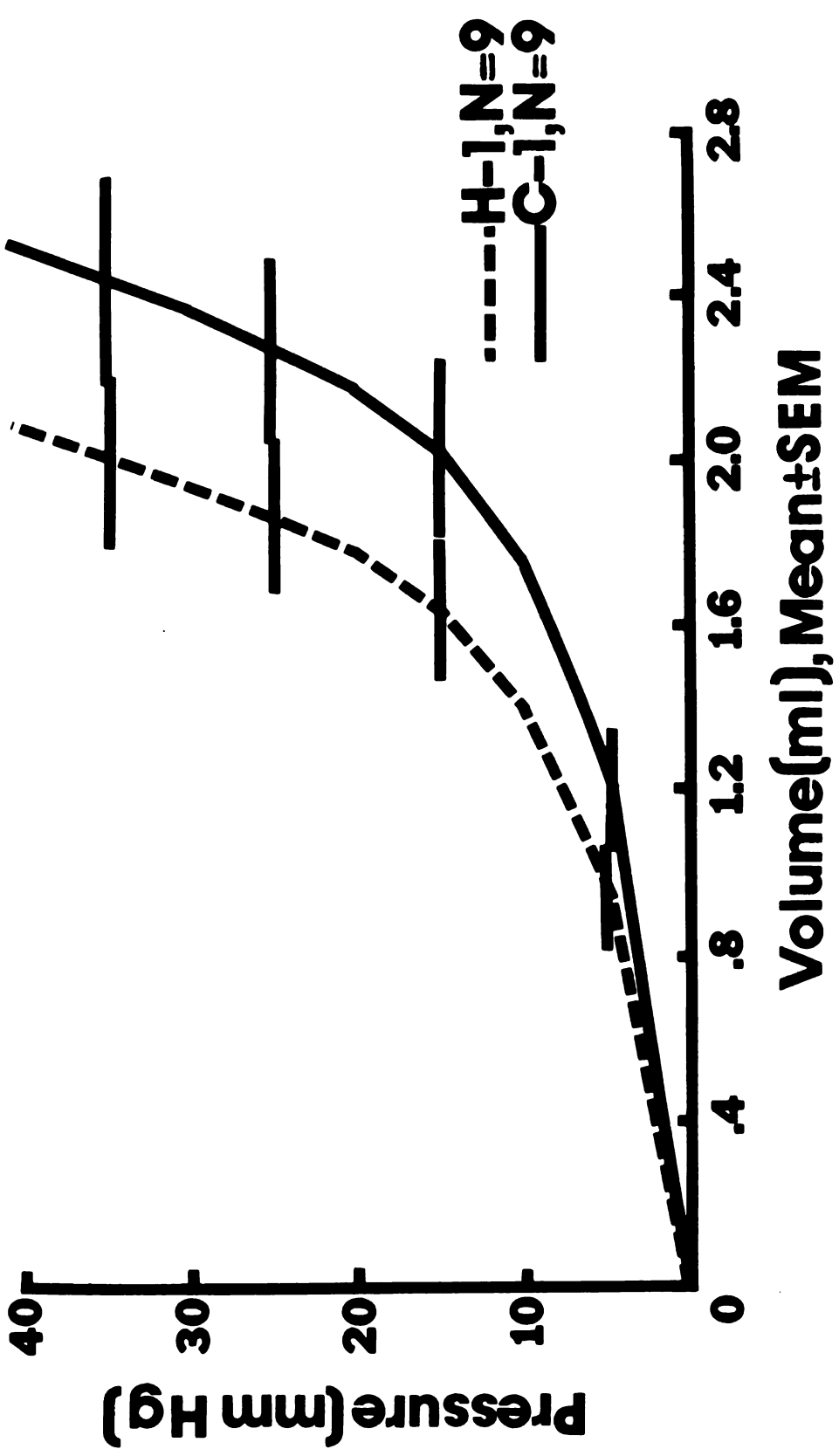

H-1,N=9
C-1,N=9
Pressure(mm Hg)
40
30
20
10
0
.4
.8
1.2
1.6
2.0
2.4
2.8
Volume(ml),Mean±SEM

Figure 11

Figure 12. Mean ± SEM *in vitro* superior mesenteric vein pressure-volume relationships (injection phase) in unilaterally-nephrectomized, sham-operated control (C-1) and early, one-kidney hypertensive (H-2) dogs. Withdrawal curve for controls and hypertensives is also shown. *P < 0.05; #P < 0.02.

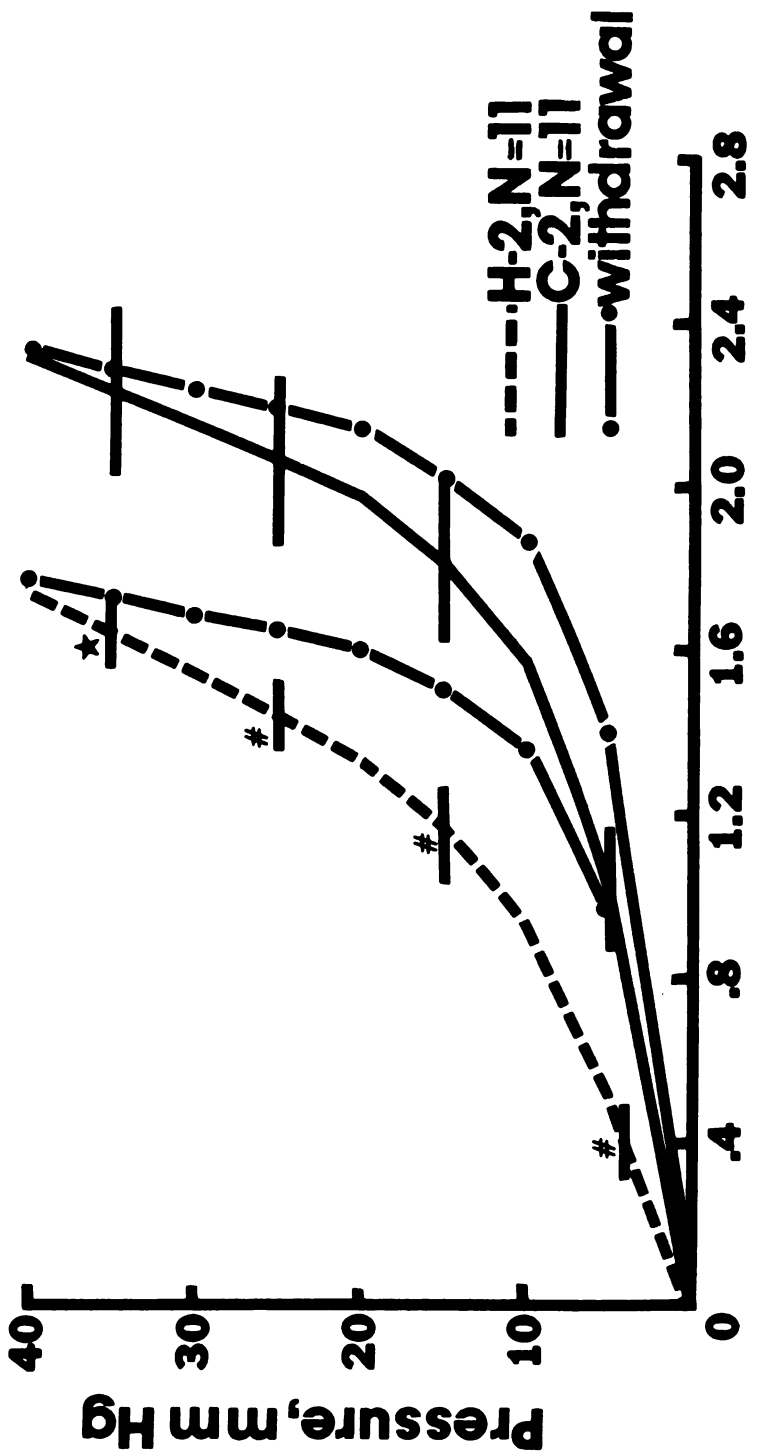

Pressure, mm Hg
40
30
20
10
0
.4
.8
1.2
1.6
2.0
2.4
2.8
Volume, ml, Mean±SEM
H-2, N=11
C-2, N=11
withdrawal
*
#
#
#

Figure 12

Figure 13. Mean ± SEM *in vitro* superior mesenteric vein pressure-volume relationships during infusion at constant rate of 9.88 ml/min in unilaterally-nephrectomized, sham-operated control (C-2) and early, *one*-kidney hypertensive (H-2) dogs. *$P < 0.05$.

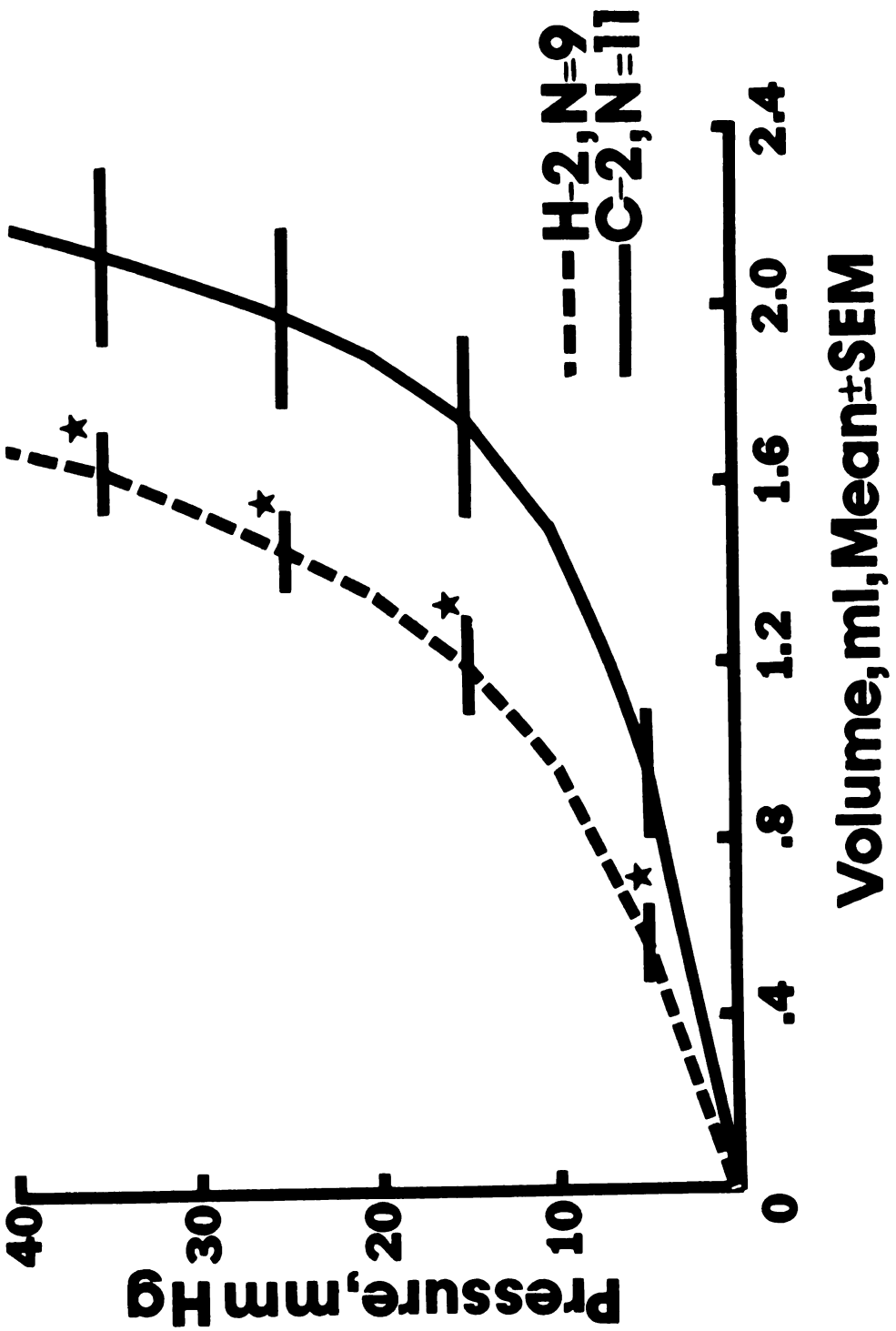

Pressure,mm Hg
40
30
20
10
0
.4
.8
1.2
1.6
2.0
2.4
Volume,ml,Mean±SEM
H-2,N=9
C-2,N=11

Figure 13

Table 8. Group mean ± SEM of *in vitro* superior mesenteric vein pressure-volume relationships and compliance ($\Delta V/\Delta P$) in control (C-2) and in hypertensive (H-2) dogs, during infusion at constant rate of 9.88 ml/min

Intravenous pressures	C-2 N = 11	H-2 N = 9
	Volume (ml)	
5 mm Hg	0.028 ± 0.140	0.548 ± 0.081*
15 mm Hg	1.723 ± 0.196	1.182 ± 0.105*
25 mm Hg	1.972 ± 0.196	1.446 ± 0.094*
35 mm Hg	2.113 ± 0.192	1.604 ± 0.084*
Pressure range	C-2 N = 11	H-2 N = 9
	Compliance, ml/mm Hg	
5-15 mm Hg	0.0784 ± 0.0071	0.0634 ± 0.0044
15-25 mm Hg	0.0264 ± 0.0013	0.0264 ± 0.0013
25-35 mm Hg	0.0140 ± 0.0006	0.0158 ± 0.0013

*$P < 0.05$, for comparison of hypertensive group with control group.

group means for hypertensive veins because a smaller number of veins were studied by rapid infusion, 9, than by stepwise injection, 11. The superior mesenteric vein pressure-volume relationships by rapid infusion in H-1 and C-1 dogs (see Table 14 in the Appendix) was also similar to the pressure-volume relationships obtained during the slower injection (Figure 8).

Finally, perfusing the in vitro vein with NaCN (500 mg/liter) for 20 minutes prior to the measurement of superior mesenteric vein pressure-volume relationships by rapid infusion failed to shift the pressure-volume curves of 3 H-2 and 3 C-2 dogs.

Since the hypertensive superior mesenteric veins had a tendency to weigh less than the control veins (Table 5), I calculated the correlation between the superior mesenteric vein weights and the total volume required to reach 40 mm Hg intravenous pressure, on the one hand, and superior mesenteric vein weights and compliance in the pressure range of 5-15 mm Hg, on the other hand, in both hypertensives and normotensives. Tables 9 and 10 show my analysis. There was no significant correlation ($P > 0.05$) between the weight of vein and the total volume injected and the weight of vein and the compliance in either hypertensives or normotensives. In Figure 14, the weight of superior mesenteric veins and the total volume injected to reach 40 mm Hg intravenous pressure are plotted for groups H-2 and C-2.

Table 9. Correlation between weight of superior mesenteric vein (mean ± SEM) and total volume (mean ± SEM) injected to reach 40 mm Hg intravenous pressure in groups H-2 and C-2

	Weight of vein (gm)	Volume (ml) at 40 mm Hg	Correlation coefficient (r)
H-2, N = 10	0.266 ± 0.018	1.78 ± 0.08	-0.02
C-2, N = 11	0.284 ± 0.019	2.23 ± 0.20	0.20

Table 10. Correlation between weight of superior mesenteric vein (mean ± SEM) and compliance (mean ± SEM) in pressure range of 5-15 mm Hg, during injection phase, in groups H-2 and C-2

	Weight of vein (gm)	Compliance, $\Delta V/\Delta P$ (ml/mm Hg)	Correlation coefficient (r)
H-2, N = 10	0.266 ± 0.018	0.065 ± 0.005	0.27
C-2, N = 11	0.284 ± 0.019	0.082 ± 0.007	0.44

Figure 14. Scatter diagram for the weight (gm) of superior mesenteric vein and the total volume (ml) injected to reach 40 mm Hg intravenous pressure in 11 control (C-2) and 10 hypertensive (H-2) dogs.

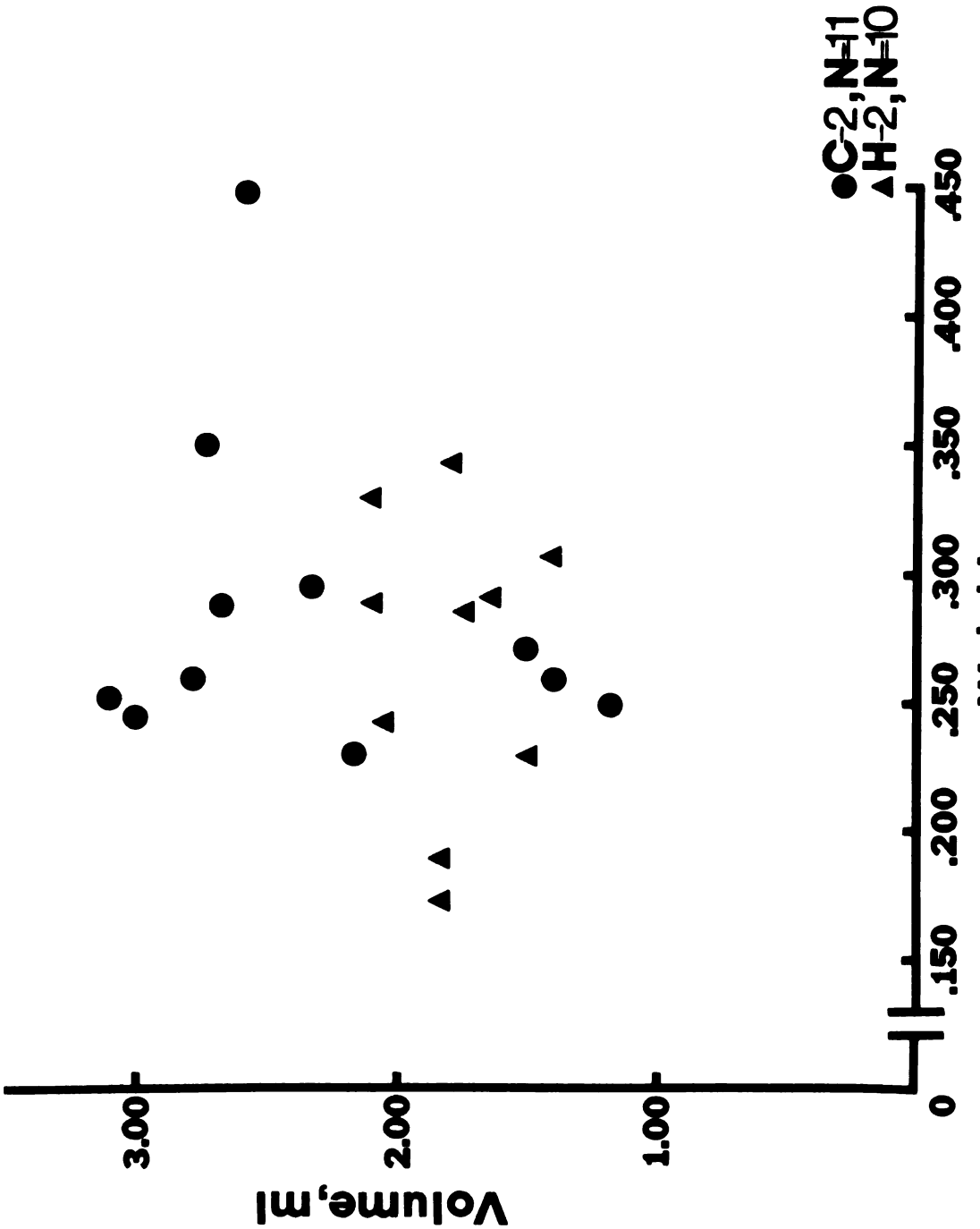

●C-2, N=11
▲H-2, N=10
Volume, ml
3.00
2.00
1.00
0
.150
.200
.250
.300
.350
.400
.450
Weight, gm

Figure 14

Femoral Vein Pressure-Volume Relationships In Vitro

I studied the femoral vein *in vitro* from 3 H-2, 8 H-3, 3 C-2 and 8 C-3 dogs. All experiments were successfully completed. Table 11 presents the body and vein weights of hypertensive and control dogs. While the body weight of the two groups was similar, the average weight was less in hypertensive veins, but the difference was not statistically significant ($P > 0.10$).

Table 11. Body weights and vein weights (mean ± SEM) in groups subjected to the study of *in vitro* femoral vein pressure-volume relationships

	C-2, C-3 N = 11	H-2, H-3 N = 11
Body weight (kg)	27.0 ± 0.4	26.6 ± 0.6
Weight of vein (gm)	0.136 ± 0.007	0.122 ± 0.007

Table 12 presents the group mean ± SEM femoral vein pressure-volume relationships and compliance, $\Delta V/\Delta P$, at a constant infusion rate of 3.88 ml/min. The total volume to produce intravenous pressures of 5, 15 and 25 mm Hg was similar in hypertensives (H-2, H-3) and normotensives (C-2, C-3). The total volume required to produce 35 mm Hg intravenous pressure, on the other hand, was significantly lower ($P < 0.05$) in H-2, H-3 dogs. Similarly, the compliance in the pressure ranges of 5-15 and 15-25, but not 25-35, mm Hg was significantly lower ($P < 0.05$) in hypertensives than in normotensives. Pressure-volume relationships during withdrawal of Krebs-Ringer solution were not studied in these dogs.

Table 12. Group mean ± SEM of *in vitro* femoral vein pressure-volume relationships and compliance (ΔV/ΔP) in control (C-2, C-3) and in hypertensive (H-2, H-3) dogs, during infusion at constant rate of 3.88 ml/min

Intravenous pressures	C-2, C-3 N = 11	H-2, H-3 N = 11
	Volume (ml)	
5 mm Hg	0.241 ± 0.043	0.189 ± 0.046
15 mm Hg	0.537 ± 0.062	0.380 ± 0.051
25 mm Hg	0.649 ± 0.065	0.471 ± 0.048
35 mm Hg	0.709 ± 0.067	0.526 ± 0.047*
Pressure range	C-2, C-3 N = 11	H-2, H-3 N = 11
	Compliance, ml/mm Hg	
5-15 mm Hg	0.0296 ± 0.0039	0.0175 ± 0.0017#
15-25 mm Hg	0.0112 ± 0.0011	0.0090 ± 0.0008#
25-35 mm Hg	0.0060 ± 0.0006	0.0055 ± 0.0005

*P < 0.05; #P < 0.02, for comparison of hypertensive group with control group.

Figure 15 illustrates the in vitro femoral vein pressure-volume data. There is a statistically significant ($P < 0.05$) shift of the hypertensive pressure-volume curve in the direction of the pressure axis at 35, but not at 5 ($P > 0.4$), 15 ($0.10 > P > 0.05$) or 25 ($0.10 > P > 0.05$) mm Hg pressures.

Since the hypertensive femoral veins, like the hypertensive superior mesenteric veins, had a tendency to weigh less than the control veins, I calculated the correlation between femoral vein weight and total volume required to reach 40 mm Hg intravenous pressure, on the one hand, and femoral vein weight and compliance in the pressure range of 5-15 mm Hg, on the other hand, in both hypertensives and normotensives. There was no significant correlation between the weight of veins and the total volume infused in hypertensives ($r = 0.14$) or between the weight of veins and compliance in hypertensives ($r = -0.02$) and normotensive controls ($r = 0.56$). There was a slight correlation ($r = 0.70$, $P < 0.05$) between the weight of veins and the total volume infused in normotensive controls.

Venous Wall Water, Na and K Content

Table 13 presents data on the water, Na and K content of mesenteric vein, femoral vein and vena cava in early, one-kidney (H-2), chronic, one-kidney (H-3) hypertensive and control (C-2, C-3) dogs. Because of the small number of a particular vein that I have studied and the large experimental variation, the composition of hypertensive mesenteric veins, femoral veins and venae cavae was not significantly

Figure 15. Mean ± SEM *in vitro* femoral vein pressure-volume relationships during infusion at constant rate of 3.88 ml/min in unilaterally nephrectomized, sham-operated control (C-2, C-3) and early (H-2) and chronic (H-3) *one*-kidney hypertensive dogs. *$P < 0.05$.

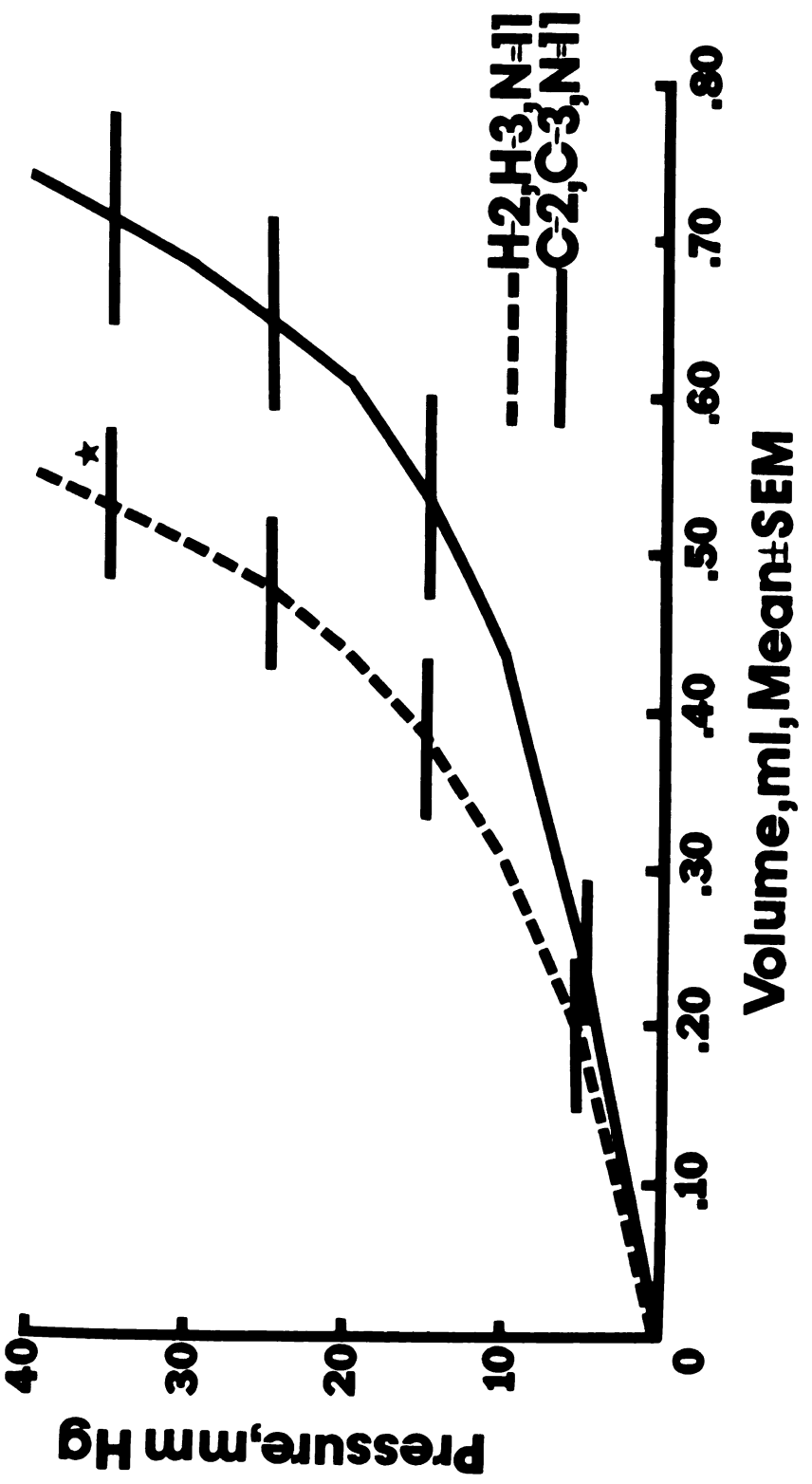

Pressure,mm Hg
40
30
20
10
0
.10
.20
.30
.40
.50
.60
.70
.80
Volume,ml,Mean±SEM
H-2,H-3,N=11
C-2,C-3,N=11
★

Figure 15

Table 13. Mean ± SEM of venous wall water, Na and K content in early, one-kidney (H-2), chronic, one-kidney (H-3) hypertensive and control (C-2, C-3) dogs

		Water content (% wet weight)	Na content (mEq/kg dry weight)	K content (mEq/kg dry weight)
Mesenteric vein	C-2 N = 8	65.3 ± 2.1	271.7 ± 25.3	68.8 ± 12.0[a]
	H-2 N = 8	67.6 ± 1.9	334.5 ± 34.8	113.2 ± 15.0[a]
Femoral vein	C-3 N = 8	63.2 ± 2.1	277.6 ± 21.5	73.2 ± 13.6
	H-3 N = 8	69.0 ± 1.3	353.1 ± 21.8*	93.5 ± 24.9
Vena cava	C-3 N = 5	63.4 ± 2.3	265.0 ± 25.5	69.6 ± 11.9[b]
	H-3 N = 5	65.6 ± 2.8	333.6 ± 28.2	135.2 ± 35.0
All veins	C-2, C-3 N = 21	64.0 ± 1.2	272.4 ± 13.4	70.9 ± 7.3[c]
	H-2, H-3 N = 21	67.4 ± 1.1*	341.4 ± 16.3**	110.8 ± 16.0[d]

*P < 0.05; **P < 0.01, for comparison of hypertensive group with appropriate control group.

[a]7 dogs; [b]4 dogs; [c]19 dogs; [d]20 dogs.

different from that of controls, with one exception. The Na content of hypertensive (H-3) femoral veins, 353.1 mEq/kg dry weight, was significantly higher ($P < 0.05$) than that of controls (C-3), 277.6 mEq/kg. The difference in femoral vein water content between hypertensives, 69.0%, and normotensives, 63.2%, was of borderline significance ($0.10 > P > 0.05$). On the other hand, when I combined the data on all the hypertensive and control veins, the water, Na and K content of hypertensive veins, 67.4%, 341.4 and 110.8 mEq/kg, respectively, became significantly higher ($P < 0.05$) than corresponding values in controls, 64.0%, 272.4 and 70.9.

Histological Examination of the Mesenteric Vascular Arcade and the Femoral Vein

The mesenteric and the femoral veins of 1 H-1, 2 H-2 and 1 H-3 hypertensive dogs were examined and compared to veins from control (1 C-1, 2 C-2 and 1 C-3) dogs. The veins were studied with respect to the number of smooth muscle cell layers, the size and branching of smooth muscle cells, the content of neutral or acid polysaccharides, the ratio of vein wall thickness to adventitial collar of collagen, and the density and size of collagen fibers. The amount of PAS material, edema and fibrosis in the mesentery was also evaluated. No significant differences between veins from hypertensive and normotensive dogs were identified. Figures 16 and 17 illustrate some of the histological features that Dr. Dunkel and I looked for. Figure 16 shows the relative thickness of the inner, darkly-stained, laminated smooth muscle cell

Figure 16. Cross section through portion of a small artery (left) and its accompanying vein from the mesentery. Trichrome stain. x 80.

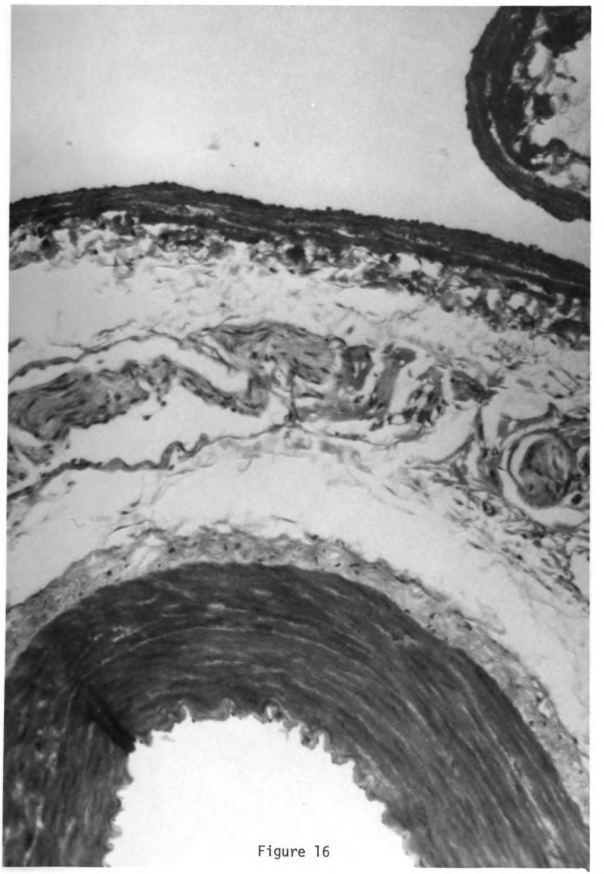


Figure 16

Figure 17. Cross section through portion of a small mesenteric vein. Trichrome stain. x 160.

Figure 17

layer and of the loose, adventitial collagen collar in a small mesenteric vein (on the right in the figure). Figure 17 is a close-up of the same vein showing the arrangement of the smooth muscle cells and the appearance of their nuclei.

CHAPTER V

DISCUSSION

These studies show that, under pentobarbital anesthesia, the resistance to flow through the mesenteric vascular bed is normal, and flow is slightly but not significantly ($0.10 > P > 0.05$) increased in early, two-kidney (H-1) and early, one-kidney (H-2) perinephritic hypertensive dogs (Table 2). In the combined group of hypertensive dogs (H-1 plus H-2), however, mesenteric (ileum) blood flow is increased ($P < 0.05$). Mesenteric venous compliance, measured by *in vivo* and *in vitro* pressure-volume studies, is decreased in early, one-kidney, but *not* in early, two-kidney perinephritic hypertension (Tables 3 and 6). Decreased venous compliance is also present in the more chronic stage of one-kidney (H-3) perinephritic hypertension, as shown by the *in vitro* femoral vein pressure-volume studies (Table 12). Decreased venous compliance is accompanied by increased water, Na and K content of veins from one-kidney perinephritic hypertensive dogs.

The induction of unilateral perinephritis by wrapping one kidney in cellophane or silk, with the contralateral kidney intact or removed, is an effective way of creating hypertension in experimental animals. In this study, every dog with one of its kidneys wrapped in silk became hypertensive, thus confirming the experience of previous investigators (Page, 1939; Ferrario *et al.*, 1970; Overbeck, 1972). Except for the

development of malignant hypertension (possibly, one dog in my series), the general health of dogs, following the induction of perinephritis, remained good. The small drop in hematocrit of early, one-kidney controls (C-2) and hypertensives (H-2) was probably due to the fact that these dogs underwent two separate operations in the course of two to three weeks. The stable hematocrit of C-3 and H-3 dogs supports my suggestion. The latter underwent sham operation and wrapping, plus contralateral nephrectomy, in the course of one operation, instead of two. However, the possibility that the drop in hematocrit of H-2 dogs was due to plasma volume expansion cannot be ruled out. In this regard, Ferrario et al. (1970) was unable to demonstrate plasma volume expansion in similarly prepared dogs. A possible disturbance in the water metabolism of perinephritic dogs is also suggested by the decreased urinary specific gravity in early, two-kidney hypertensive (H-1) dogs. The decreased urinary specific gravity could reflect an increased water intake. Alternately, the decrease in urinary specific gravity could be due to the perinephritis itself, with impairment of the concentrating ability of the wrapped kidney. The kidney function of hypertensive dogs, as measured by the blood urea nitrogen concentration was, however, normal.

The rise of arterial blood pressure is a well-known effect of pentobarbital anesthesia in normal dogs, and was also observed by Overbeck (1972) in perinephritic hypertensive dogs. The significantly greater rise of mean arterial blood pressure under anesthesia in two-kidney controls (C-1) than in one-kidney controls (C-2) is difficult

to explain, since this difference was not observed by Overbeck (1972) in similarly prepared control dogs. Although the C-2 controls had a significant drop in hematocrit after the preceding two operations (see above), the hematocrit of the two groups was identical at the time of the hemodynamic studies. Pentobarbital anesthesia, when combined with surgical trauma, in this case, laparatomy and manipulation of the small intestines, results in the secretion of renin via the activation of the sympathetic nervous system (Fray et al., 1974). It is conceivable that renin secretion was greater when both kidneys were present (C-1 controls) than in the presence of only one kidney (C-2 controls). This difference could explain the greater rise of mean arterial blood pressure in the two-kidney controls (C-1).

Mesenteric (Ileum) Blood Flow and Pressure Relationships

Regional hemodynamics in experimental renovascular hypertension have received little attention, with the possible exception of the kidney. The studies which have been performed indicate that in chronic, one-kidney renovascular hypertension, blood flow to the limbs (Overbeck et al., 1971), heart (West et al., 1959), and brain (Flohr et al., 1971), and blood flow to the non-stenotic kidney in chronic two-kidney renovascular hypertension (Corcoran et al., 1942; Bounous et al., 1962) is normal, as is cardiac output in the chronic stage of the hypertensive process. The hypertension is accounted for by an increase in total peripheral vascular resistance, which appears to be uniformly distributed to the various organs.

In contrast to the hemodynamics of chronic stages of experimental renovascular hypertension, there is now evidence that in the early stages (less than 4 weeks) of one-kidney Goldblatt hypertension in rats, and of two- and one-kidney perinephritic and Goldblatt hypertension in dogs, cardiac output is elevated (Ledingham et al., 1967; Ferrario et al., 1970; Bianchi et al., 1970 and 1972; Ferrario, 1974). In dogs in the early stages of two-kidney perinephritic and one-kidney Goldblatt hypertension, the total peripheral vascular resistance is normal or decreased. Thus a change in systemic hemodynamics apparently occurs between the early and chronic stages of perirephritic and Goldblatt hypertension. In perinephritic hypertensive dogs, Ferrario et al. (1970) found that this transition took place between the fourth and sixth week: cardiac output, previously elevated, returned to normal levels and total peripheral vascular resistance, previously decreased, increased and became responsible for the sustained hypertension. In unilaterally nephrectomized dogs with Goldblatt hypertension, the transition takes place somewhat earlier: during the first week, according to Bianchi et al. (1970), between the second and third week, according to Ferrario (1974). With regard to an initial rise in cardiac output, followed by a rise in total peripheral vascular resistance, the "autoregulatory theory" of the development of hypertension was proposed. According to this theory, the increase in blood flow through all or some of the regional vascular beds gradually leads to an increase in total peripheral vascular resistance (Coleman et al., 1971).

Overbeck (1972) previously investigated the possible "autoregulatory role" of the forelimb vascular beds in dogs with early, two- and one-kidney perinephritic hypertension, under pentobarbital anesthesia. His studies were performed at the stage of hypertension when Ferrario et al. (1970) found cardiac output first elevated, and also at the stage when cardiac output is at its maximum. Contrary to his expectations, he did not find evidence of increases in blood flow. Actually, forelimb total blood flow per 100 g weight was slightly, though not significantly, lower in early, two-kidney and early one-kidney hypertensives than in control dogs. As in the chronic stages of experimental one-kidney perinephritic hypertension, there were significant elevations of limb vascular resistance in the two hypertensive groups. The author concluded that the limb vascular beds probably do not participate in the change in systemic hemodynamics between the early and the chronic stage of perinephritic hypertension. Without evidence for increased blood flow through the forelimb vascular beds, even in the very early (less than two weeks) stage of the development of hypertension, it was unlikely that the increase in forelimb vascular resistance was due to "autoregulatory response" to increased blood flow. It was, therefore, of great interest to me to determine how other vascular beds behave during the developmental stage of experimental renovascular hypertension. Specifically, I was interested in finding out which vascular bed receives the excess blood flow and whether "autoregulatory response" is a plausible explanation for arteriolar constriction in that bed. I chose to study the mesenteric

vascular bed because it had not been previously investigated in experimental renovascular hypertension. I studied the very same stages of perinephritic hypertension in dogs that had been previously investigated by Ferrario et al. (1970) from the point of view of systemic hemodynamics, and by Overbeck (1972) from the point of view of limb hemodynamics. I used experimental techniques and anesthesia similar to those used by Overbeck in order to allow for comparison between his study and mine.

In the early stages of perinephritic hypertension, the regional hemodynamics of the mesentery (ileum) (Table 2) appear to be different from those of the forelimb (Overbeck, 1972). There is, however, little difference in the mesenteric hemodynamics of early, two-kidney (H-1) and of early, one-kidney (H-2) perinephritic hypertension. The two groups, therefore, have been considered together. I found the mesenteric (ileum) total blood flow per 100 gm weight in the combined group of hypertensives to be increased 17% above normal. Interestingly, the maximum increase in cardiac output reported by Ferrario et al. (1970) in early perinephritic dogs was 18%. Total mesenteric (ileum) vascular resistance in hypertensives, on the other hand, was practically identical to that of controls. Although the average small vessel segmental resistance was slightly lower and large vein segmental resistance slightly higher in hypertensives than in normotensive controls, these differences were not statistically significant. In view of the arterial hypertension, if the mesenteric (ileum) vascular bed of hypertensives behaved in a passive manner, I would have expected

the mesenteric total and segmental vascular resistances to be less than normal in hypertension. The normal total and segmental vascular resistances, despite elevated intravascular distending pressures (large artery, small artery and small vein), especially in one-kidney (H-2) hypertensives, suggest decreased vascular distensibility in hypertension. Decreased vascular distensibility is present not only on the arterial side, but also on the venous side of the circulation, as shown by the increased mean (large) venous pressure in early, one-kidney (H-2) hypertensives, accompanied by normal large vein resistance. Decreased mesenteric vein distensibility was also shown to be present by the venous pressure-volume studies (see below). The decreased vascular distensibility of hypertensives could result from activation of vascular smooth muscle (washout of local vasodilator metabolites, Bayliss response, circulating vasoconstrictors, etc.) and/or from structural changes (muscle hypertrophy, edema, increased vascular wall collagen, etc.). Decreased distensibility of the hypertensive resistance vessels suggests the onset of a "regulatory response" to increased blood flow. However, to further support the "autoregulatory theory" of the development of hypertension, it would be necessary to demonstrate that mesenteric vascular resistance eventually becomes elevated and that mesenteric blood flow approaches normal in chronic, one-kidney (H-3) hypertensive dogs. This remains to be done.

Flow-pressure and flow-resistance curves in the same hypertensive dogs overlapped with those of controls. No discernible change in the shape of the curves occurred in hypertension. The increase in

pressure as a function of flow was similar in hypertensives and normotensives (Figure 6), as was the decrease in resistance as a function of flow (Figure 7). These findings are not what I would have expected on the basis of the natural flow-pressure studies. Under natural flow conditions, the evidence suggests decreased distensibility of hypertensive resistance vessels. If vascular distensibility were decreased in hypertension, at the same pressure, I would have expected the total vascular resistance of the pump-perfused mesenteric bed of hypertensives to be increased, instead of being the same as that of normotensive controls. I have no good explanation for this discrepancy in findings between flow-pressure relationships under natural flow conditions and during pump-perfusion. The discrepancy may be related to the small number of dogs studied during pump-perfusion. The six hypertensive (3 H-1 and 3 H-2) and the six normotensive (3 C-1 and 3 C-2) dogs selected at random for the pump-perfusion study were not representative of the total combined group of hypertensives (H-1 plus H-2) and of normotensives (C-1 plus C-2) (Table 2). Under natural flow conditions, the total mesenteric vascular resistance of the same six hypertensive dogs was lower than that of hypertensives in general, and the total mesenteric vascular resistance of the same six normotensive dogs was higher than that of normotensives in general. The lumping together of data from early, two-kidney (H-1) and early, one-kidney (H-2) hypertensives could also contribute to the discrepancy, since the evidence for decreased vascular distensibility in H-1 hypertensive dogs is not conclusive. In this regard, under natural flow conditions,

there was no significant difference in vascular distending pressures and resistances between the total group of early, two-kidney (H-1) hypertensives and the appropriate control (C-1) group (Table 2).

Venous Pressure-Volume (Compliance) Relationships

The compliance of large arteries is decreased in one-kidney perinephritic hypertensive dogs (Feigl et al., 1963) and in men with chronic essential hypertension (Greene et al., 1966). The decreased arterial compliance is felt to reflect structural changes which, in turn, may be secondary to sustained elevation of intraluminal pressure. The first direct indication that large vein compliance may be decreased in experimental renovascular hypertension came from the work of Overbeck (1972). He showed that the pressure-volume curve of the femoral vein, but not of the jugular vein, in early, one-kidney perinephritic hypertensive dogs is shifted in the direction of the pressure axis, suggesting decreased compliance of this vein in the early stage of the hypertensive process. The author suggested that decreased femoral vein compliance, like decreased arterial compliance, may be due to structural changes, but offered no direct evidence to support his suggestion.

Until the work of Overbeck (1972), the evidence suggesting an abnormality of venous function in hypertension was mainly indirect. Plethysmography of the extremities and of the digits in chronically hypertensive men showed decreased vascular distensibility in two studies (Caliva et al., 1963; Walsh et al., 1969), but not in two earlier studies (Abramson et al., 1942; Wood, 1961). Furthermore, the

possibility that the decreased vascular distensibility of the extremity is due to decreased arterial compliance cannot be entirely excluded by plethysmography. The same criticism applies to the work of Anderson (1954), showing increased mean forearm circulatory pressure in chronically hypertensive men, and to the work of Richardson et al. (1964) and Ferrario et al. (1970), showing increased mean systemic circulatory pressure in dogs with experimental one-kidney renovascular hypertension. Finally, the demonstration by Ulrych et al. (1969) of an increased central and decreased peripheral blood volume in patients with renovascular hypertension could reflect decreased arterial, rather than decreased peripheral venous compliance, not to mention the possibility of impaired myocardial function in these hypertensive subjects.

The finding of decreased venous compliance in early, one-kidney and, possibly, early, two-kidney perinephritic hypertension by Overbeck (1972) is of great interest from the pathogenetic point of view of hypertension. On the low pressure side of the circulation, increased intraluminal pressure is unlikely to account for the observed changes, leaving one with the consideration of humoral, nervous and local stimuli. With regard to the recent findings of increased cardiac output in the developmental stages of experimental hypertension and in early, borderline human hypertension, decreased venous distensibility has been proposed as one possible mechanism responsible for increased venous return and cardiac output in turn. It was, therefore, of great interest to me to extend the study of venous distensibility in experimental renovascular hypertension to the mesenteric veins and, at the

same time, to re-study the femoral vein at a later, more chronic stage of the hypertensive process. The important role of the mesenteric veins in storing blood is well known. Fourteen percent of the total blood volume, at any one time, is contained in these veins (Texter *et al.*, 1968).

The findings of my study indicate that the *in vivo* and the *in vitro* mesenteric vein compliance is decreased in the early, *one*-kidney (H-2), but not in the early, *two*-kidney (H-1), stage of perinephritic hypertension in dogs. The decrease in venous compliance persists into the chronic stage (H-3) of *one*-kidney hypertension, as demonstrated by the *in vitro* femoral vein pressure-volume studies. The similarity of the results between the *in vivo* and the *in vitro* experiments, using an artificial solution, rules out nervous and humoral factors as responsible for the observed changes in hypertension. One is left to consider structural and myogenic mechanisms.

The generally convex shape of pressure-volume curves toward the volume axis in hypertensives and normotensives suggests that the mechanism responsible for decreased compliance may not involve contraction of the venous smooth muscle. Venoconstriction characteristically changes the pressure-volume curve to a sigmoid configuration (Alexander, 1963).

In the case of the mesenteric and the superior mesenteric vein, I have studied "delayed compliance," that is, following each injection, I have allowed ten seconds for equilibration of intravenous pressure. During the ten seconds, the smooth muscle that is stretched will tend

to relax. "Delayed compliance" measurements are not very sensitive for demonstrating venoconstriction. For this reason, I have also studied the superior mesenteric vein by rapid intravenous infusion of Krebs-Ringer solution. There were no differences in the results obtained by step-wise injections and the results obtained by rapid infusion. This finding would suggest that venoconstriction did not contribute significantly to the shift of the hypertensive pressure-volume curves (Alexander, 1963).

During withdrawal of injected fluid, the venous smooth muscle is considered to be relaxed. Withdrawal curves are always convex to the volume axis, even when the injection curve shows the characteristic sigmoid (vasoconstriction) configuration. During withdrawal, the shift of the mesenteric and superior mesenteric vein pressure-volume curve, in the direction of the pressure axis, persisted in early, one-kidney (H-2) hypertensive dogs. The shift of the hypertensive pressure-volume curves during withdrawal would suggest that structural changes were responsible for the shift (Alexander, 1963).

In a few hypertensive (H-2) and control (C-2) superior mesenteric veins, I attempted to shift the pressure-volume curve in the direction of the volume axis by abolishing venoconstriction with NaCN, a metabolic poison. There was, however, no shift of either the hypertensive or normotensive pressure-volume curves toward the volume axis, as one might have expected, again suggesting that venoconstriction did not contribute significantly to the shape of the pressure-volume curves.

Despite the evidence favoring factors other than venoconstriction as the basis for decreased compliance in one-kidney renovascular

hypertension, the contributing role of venoconstriction cannot be completely ruled out. Although the shift of the hypertensive (H-2) superior mesenteric vein pressure-volume curve in the direction of the pressure axis persisted during withdrawal, the calculated compliance in the pressure range of 5-15 mm Hg was no longer significantly different from that of controls. Furthermore, during injection, in the pressure range of 25-35 mm Hg, the calculated compliance of control (C-2) superior mesenteric veins was actually lower than that of hypertensives. The latter finding is difficult to explain, unless some degree of sigmoidicity of the hypertensive injection curve existed. The sigmoid character of the hypertensive injection curve is not readily apparent from simple inspection of Figure 12. Decreased compliance of the convex (vasodilated) pressure-volume curve, in comparison with the sigmoid curve, is, however, expected in the higher pressure ranges on the basis of Figure 1. What is apparent from the inspection of Figure 12 is that the hysteresis loop (the area enclosed by the injection and the withdrawal curve) is greater for the hypertensive veins. These findings suggest that venoconstriction may, to some degree, contribute to decreased venous compliance in hypertension.

The findings of increased water, Na and K content of veins from early, one-kidney (H-2) and chronic, one-kidney (H-3) hypertensive dogs suggest the presence of structural changes. I have a broad definition of structural change in mind, according to which any alteration in the thermoelastic properties and/or physical dimensions of the vessel wall is considered a structural change (Friedman et al., 1967). The increase

in Na and K, 25% and 56%, respectively, far exceeds the increase, 5%, in water content. The extra Na and K of hypertensive veins, therefore, appear to be, to a large extent, osmotically inactive, and are probably bound to ion binding polysaccharides that constitute a large portion of the cellular and paracellular matrix of the vessel wall.

The histological studies were apparently not sensitive enough to demonstrate the structural changes that are strongly suggested by the pressure-volume studies and the venous tissue water and electrolyte analysis in one-kidney hypertensive dogs (H-2, H-3). Notably, there was no evidence for venous wall hypertrophy in hypertension. In addition, following in vitro perfusion, the 5 cm segments of the superior mesenteric and of the femoral vein from hypertensive dogs weighed the same or slightly less than the 5 cm venous segments from normotensive controls (Tables 5 and 11). General hypertrophy of hypertensive veins is, therefore, unlikely on the basis of weight measurements and of histological studies. However, vascular wall hypertrophy is neither a necessary consequence nor an invariable concomitant of decreased vascular distensibility (Friedman et al., 1971). In my study, for instance, there was no correlation between the weight of the vein and its compliance (Tables 9 and 10). Perhaps the structural changes, suggested by the findings of my study, are the kind that are hard to see--edema, for instance, or an increase in paracellular matrix (Friedman et al., 1967). An excessive paracellular matrix, binding Na and K, may account for the decreased arterial and venous distensibility in one-kidney perinephritic hypertension.

The pressure-volume measurements of this study suggest that the structural changes in the veins of one-kidney hypertensive (H-2 and H-3) dogs involve the smooth muscle elements of the venous wall. The decrease in compliance of hypertensive veins is over the lower, physiologic pressure range, 5-15 mm Hg, where the resistance to stretch is due mainly to venous smooth muscle. In other words, the pressure-volume curves of one-kidney hypertensives (H-2 and H-3) are steeper in the low pressure range (0-15 mm Hg) than those of controls. The shift of the hypertensive pressure-volume curves in the higher pressure ranges could be a cumulative effect on total volume, due to decreased smooth muscle compliance. In this regard, calculated compliance in the higher pressure range, 25-35 mm Hg, is the same or actually higher (see above) in hypertensives than in normotensives, i.e., the pressure-volume curves of hypertensives and normotensives run parallel to one another in this range.

In the case of the mesenteric veins, which were studied in situ, as they were imbedded in surrounding tissue and covered by the mesentery, decreased interstitial space compliance, as suggested by Lucas et al. (1973), could have contributed to the shift of the hypertensive (H-2) pressure-volume curve in the direction of the pressure axis.

Finally, I would like to consider the possibility that the decreased compliance of hypertensive (H-2, H-3) veins was due to a greater initial, unstressed volume and, therefore, more apparent than real. This possibility cannot be entirely ruled out in the case of the mesenteric vein, where complete emptying of the veins could not be

ascertained at the time when the intravenous pressure was reduced to atmospheric level. It is possible that, at this point, the volume of blood in the hypertensive veins was greater than in normotensives. This criticism, however, cannot apply to the *in vitro* study of the larger superior mesenteric and femoral veins, where complete collapse of the veins, as intravenous pressure was reduced to atmospheric level, could be seen.

Since venous compliance of the mesenteric and superior mesenteric veins was found to be normal in early, *two*-kidney (H-1) hypertension, it is unlikely that these veins contribute to the initial rise in cardiac output described by Ferrario *et al.* (1970) in dogs prepared in exactly the same way as my H-1 group. Decreased compliance of the mesenteric veins, however, may be responsible, at least in part, for the rise in cardiac output, reported by Ferrario *et al.* (1970) to occur in early, one-kidney perinephritic hypertension (the stage of hypertension that was reproduced by my H-2 group of dogs). Decreased venous compliance, as suggested by my study of hypertensive (H-3) femoral veins *in vitro*, seems to persist into the more chronic stage of the hypertensive process, while cardiac output returns to normal. Mechanisms other than the return to normal of venous compliance must account for the return to normal of cardiac output.

CHAPTER VI

SUMMARY AND CONCLUSIONS

These studies show that, under pentobarbital anesthesia, the resistance to flow through the mesenteric (ileum) vascular bed is normal and that flow is slightly, but not significantly ($0.10 > P > 0.05$), increased in early, two-kidney (H-1) and early, one-kidney (H-2) perinephritic hypertensive dogs. In the combined group of hypertensive dogs (H-1 plus H-2), however, mesenteric (ileum) blood flow is increased ($P < 0.05$). The normal mesenteric (ileum) total and segmental vascular resistances, despite elevated intravascular pressures, especially in early, one-kidney (H-2) hypertensives, suggest decreased arterial and venous distensibility.

Mesenteric venous compliance, measured by *in vivo* and *in vitro* pressure-volume studies, is decreased in early, one-kidney (H-2), but not in early, two-kidney (H-1) perinephritic hypertension. Decreased venous compliance is also present in the more chronic stage of one-kidney (H-3) perinephritic hypertension, as shown by the *in vitro* femoral vein pressure-volume studies. Decreased venous compliance is accompanied by increased water, Na and K content of veins from one-kidney (H-2 and H-3) hypertensive dogs. Based on the analysis of the hypertensive and normotensive pressure-volume curves and the findings of increased water and electrolyte content of hypertensive

veins, it is suggested that structural changes rather than activation of vascular smooth muscle are mainly responsible for the decreased venous compliance in one-kidney (H-2 and H-3) perinephritic hypertension. The structural changes appear to be associated with the smooth muscle elements of the venous wall, since the change in compliance occurs over the lower, physiologic pressure range, 0-15 mm Hg, where the smooth muscle is stretched.

APPENDIX

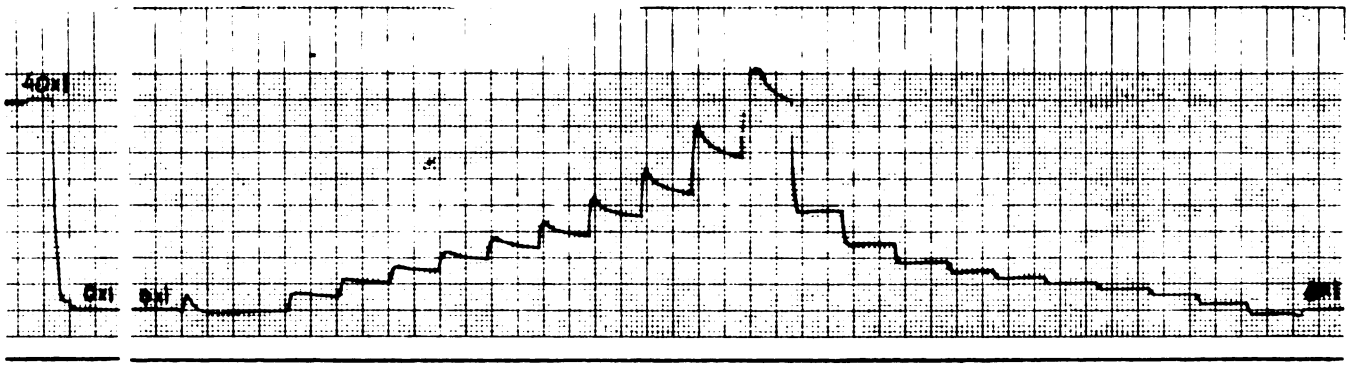
APPENDIX

Table 14. Group mean ± SEM of *in vitro* superior mesenteric vein pressure-volume relationships and compliance ($\Delta V/\Delta P$) in control (C-1) and in hypertensive (H-1) dogs, during infusion at constant rate of 9.88 ml/min

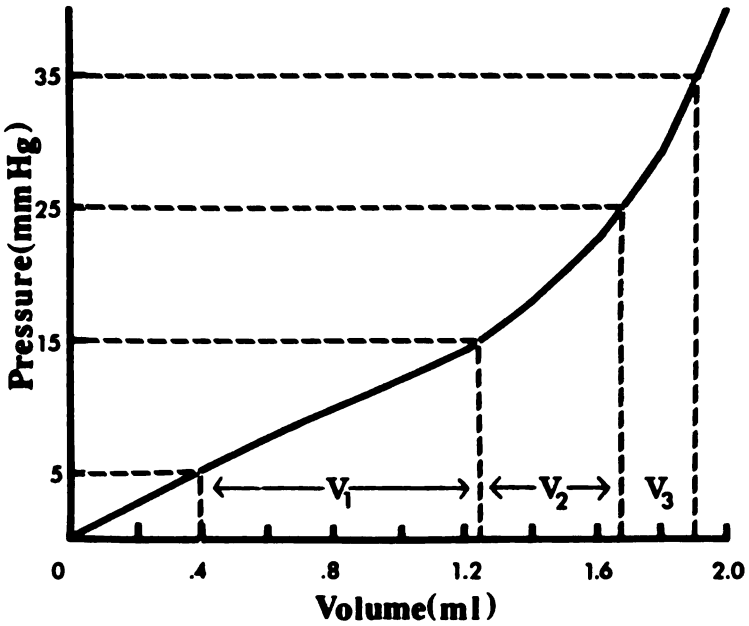
Intravenous pressures	C-1 N = 9	H-1 N = 9
	Volume (ml)	
5 mm Hg	1.003 ± 0.099	0.891 ± 0.133
15 mm Hg	1.860 ± 0.171	1.510 ± 0.131
25 mm Hg	2.081 ± 0.183	1.731 ± 0.129
35 mm Hg	2.208 ± 0.188	1.855 ± 0.131
Pressure range	**C-1 N = 9**	**H-1 N = 9**
	Compliance, ml/mm Hg	
5-15 mm Hg	0.0856 ± 0.0135	0.0619 ± 0.0040
15-25 mm Hg	0.0223 ± 0.0018	0.0221 ± 0.0124
25-35 mm Hg	0.0130 ± 0.0008	0.0124 ± 0.0008

Figure 18. Analysis of venous pressure-volume data.
A. Actual record of superior mesenteric vein pressure-volume relationships, injection and withdrawal phase, *in vitro*. Stepwise injection and withdrawal of 0.2 ml aliquots of Krebs-Ringer solution, horizontal axis, vs. intravenous pressure (mm Hg), vertical axis. Paper speed at 1 mm/sec.
B. Plot of pressure-volume measurements, injection phase. Points were taken at 10 seconds following each injection. The calculation of venous compliance in the pressure ranges of 5-15, 15-25 and 25-35 mm Hg is also shown.

A,



B,



Pressure range	Compliance, $\Delta V/\Delta P$
25-35 mm Hg	$\frac{V_3}{10}$
15-25 mm Hg	$\frac{V_2}{10}$
5-15 mm Hg	$\frac{V_1}{10}$

Figure 18

BIBLIOGRAPHY

BIBLIOGRAPHY

Abramson, D.I., and S. M. Fierst. Resting blood flow and peripheral vascular responses in hypertensive subjects. Am. Heart J. 23:84, 1942.

Alexander, R.S. In vivo observations on the distensibility of the femoral venous system. Proc. Soc. Exper. Biol. Med. 67:410, 1948.

Alexander, R.S., W.S. Edwards and J.L. Ankeney. The distensibility characteristics of the portal vascular bed. Circ. Res. 1:271, 1953.

Alexander, R.S. The influence of constrictor drugs on the distensibility of the splanchnic venous system analyzed on the basis of an aortic model. Circ. Res. 2:140, 1954.

Alexander, R.S. Venomotor tone in hemorrhage and shock. Circ. Res. 3:181, 1955.

Alexander, R.S. The peripheral venous system. Handbook of Physiology, Circulation Vol. 2, p. 1075, Hamilton, W.E. (ed.), 1963.

Amery, A., H. Bossaert and M. Verstraete. Muscle blood flow in normal and hypertensive subjects. Am. Heart J. 78:211, 1969.

Anderson, R.M. Intrinsic blood pressure. Circulation 9:641, 1954.

Bader, H. The anatomy and physiology of the vascular wall. Handbook of Physiology, Circulation Vol. 2, p. 865, Hamilton, W.E. (ed.), 1963.

Baldwin, D.S., E.A. Gombos and H. Chasis. Urinary concentrating mechanism in essential hypertension. Am. J. Med. 38:864, 1965.

Bello, C.T., R.W. Sevy and C. Harakal. Varying hemodynamic patterns in essential hypertension. Am. J. Med. Sci. 250:24, 1965.

Bello, C.T., R.W. Sevy, C. Harakal and P.N. Hilyer. Relationship between clinical severity of disease and hemodynamic patterns in essential hypertension. Am. J. Med. Sci. 253:194, 1967.

Bianchi, G., L.T. Tenconi and R. Lucca. Effect in conscious dog of constriction of the renal artery to a sole remaining kidney on hemodynamics, sodium balance, body fluid volumes, plasma renin concentration and pressor responsiveness to angiotensin. Clin. Sci. 38:741, 1970.

Bianchi, G., E. Baldoli, R. Lucca and P. Barbin. Pathogenesis of arterial hypertension after constriction of the renal artery leaving the opposite kidney intact both in the anaesthetized and in the conscious dog. Clin. Sci. 42:651, 1972.

Bounous, G., and H.B. Shumaeker. Experimental unilateral renal artery stenosis. Surg. Gyn. Obst. 114:415, 1962.

Brod, J. Essential hypertension. Hemodynamic observations with a bearing on its pathogenesis. Lancet 2:773, 1960.

Brod, J., V. Fencl, Z. Hejl, J. Jirka and M. Ulrych. General and regional hemodynamic pattern underlying essential hypertension. Clin. Sci. 23:339, 1962.

Brod, J., Z. Hejl, A. Hornych, J. Jirka and V. Slechta. Hemodynamic changes underlying renovascular hypertension. Third Internat. Congress of Nephrology, Washington, D.C., 1966.

Burch, G.E. The George E. Brown Memorial Lecture: Digital rheoplethysmography. Circulation 13:641, 1956.

Caliva, F.S., R.J. Napodano, R.M. Stafford, W. Loftus and R.H. Lyons. Digital hemodynamics in the normotensive and hypertensive states. I. Digital mean arterial and venous pressures, blood flow and vascular resistance. Circulation 28:415, 1963.

Caliva, F.S., R.J. Napodano and R.H. Lyons. Digital hemodynamics in the normotensive and hypertensive states. II. Venomotor tone. J. Clin. Invest. 28:421, 1963.

Cohn, J.N., T.E. Liptak and E.D. Freis. Comparison of the colloidal chromic phosphate and BSP clearance methods for estimating hepatic blood flow. Am. Heart J. 64:661, 1962.

Coleman, T.G., and A.C. Guyton. Hypertension caused by salt loading in the dog. III. Onset transients of cardiac output and other circulatory variables. Circ. Res. 25:153, 1969.

Coleman, T.G., H.J. Granger and A.C. Guyton. Whole body circulatory autoregulation and hypertension. Circ. Res. 28 and 29: Supplementum II:76, 1971.

Conway, J. A vascular abnormality in hypertension. A study of blood flow in the forearm. Circulation 27:520, 1963.

Corcoran, A.C., and I.H. Page. Renal blood flow in experimental renal hypertension. Am. J. Physiol. 135:361, 1942.

Culbertson, J.W., R.W. Wilkins, F.J. Ingelfinger and S.E. Bradley. The effect of the upright posture upon hepatic blood flow in normotensive and hypertensive subjects. J. Clin. Invest. 30:305, 1951.

Dickinson, D.J., and A.D. Thomson. A post-mortem study of the main cerebral arteries with special reference to their role in blood pressure regulation. Clin. Sci. 19:513, 1960.

Dustan, H.P., R.C. Tarazi, E.L. Bravo and R.A. Dart. Plasma and extracellular fluid volumes in hypertension. Circ. Res. 21: Supplementum I:73, 1973.

Eich, R.H., R.P. Cuddy, H. Smulyan and R.H. Lyons. Hemodynamics in labile hypertension. A follow-up study. Circulation 34:299, 1966.

Eichna, L.W., and J. Bordley. Capillary blood pressure in man. Direct measurements in the digits of normal and hypertensive subjects during vasoconstriction and vasodilatation variously induced. J. Clin. Invest. 21:711, 1942.

Ellis, L.B., and S. Weiss. The measurement of capillary pressure under natural conditions and after arteriolar dilatation; in normal subjects and in patients with arterial hypertension and with arteriosclerosis. J. Clin. Invest. 8:47, 1929.

Feigl, E.O., L.H. Peterson and A.W. Jones. Mechanical and chemical properties of arteries in experimental hypertension. J. Clin. Invest. 42:1640, 1963.

Ferrario, C.M., I.H. Page and J.W. McCubbin. Increased cardiac output as a contributory factor in experimental renal hypertension in dogs. Circ. Res. 27:799, 1970.

Ferrario, C.M., and J.W. McCubbin. Renal blood flow and perfusion pressure before and after development of renal hypertension. Am. J. Physiol. 224:102, 1973.

Ferrario, C.M. Contribution of cardiac output and peripheral resistance to experimental renal hypertension. Am. J. Physiol. 226:711, 1974.

Flohr, H., H.W. Dahners, H. Conradi, D. Redel, W. Breull, D. Kikis and K. Stoepel. Cerebral vascular resistance in experimental renal and DCA hypertension. Europ. Neurol. 6:39, 1971/72.

Floyer, M.A., and P.C. Richardson. Mechanism of arterial hypertension. Role of capacity and resistance vessels. Lancet 1:253, 1961.

Folkow, B., M. Hallback, Y. Lundgren and L. Weiss. Background of increased flow resistance and vascular reactivity in spontaneously hypertensive rats. Acta Physiol. Scand. 80:93, 1970.

Folkow, B., M. Hallback, Y. Lundgren and L. Weiss. Renal vascular resistance in spontaneously hypertensive rats. Acta Physiol. Scand. 83:96, 1971.

Folkow, B., M. Hallback, Y. Lundgren, R. Silvertsson and L. Weiss. Importance of adaptive changes in vascular design for establishment of primary hypertension, studied in man and in spontaneously hypertensive rats. Circ. Res. 22 and 23: Supplementum II:2, 1973.

Fray, C.S., R.N. Steller, J.M. Wilson and A.C. Barger. Arterial pressure and renin activity during pentobarbital anesthesia. (abstr.) Fed. Proc. 33(3):340, 1974.

Friedman, S.M., and C.L. Friedman. The ionic matrix of vasoconstriction. Circ. Res. 20 and 21: Supplementum II:147, 1967.

Friedman, S.M., M. Nakashima and M.A. Mar. Morphological assessment of vasoconstriction and vascular hypertrophy in sustained hypertension in the rat. Microvasc. Res. 3:416, 1971.

Frohlich, E.D., M. Ulrych, R.C. Tarazi, H.P. Dustan and I.H. Page. A hemodynamic comparison of essential and renovascular hypertension. Circulation 35:289, 1967.

Frohlich, E.D., R.C. Tarazi and H.P. Dustan. Re-examination of the hemodynamics of hypertension. Am. J. Med. Sci. 257:9, 1969.

Goldblatt, H., J. Lynch, R.F. Hanzal and W.W. Summerville. Studies on experimental hypertension. I. The production of persistent elevation of systolic blood-pressure by means of renal ischemia. J. Exper. Med. 59:347, 1934.

Goldring, W., H. Chasis, H.A. Ranges and H.W. Smith. Effective renal blood flow in subjects with essential hypertension. J. Clin. Invest. 20:637, 1941.

Gomez, D.M. Evaluation of renal resistances, with special reference to changes in essential hypertension. J. Clin. Invest. 30:1143, 1951.

Greene, M.A., R. Friedlander, A.J. Boltax, C.G. Hadjigeorge and G.A. Lustig. Distensibility of arteries in human hypertension. Proc. Soc. Exper. Biol. Med. 121:580, 1966.

Gresson, C.R., D.L. Bird and F.O. Simpson. Plasma volume and extracellular fluid volume and exchangeable sodium concentrations in the New Zealand strain of genetically hypertensive rat. Clin. Sci. 44:349, 1973.

Grollman, A., and A.P. Shapiro. The volume of the extracellular fluid in experimental and human hypertension. J. Clin. Invest. 32:312, 1953.

Hollenberg, N.K., M. Epstein, R.I. Basch and J.P. Merrill. No man's land of the renal vasculature. An arteriographic and hemodynamic assessment of the interlobar and arcuate arteries in essential and accelerated hypertension. Am. J. Med. 47:845, 1969.

Howard, J.E., M. Berthrong, D.M. Gould and E.R. Yendt. Hypertension resulting from unilateral renal vascular disease and its relief by nephrectomy. Bull. Johns Hopk. Hosp. 94:51, 1954.

Iriuchijima, J. Cardiac output and total peripheral resistance in spontaneously hypertensive rats. Jap. Heart J. 14:267, 1973.

Jones, W.R., and D.A. Dowd. Development of elevated blood pressure in young genetically hypertensive rats. Life Sciences 9:247, 1970.

Julius, S., and M.A. Schork. Borderline hypertension--a critical review. J. Chron. Dis. 23:723, 1971.

Kettel, L.J., H.W. Overbeck, R.M. Daugherty, J.P. Lillehei, R.F. Coburn and F.J. Haddy. Responses of the human upper extremity vascular bed to exercise, cold, levarterenol, angiotensin, hypertension, heart failure and respiratory tract infection with fever. J. Clin. Invest. 43:1561, 1964.

Kety, S.S., J.H. Hafkenschiel, W.A. Jeffers, I.H. Leopold and H.A. Shenkin. The bloodflow, vascular resistance and oxygen consumption of the brain in essential hypertension. J. Clin. Invest. 27:511, 1948.

Kioschos, J.M., W.M. Kirkendall, M.R. Valenca and A.E. Fitz. Unilateral renal hemodynamics and characteristics of dye-dilution curves in patients with essential hypertension and renal disease. Circulation 35:229, 1967.

Ladefoged, J., and F. Pedersen. Renal blood flow in patients with hypertension. Clin. Sci. 37:253, 1969.

Laverty, R., and F.H. Smirk. Observations on the pathogenesis of spontaneous inherited hypertension and constricted renal artery hypertension in rats. Circ. Res. 9:455, 1961.

Ledingham, J.M., and R.D. Cohen. Changes in the extracellular fluid volume and cardiac output during the development of experimental renal hypertension. Canad. Med. Ass. J. 90:292, 1964.

Ledingham, J.M., and D. Pelling. Cardiac output and peripheral resistance in experimental renal hypertension. Circ. Res. 21: Supplementum II:187, 1967.

Logan, A.G., M.T. Velasquez and J.N. Cohn. Renal cortical blood flow, cortical function and cortical blood volume in hypertensive subjects. Circulation 47:1306, 1973.

Lucas, J., and M.A. Floyer. Renal control of changes in the compliance of the interstitial space: a factor in the etiology of renoprival hypertension. Clin. Sci. 44:397, 1973.

Mallett, B.L., N. Veall. Investigation of cerebral blood-flow in hypertension, using radioactive-xenon inhalation and extracranial recording. Lancet 1:1081, 1963.

McGregor, D.D., and F.H. Smirk. Vascular responses in mesenteric arteries from genetic and renal hypertensive rats. Am. J. Physiol. 214:1429, 1968.

Nikodijevic, B., V. Dolgova-Korubin and I.S. Tadzer. Blood volume and spontaneously hypertensive rats. Acta Iugoslavica 26:251, 1972.

Okamoto, K., and K. Aoki. Development of a strain of spontaneously hypertensive rats. Jap. Circ. J. 27:282, 1963.

Oppenheimer, E.T., and M. Prinzmetal. Role of the arteries in the peripheral resistance of hypertension and related states. Arch. Int. Med. 60:772, 1937.

Overbeck, H.W., R.M. Daugherty and F.J. Haddy. Continuous infusion indicator dilution measurement of limb blood flow and vascular response to magnesium sulfate in normotensive and hypertensive men. J. Clin. Invest. 48:1944, 1969.

Overbeck, H.W., B.T. Swindall, D.F. Cowan and M.C. Fleck. Experimental renal hypertension in dogs: forelimb hemodynamics. Circ. Res. 29:51, 1971.

Overbeck, H.W. Hemodynamics of early experimental renal hypertension in dogs. Normal limb blood flow, elevated limb vascular resistance and decreased venous compliance. Circ. Res. 31:653, 1972.

Page, I.H. Production of persistent arterial hypertension by cellophane perinephritis. J.A.M.A. 113:2046, 1939.

Pedersen, F., and J. Ladefoged. Renal vascular volume, blood flow and resistance in hypertension and renal arterial stenosis. Scand. J. Lab. Clin. Invest. 23:291, 1969.

Pfeffer, M.A., and E.D. Frohlich. Hemodynamic and myocardial function in young and old normotensive and spontaneously hypertensive rats. Circ. Res. 22 and 23: Supplementum II:28, 1973.

Pickering, G.W. High Blood Pressure, Third edition. Grune and Stratton, New York, 1972.

Richardson, T.Q., J.D. Fermoso and A.C. Guyton. Increase in mean circulatory pressure in Goldblatt hypertension. Am. J. Physiol. 207:751, 1964.

Rowe, G.C., C.A. Castillo, G.M. Maxwell and C.W. Crumpton. A hemodynamic study of hypertension including observations on coronary blood flow. Ann. Int. Med. 54:405, 1961.

Scott, J.B., and J.M. Dabney. Relation of gut motility to blood flow in the ileum of the dog. Circ. Res. 14 and 15: Supplementum T: 234, 1964.

Smirk, G.H., and W.H. Hall. Inherited hypertension in rats. Nature (London) 182:727, 1958.

Spencer, M.P., and A.B. Denison. Pulsatile blood flow in the vascular system. Handbook of Physiology, Circulation Vol. 2, p. 839, Hamilton, W.E. (ed.), 1963.

Stamey, T.A. Functional characteristics of renovascular hypertension with emphasis on the relationship of renal blood flow to hypertension. Circ. Res. 11:209, 1962.

Stead, E.A., and P. Kunkel. Nature of peripheral resistance in arterial hypertension. J. Clin. Invest. 19:25, 1940.

Texter, E.C., C.C. Chou, H.C. Laureta and G.R. Vantrappen. Physiology of the gastrointestinal tract. The C.V. Mosby Company, Saint Louis, 1968.

Tibblin, G., S.E. Bergentz, J. Bjure and L. Wilhelmsen. Hematocrit, plasma protein, plasma volume and viscosity in early hypertensive disease. Am. Heart J. 72:165, 1966.

Traeger, J., J. Perrin and N. Pozet. Etude critique des critères fonctionnels d'ischémie mesurés par exploration fonctionnelle séparée des deux reines au cours des hypertensions d'origine rénale, Sec. Internal. Cong. of Nephrology, Prague, 1963.

Ulrych, M., J. Hofman and Z. Hejl. Cardiac and renal hyperresponsiveness to acute plasma volume expansion in hypertension. Am. Heart J. 68:193, 1964.

Ulrych, M., E.D. Frohlich, R.C. Tarazi, H.P. Dustan and I.H. Page. Cardiac output and distribution of blood volume in central and peripheral circulations in hypertensive and normotensive man. Brit. Heart J. 31:570, 1969.

Vanhoutte, P.M., and J.T. Shephered. Effect of temperature on reactivity of isolated cutaneous veins of the dog. Am. J. Phys. 218:187, 1970.

Varnauskas, E. Studies in hypertensive cardiovascular disease with special reference to cardiac function. Scandinav. J. Clin. and Lab. Invest. 7: Supplementum 17, 1965.

Walsh, J.A., C. Hyman and R.F. Maronde. Venous distensibility in essential hypertension. Cardiovasc. Res. 3:338, 1969.

West, J.W., H. Mercker, H. Wendel and E.L. Foltz. Effects of renal hypertension on coronary blood flow, cardiac oxygen consumption and related circulatory dynamics of the dog. Circ. Res. 7:476, 1959.

Wiederhielm, C.A. Distensibility characteristics of small blood vessels. Fed. Proc. 24:1075, 1965.

Wilkins, R.W., J.W. Culbertson and A.A. Rymut. The hepatic blood flow in resting hypertensive patients before and after splanchnicectomy. J. Clin. Invest. 31:529, 1952.

Wood, J.E. Peripheral venous and arteriolar response to infusion of angiotensin in normal and hypertensive subjects. Circ. Res. 9:768, 1961.