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LOCAL REGULATION OF BLOOD FLOW

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CHAPTER I

INTRODUCTION

Experimental data over the last five decades demonstrate that blood flow to an organ or vascular bed is controlled by both local and remote mechanisms (22). Perhaps the most dramatic way to provoke a remote mechanism that controls flow is to change intraluminal pressure at the bifurcation of the carotid arteries, thus attenuating or enhancing the activity of the sympathico-adrenal system. Local regulation is best demonstrated when arterial pressure, venous pressure or metabolic rate is changed in an isolated vascular bed or organ. However, local regulation can be demonstrated in a virtually intact preparation if proper precautions are taken to avoid eliciting remote mechanisms. Increased metabolic rate, produced by activation of skeletal muscle, produces an increase in blood flow at a constant perfusion pressure. This response has been designated active hyperemia. When perfusion pressure to most vascular beds is changed over the approximate range 50 to 200 mm Hg there is a less than proportionate change in blood flow through most of the area. This ability to maintain a relatively constant blood flow in the face of varying perfusion pressure is called autoregulation of blood flow. Temporary occlusion of arterial inflow to a vascular

bed is usually associated with a transient increase in blood flow above the basal value upon release of the occlusion. This response has been termed reactive hyperemia. Also, slight elevation of venous pressure, in some vascular beds, produces a greater than proportionate fall in blood flow. This effect has been designated the venous-arteriolar reflex (23) or perhaps more correctly, the venous-arteriolar response (35).

The efficiency of the local responses in controlling blood flow appears to differ from one vascular bed to another. Autoregulation is highly efficient in the kidney where a marked change in perfusion pressure may produce little or no change in renal blood flow (57). In the lung (39) and spleen (15), the response is virtually absent. The venous-arteriolar response is readily demonstrated in the intestine, but has not been shown in the lung or spleen. Its presence (29) or absence (31) in the renal vascular bed may depend upon the technique used to demonstrate the response. Reactive hyperemia occurs regularly in the limb (44) and coronary (4) vascular beds, whereas the response of the renal vascular bed to ischemia apparently is dependent upon the length of the occlusion (33); short occlusion (1 - 5 min) consistently produces reactive hyperemia, while longer occlusions (6 - 20 min) are often followed by periods of reactive ischemia. Active hyperemia (54) is readily shown in the gastronemiusplantaris muscle of the dog. In this bed an increase in metabolic rate is consistently associated with an increase in blood flow. It is also well documented that an increase in cardiac metabolism, as seen in mild tachycardia, hyperthyroidism and exercise, increases coronary blood flow. However, since any effect on cardiac metabolism invariably alters many other vascular parameters,

i.e., aortic pressure, left atrial pressure, intramyocardial pressure and sympathico-adrenal activity, it is impossible to assess the direct effect of change in metabolism upon the coronary vasculature.

Some of the differences in efficiency of local regulation might be related to differences in anatomical structure. The apparent absence of any local or remote flow controlling mechanisms in the lung may be directly related to the fact that lung arterioles possess very little smooth muscle. Many other of the inter-organ differences are harder to explain. Certainly, it is difficult to explain why autoregulation is so exact in the kidney, relative to other organs in the systemic circuit.

The value of these local regulatory mechanisms are their tendency toward: 1) maintenance of a relatively constant ratio of metabolic rate to blood flow rate, 2) maintenance of a constant capillary hydrostatic pressure, and 3) rapid repayment of an oxygen debt incurred during periods of ischemia. Thus, like the remote controlling mechanism, the local mechanisms act to maintain cardiovascular homeostasis.

At the present time most of the controversy in the field of local regulation revolves around the mechanism or mechanisms responsible for the local regulatory responses. Numerous theories have been advanced to explain the mechanism of local regulation. Currently, however, only four of these are considered to be plausible explanations.

In brief, the four theories of local regulation state that the caliber changes result from: 1) a change in tissue pressure, 2) change in oxygen tension, 3) change in vasoactive metabolite concentration, or 4) a myogenic response to change in transmural pressure. The latter three theories imply an active change in the contractile state of the

vascular smooth muscle, while the first theory implies a passive change in vascular size subsequent to a change in extravascular pressure.

The main support of the tissue pressure hypothesis is gained from studies on the kidney. Hinshaw et al. (32, 33) and Scher (48) found in association with autoregulation of renal blood flow, a large change in tissue pressure, as measured through a hypodermic needle plunged into the renal parenchyma (32, 34) and a large change in deep renal venous pressure measured through a small bore polyethylene catheter passed retrogradely up the renal vein (34). Also, Hinshaw et al. (33) often observed a substantial drop in deep renal venous pressure upon occlusion of the renal artery. However, Haddy et al. (26) found that renal autoregulation was not associated with a significant change in the rate of lymph flow from the kidney. Also, autoregulation is said to be abolished upon inactivation of vascular smooth muscle (25, 40, 42).

The oxygen theory states that when tissue oxygen tension falls, thus reducing the amount of oxygen available to the smooth muscle, the muscle becomes weakened and dilation ensues. Guyton is probably the foremost proponent of this concept. Over the past 8 to 10 years a series (8, 9, 46) of investigations from Guyton's laboratory, have demonstrated that, in intact and isolated blood vessels, a reduction in oxygen tension in the perfusing fluid always results in vascular dilation. The dilation is especially evident when the oxygen tension was reduced below 40 mm Hg. On the other hand, Molnar et al. (41) found that varying oxygen saturation over the normal range (19 to 14 volumes percent) had little effect upon resistance to blood flow through the dog forelimb.

The metabolic theory, strongly supported by Berne (5), Stainsby (54) and Repela (45), assumes that metabolizing tissue produces by-products that are vasodilator. A priori, the concentration of these products would increase with a decrease in blood flow or an increase in metabolic rate and their concentration would decrease with an increase in blood flow or a decrease in metabolic rate. The theory implies increase in the metabolite concentration would produce vascular dilation, and a decrease in the concentration would produce constriction.

The metabolite or metabolites supposedly responsible for local regulation have not yet been identified. However, a partial list of those under consideration are hydrogen, potassium, magnesium acetate, citrate, pyruvate, other Krebs intermediates, acetylcholine, histamine and the adenyl compounds (adenosine, AMP, ADP and ATP). Each of the agents has been shown to produce dilation in one or more vascular beds (28) and many of them are involved in cell metabolism. Further, the venous concentrations of the hydrogen and potassium (38) ions rise following an increase in metabolic rate and Berne (5) has identified the breakdown products of adenosine in coronary sinus blood during cardiac hypoxia. Gordon (19) found AMP in renal venous blood following release of renal artery occlusion and Gerlach and Dreisbach (18) observed the formation of nucleosides, purines and primidines from free nucleotides in kidney and other tissues under ischemic or anoxia conditions.

The myogenic theory was originally proposed by Bayliss (3) in 1902. He stated that an increase in intraluminal pressure in some manner stimulated vascular smooth muscle to contract. Although the mechanism responsible for this response was not clearly stated, the

implication was that smooth muscle responds to stretch, in this case produced by the increased pressure, by contraction. Conversely, with decreased stretch, the muscle would relax.

Recent supportive evidence for this hypothesis has been provided by Folkow (10, 12), Waugh (56), Johnson (36) and Bohr (7, 52, 53). Folkow (11) has very recently indicated how such an implied positive feedback system can operate without producing exceedingly high levels of resistance. The best evidence to date for the existence of this mechanism is: 1) a few types of arteries, isolated in a bath, respond to stretch with increased tension (52), 2) small vessels in the bat wing (57) and rat meso-appendix (2), studied microscopically, may remain the same size or decrease in size upon sudden elevation of intraluminal pressure, which according to the metabolite and oxygen theories should dilate, and 3) elevation of venous pressure often increases small vessel (23) or total resistance (35) to blood flow. The latter maneuver should decrease flow, thus increase metabolite concentration and reduce oxygen tension, both of which, according to the oxygen and metabolite theories, should relax vessels. Thus, according to the myogenic theory local regulation results from a change in transmural pressure rather than from a change in oxygen tension or metabolite concentration. It is important to keep in mind that this hypothesis states a change in transmural pressure elicits an active response from the smooth muscle which is directly opposite from the expected passive effect. For example, when transmural pressure is increased the elastic vessels should passively enlarge; however, according to Bayliss' myogenic response the vessels will tend to resist the passive expansion and,

depending upon the efficiency of the response in a particular vessel, may even decrease in size. Conversely, if transmural pressure falls, the expected passive decrease in vessel size would be resisted by active dilation.

The purpose of the present investigation was four fold: 1) to characterize more precisely the local regulatory responses in several systemic vascular beds, 2) to evaluate the four major theories which have been suggested to explain the local control of blood flow by utilizing either entirely new or greatly modified techniques, 3) to characterize the local reactions of several naturally occurring vaso-active agents in two systemic vascular beds in which their effects are substantially unknown, and 4) to investigate the inter-play between local and remote regulatory mechanisms in a stressfull situation designed to envoke both mechanisms. The stress chosen for this part of the study was hemorrhagic shock.

CHAPTER II

METHODS

In anesthetized dogs, local regulation of blood flow was studied in four systemic vascular beds and the interplay between local and remote controlling mechanisms during hemorrhage was studied in three vascular beds. Three basic types of preparations were employed to elucidate the mechanisms that act locally to control blood flow.

In the first, blood flow to the organ under study was controlled by interposition of a blood pump into the arterial supply and the measured or independent variable was pressure. The advantages of this preparation are: 1) accuracy (it is technically much easier to measure a change in pressure than a change in flow), 2) changes in blood flow rate may be made quickly and reproducibly, and 3) one variable can be studied at a time (for example, the effect of metabolic rate may be studied alone, uncomplicated by changes in blood flow).

In the second, the organ received natural arterial inflow at constant perfusion pressure and the measured variable was venous outflow. The advantages of this method are: 1) the system operates in a situation more like that occurring under natural conditions, and 2) it obviates the possible objection that a blood pump may impart artifactual vasoactive properties to blood causing hemolysis of erythrocytes.

Use of both methods permits a comparison of the local responses when flow is the independent variable and when pressure is the independent variable. It was felt that such a comparison might be useful in determining the mechanism of local regulation. For example, if the cause of local regulation is the change in flow rather than the change in pressure, it is possible that making flow the dependent variable might act as a positive feedback mechanism, and thus enhance the responses.

In the third type of preparation, venous efflux from an organ undergoing local regulation was used to perfuse the forelimb of the same dog. Thus, the forelimb was used as a biological assay organ to determine if vasoactivity of the venous blood coming from a regulating organ was altered.

The studies to be reported were performed on mongrel dogs of both sexes, weighing between 10 and 18 kg that were anesthetized with sodium pentobarbital and anti-coagulated with heparin sodium. All animals were placed on positive pressure ventilation soon after anesthetization. Pressures were recorded with resistance wire pressure transducers (model P23 Gb, Statham Laboratories, Los Angeles, California) and recorded on a direct writing oscillograph (model 60-1300, Sanborn Company, Cambridge, Massachusetts), which had a switch that allowed electronic meaning. Blood flow was controlled to the various organs studied by interposition of finger-type pumps (models T-65, T-6SH and TM-10, Sigmamotor, Inc., Middleport, New York). All the pumps had micrometer type variable speed changes for precise adjustment of flow rates and each pump was precalibrated over its entire flow range. Because of

the spring tension and type of rubber tubing utilized in the pump, flow rate was not measurably affected by changes in inflow or outflow pressures over the range 0 - 300 mm Hg. Chemicals were administered with a constant infusion pump (model 600-900, Harvard Apparatus Company, Dover, Massachusetts). Blood flow was measured in several experiments with a rotometer (Shipley-Wilson). Oxygen tension was measured with a macro-oxygen probe connected to a physiological gas analyzer (model 160, Beckman Instruments, Inc., Fullerton, California). The analyzer was electronically adapted to direct writing oscillograph.

Resistance to blood flow was calculated by dividing the pressure gradient across a vascular bed or section of a vascular bed by the blood flow through the bed and is expressed as mm Hg/ml/min. Although the procedures used to investigate the various vascular beds were similar, each was somewhat unique. The methods, therefore, are separately described for each vascular bed.

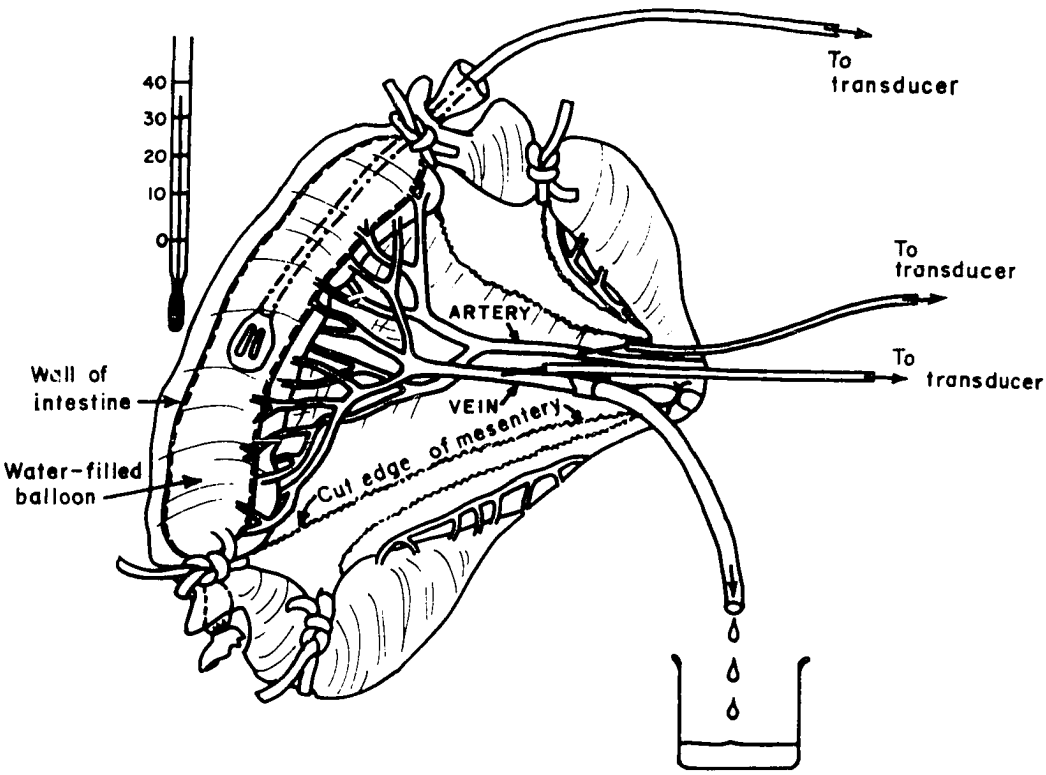
Intestine

Two slightly differing techniques were employed in these studies. A short section of the ileum was studied *in situ* by either controlling inflow and measuring perfusion pressure or measuring venous outflow at constant perfusion pressure. In addition, gut lumen pressure and gut motility were monitored continuously in both types of experiments. A total of 56 dogs were used in these studies. A section of the ileum (15 - 20 cm in length) was exteriorized through a left flank incision. The main artery and vein to this section were dissected free, collaterals tied, and the mesentery cut on both ends of the section from the gut to the level of cannulation such that all flow through the section was

carried by these vessels (Figure 1). No attempt was made to preserve extrinsic nerves to the ileal section. If venous outflow was to be studied, a polyethylene catheter (PE320) was inserted into the vein. Flow from the isolated section was allowed to drain into a reservoir. Blood flow measurements were made by collecting one minute samples into a small beaker held under the tip of the catheter. Since flow from this section was necessarily small, weighing the blood was found to be the most accurate method for measuring flow. Thus, flow is reported as grams of blood/minute/gram tissue. Venous blood was returned from the reservoir to the femoral vein of the dog by a pump. A 27 gauge needle was inserted into the artery such that its tip pointed in a downstream direction. This was used for monitoring pressure or for the infusion of various solutions. Venous pressure was measured through a 24 gauge needle inserted proximal to the polyethylene catheter. Systemic arterial pressure was measured through a catheter inserted into a femoral artery. Occlusive ligatures, of heavy cord, were placed at each end of the ileal section under study. A thin walled rubber balloon, with a tube attached for measuring pressure, was inserted into the lumen of the section. The balloon filled the entire section of lumen and contained sufficient water to give an initial pressure of 10 - 15 mm Hg. All pressures were recorded with a resistance wire pressure transducer and direct writing recorder. Lumen pressure was recorded with a separate transducer.

In experiments in which blood flow was controlled, one end of a length of polyethylene tubing (PE320) was advanced up the right femoral artery to the abdominal aorta and the other end attached through a 15

Figure 1. Schematic drawing of the intestinal natural flow preparations showing placement of ligatures, catheters for measurement of pressures and flow, and balloon for recording gut pressure and activity. In the pump perfused preparation, the vein was left intact and the artery was cannulated.


40
30
20
10
0
To transducer
To transducer
To transducer
ARTERY
VEIN
Wall of intestine
Water-filled balloon
Cut edge of mesentery

gauge right angle stainless steel cannula to the distal segment of the gut artery. Interposed in the polyethylene tubing were two short segments of latex rubber tubing. The first segment was placed in a pre-calibrated pump. The second segment just preceded the stainless steel cannula and was needled for the measurement of perfusion pressure. The pressure drop across this cannula was 3, 5, 5, 8, 10 and 11 mm Hg for flow rates of 6.5, 13.0, 19.0, 25.5, 32.0, and 39.5 ml/min.

The vein from the section was left intact except that a needle was inserted into the vein for pressure measurement. The rest of the procedure was identical to that used in the natural flow preparation.

After all operative procedures were completed, the section of gut was moistened with saline, and carefully covered with a sheet of parafilm. A thermometer was fixed against the gut and a heat lamp was used to maintain a temperature of 36^{o} - 38^{o} C.

Pressure flow relationships were obtained in the dog ileum by increasing blood flow rate and monitoring steady state perfusion pressure at each increment in flow.

The effect of ischemia on subsequent flow and perfusion pressure was studied in the natural flow and pump-perfused preparations, respectively. Ischemia was produced in the natural flow preparation by sudden occlusion of the gut artery with a small hemostat. The jaws of the clamp were covered with rubber tubing to insure a minimum of trauma to the artery. Blood flow measurements were obtained immediately before and after the period of ischemia. In the constant flow studies, blood flow to the section of ileum was suddenly interrupted and re-established by shutting off and turning on the blood pump. The periods of ischemia

ranged from 30 seconds to two minutes in both preparations.

The effect of elevation of venous pressure upon ileal blood flow and resistance was also studied in both the natural and pump perfused preparations. In the natural flow preparation venous pressure elevation was produced by raising the tip of the venous outflow catheter to a level that produced the desired venous pressure. In the pump-perfused studies venous pressure was elevated to desired levels by partial constriction of the gut vein distal to the site of venous pressure measurement with flow held constant.

In the natural flow preparation, dose-response effects were determined for several naturally occurring vasoactive agents which were infused directly into the gut artery. Adenosine, AMP (adenylic acid muscle), ADP (adenosine diphosphate) and ATP (adenosine triphosphate) were dissolved in saline and infused separately into the gut artery at rates ranging from 0.51 to 10.3 μg/minute. Acetylcholine chloride and serotonin creatinine sulfate, also in saline, were infused intra-arterially at rates ranging from 1 to 20.6 μg of the salt/minute. Isotonic solutions of $MgCl_2$ (302 mOsm/1), $CaCl_2$ (303 mOsm/1), KCl (310 mOsm/1), and KCl plus atropine sulfate (100 μg/cc) were also infused individually into the gut artery at rates ranging from .05 to 2.06 ml/min. The highest infusion rate for KCl was 1.03 ml/min. Saline infused at the same volume infusion rate was used as a control for all agents. Each infusion rate was maintained for two minutes. Pressures and flow were measured during the last minute of each period. The adenosine, AMP, ADP, ATP, and acetylcholine solutions were prepared approximately one hour before use.

The effects of hemorrhage upon the intestinal vasculature was also studied in both the naturally perfused and pump-perfused preparations. In the natural flow preparation, 25% of the animal's circulating blood volume (calculated as 8% of body weight) was quickly removed via a brachial artery. Pressures and ileal blood flow were measured immediately upon cessation of bleeding and at one minute intervals for the subsequent five minutes, and at five minute intervals for the next fifteen minutes. At the end of the twenty minute period of hypovolemia, the blood was returned rapidly to the animal. Pressures and flow were measured at one minute intervals for the first four minutes and again at the tenth minute of the post-hypovolemic period.

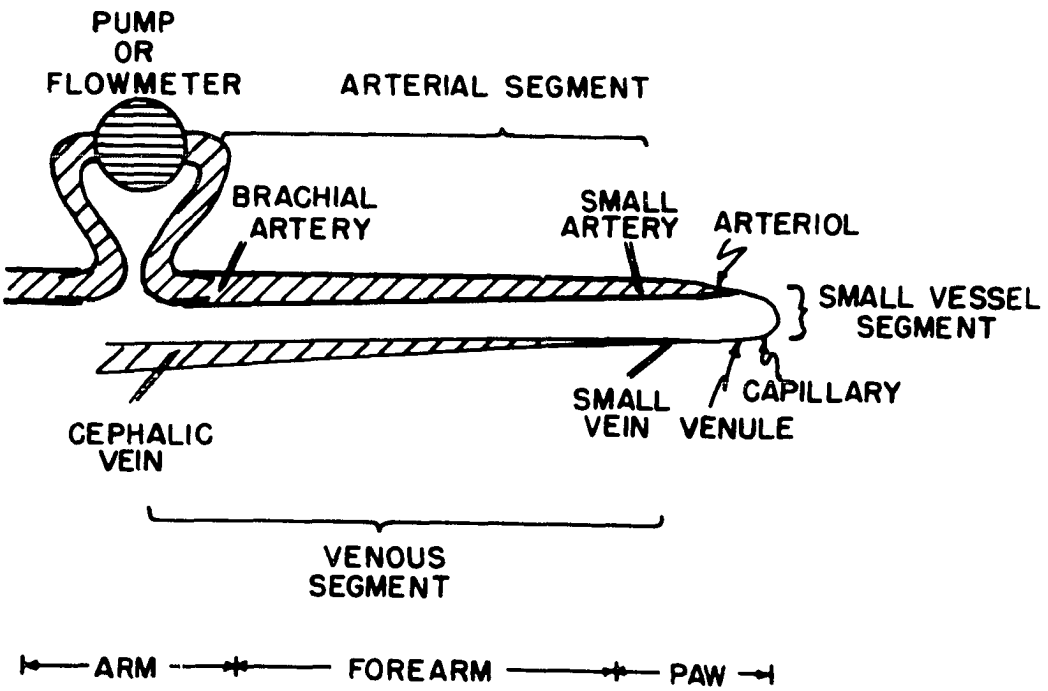
The above procedure was repeated in another series of animals. In this group ileal blood flow was held constant with a pump (model TM-10) at a rate which in the control period produced a perfusion pressure approximately equal to the animal's aortic pressure. In addition, a second blood pump (model T6SH) was used to maintain a constant blood flow through the right kidney (see Kidney methods).

Forelimb

Most studies were performed on the relatively intact forelimb perfused with a pump (model T6SH). Small artery, small vein and tissue pressure were measured in some of these experiments (Figure 2). In other studies venous outflow was measured with a rotometer interposed between the brachial and cephalic veins and an external jugular vein.

After anesthetization, the animals were positioned on their right side. The right brachial artery, brachial vein, cephalic vein, and brachial plexus were exposed. All other soft tissues were tied

Figure 2. Schematic drawing of the pump perfused forelimb preparation showing sites of pressure measurement and the four vascular segments. In the natural flow studies the pump was removed from the arterial side and a flowmeter was installed distal to the site of cephalic vein pressure measurement.


PUMP
OR
FLOWMETER
ARTERIAL SEGMENT
BRACHIAL
ARTERY
SMALL
ARTERY
ARTERIOL
SMALL VESSEL
SEGMENT
CEPHALIC
VEIN
SMALL
VEIN
CAPILLARY
VENULE
VENOUS
SEGMENT
ARM
FOREARM
PAW

with three heavy ligatures at a level midway between the elbow and shoulder. This eliminated all collateral flow to the forelimb except that through bone. The outflow from the cephalic and brachial veins with the brachial artery occluded and aortic pressure at 112 mm Hg averaged only 1.4 ml/min in ten such preparations. The right femoral and brachial arteries were ligated and a pre-calibrated blood pump (model T6SH, with 0.118" i.d., 0.375" o.d. polyethylene tubing leading to the vessels) was interposed between the proximal segment of the femoral artery and distal segment of the brachial artery. A 22 gauge needle was inserted through the skin of the upper forearm into the cephalic vein with the tip pointed centrally. The metacarpal vein was isolated, ligated and incised peripheral to the ligature. A glass tube (0.5 mm o.d. with a polished tip) was manipulated distally past values until the tip lay in the web between the second and third toe. In this position from which blood could be withdrawn and saline infused without noticeable resistance. The tube was then tied into place. A second glass tube was inserted into a volnar metacarpal artery by the same technique, except the cannula was only advanced about one centimeter distally. The perfusion tubing was needled between the pump and its insertion into brachial artery. A polyethylene catheter (PE280) was inserted proximally up the brachial artery into the aorta. The needles and tubes were connected through a multiple stopcock arrangement to a single resistance wire pressure transducer (volume replacement = 0.01 cu mm/100 mm Hg). This obviated the practical difficulties of multiple transducers and amplifiers. In order to keep the tubes and catheters open, the arrangement included a mechanism for slow sequential infusion of heparinized saline

from a pressurized drip bottle whenever pressures were not being recorded. After determination from the venous pressure levels, that venous outflow from the forelimb was unobstructed, forelimb flow was adjusted to a value that produced a brachial arterial pressure similar to aortic pressure. This flow averaged 0.23 ml/min/gm of foreleg. Because of the numerous artery to artery and vein to vein anastomoses, the pressures recorded in the small vessels are not measurably different from true lateral pressure.

Muscle and subcutaneous tissue pressure were recorded via the same pressure transducer. Twenty-seven gauge hypodermic needles were inserted into the flexor belly in the forearm and in the overlying subcutaneous tissue. These were attached through saline filled catheters to the transducer. Pressure in the transducer head was raised to 40 mm Hg by exposing it to a column of saline. By turning a stopcock the transducer head was switched from the column of saline to one of the fluid filled catheters. This maneuver displaces about 0.004 cu mm of saline into the tissue. The subsequent decay in pressure was monitored and the equilibrium pressure was taken to be interstitial pressure. Using this method, repeated measurements could be made without introducing significant amounts of fluid into the tissue or altering interstitial pressure.

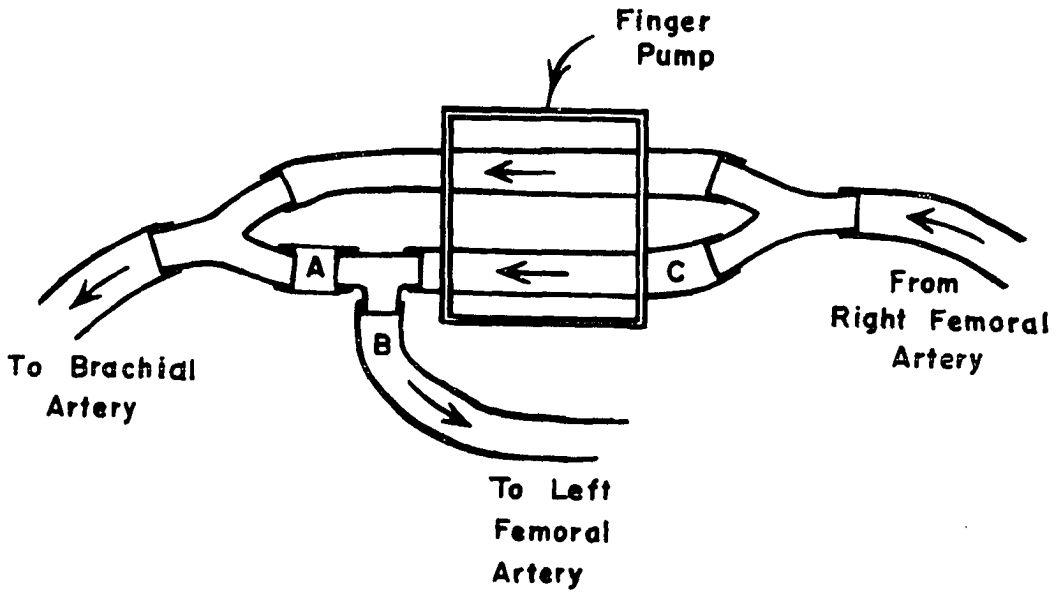
Denervation was accomplished by sectioning all forelimb nerves below the brachial plexus (musculocutaneous, median, ulnar, and radial).

Forelimb blood flow was changed in three ways. Alteration of flow by regular increments was accomplished by varying the pump speed. In these experiments pressures and resistances were determined only in

the steady state. Square wave changes in blood flow, of limited duration, were produced by aspiration or injection of blood between the pump and brachial artery. Transient or prolonged square wave changes in blood flow through the limb were produced by sudden diversion of flow to and from the limb (Figure 3). After occlusion at point B, flow through both tubes in the pump head was very nearly equal. Thus, immediate halving of forelimb flow could be accomplished by simultaneously clamping at point A and releasing occlusion at point B. Conversely, immediate doubling of forelimb flow could be accomplished by simultaneously clamping at B and releasing occlusion at A. This technique permitted alternate havling and doubling of forelimb flow without subjecting a static column of blood to the continuous roller action of the blood pump, as would occur for example if the upper tube was simply clamped.

The effect of interruption of forelimb blood flow upon brachial artery perfusion pressure immediately following re-establishment of flow was studied in 26 dog forelimbs. The effect of venous congestion upon the response was also studied in the same limbs. Blood flow to the limb was suddenly interrupted by shutting off the pump. In most of these studies the diversion system was not employed. The pump head contained only one tube. After a specified time interval (2, 10, 20, 30, 60 and 120 seconds) blood flow was re-established by turning the pump on. The effect of this maneuver upon limb perfusion pressure was compared to those caused by the same periods of flow interruption with intraluminal pressure during interruption held near the pre-occlusion level. The latter was accomplished by occluding the cephalic and brachial veins at or shortly before interrupting arterial inflow. Six of

Figure 3. Schematic drawing of the diversion system used to produce square wave changes in blood flow through the forelimb and kidney. Description in text.


Finger
Pump
A
B
C
To Brachial
Artery
From
Right Femoral
Artery
To Left
Femoral
Artery

the above forelimbs were studied in the same manner following denervation. Two measurements were used to quantitate the magnitude of the resistance change produced by the maneuver: 1) the absolute perfusion pressure immediately upon re-institution of blood flow was compared to the pre-occlusion pressure, and 2) the total area of the pressure response was measured and expressed in square mm of paper.

The effect of elevation of venous pressure at constant blood flow upon forelimb pressures in the innervated and denervated dog forelimb was studied in another series of 21 animals. Venous pressure elevation was accomplished by partial obstruction of venous outflow with a constricting ligature below the site of venous pressure measurement.

The effect of increasing blood flow through the limb by regular increments upon segmental pressure gradients and resistances was also studied in this group of animals.

Segmental resistances were calculated in the following manner: total resistance = brachial artery pressure minus cephalic vein pressure divided by blood flow; arterial resistance = brachial artery pressure minus small artery pressure divided by blood flow; small vessel resistance = small artery pressure minus small vein pressure divided by blood flow; venous resistance = small vein pressure minus large vein pressure divided by blood flow.

The effect of transient and prolonged square wave changes in blood flow upon brachial perfusion pressure was studied in another series of animals utilizing the diversion system outlined above.

The effects of hemorrhage upon the forelimb preparation was studied at both constant and natural flow. In a series of six animals

outflow from the brachial and cephalic veins was led through a rotometer into the right atrium via a large plastic cannula passed down an external jugular vein. Following a 15 minute control period, in which pressures and flows were recorded at 5 minute intervals, 25% of the animal's calculated blood volume was removed. Pressures and flows were recorded at the first, third, fifth, tenth, fifteenth and twentieth minute after bleeding. The shed blood was then returned to the animal and pressures and flows were recorded at the same time intervals during the subsequent twenty minutes.

Eleven animals were studied in the same manner while holding forelimb flow constant with the blood pump. In these studies the volume of blood shed ranged from 9 to 38.3% (average 20.7%) of the calculated blood volume.

Kidney

In these studies, blood flow to the kidney was either held constant with a pump or venous outflow from the kidney was measured. In both preparations the right kidney was exposed retroperitoneally through a right flank incision. Extreme care was taken to avoid unnecessary damage to the kidney or connective tissue in the immediate vicinity of the kidney.

When blood flow was to be measured the renal artery was encircled with a loose ligature. The renal vein was dissected free from the hilus of the kidney to the vena cava. The renal artery was then partially transected and a large bore glass or polyethylene cannula inserted up the renal vein and securely tied in place. The cannula was connected by rubber tubing to a T tube. The vertical arm of the T was used for

the insertion of a macro-oxygen probe for continuous measurement of PO_2 tension. The distal arm of the T was connected by rubber tubing to a rotometer. The outflow from the rotometer passed through another large bore polyethylene cannula which was inserted into the superior vena cava via the right external jugular vein. When the external circuit was in place, the artery clamp was removed, thus restoring renal blood flow. On the average, renal blood flow was interrupted for less than two minutes. A 22 gauge hypodermic needle was bent to a right angle and connected by a fluid filled polyethylene tube to a pressure transducer. It was then inserted into the renal artery between the kidney and the ligature surrounding the renal artery. This cannula was used for measurement of renal perfusion pressure or to introduce vasoactive agents directly into the renal artery. A small polyethylene (PE10) cannula, also fluid filled, was passed in a retrograde manner up the venous outflow cannula until its tip lay beyond the orifice of the large cannula in the renal vein. This tube was connected to the same pressure transducer and was used to measure renal venous pressure.

The effects of partial renal artery occlusion (accomplished by tightening the renal artery ligature) upon renal blood flow, renal resistance, and renal venous oxygen tension was studied in this preparation. A sample of venous blood was drawn before, during and after the renal artery constriction for determination of pH, Na^+ and K^+. The renal artery constriction was repeated in the same animals except that the animals were ventilated with 100% oxygen beginning approximately one minute prior to the artery constriction. This was accomplished by connecting the input of the respirator to a Douglas bag filled with 100%

oxygen. In the same animals, the same renal parameters were again studied during ventilation with 100% oxygen alone.

The effects of elevation of renal venous pressure, elevation, accomplished by partial occlusion of the venous outflow cannula, upon renal blood flow, renal venous oxygen tension, and calculated renal vascular resistance also were studied in the same kidneys.

An effort was also made to determine if constriction of the renal artery or vein altered the vasoactive properties of the renal venous blood. In another group of ten animals, a second T tube was inserted into the external renal venous circuit between the flowmeter and the jugular vein. The vertical branch of this T tube was connected to a length of plastic tubing which coursed through a blood pump (T6SH) and then into the distal segment of the ligated left brachial artery. Thus, the forelimb could be perfused at a constant rate with renal venous blood.

In these animals, the effects of partial occlusion of the renal artery or vein upon renal blood flow, renal venous oxygen tension, calculated renal vascular resistance, and forelimb vascular resistance was determined. Also studied in eight of these experiments were the effects of adenosine, AMP, ADP and ATP upon renal blood flow, renal venous oxygen tension, calculated renal vascular resistance and forelimb vascular resistance when injected into the renal artery. Each agent was diluted in saline to a concentration of 10 μg/cc, and 0.65 ml was the injected volume in each case.

The effects of hemorrhage upon renal blood flow and renal vascular resistance were studied in seven animals. Renal venous flow was

diverted from the renal vein to the jugular vein through external tubing and renal blood flow was measured by periodically collecting all of the venous outflow during a ten second period in a graduate. After measurement, the blood was immediately returned to the animal. The experimental sequence was as described for the studies on the forelimb during hemorrhage.

When blood flow to the kidney was to be controlled both femoral arteries as well as the right renal artery were exposed. A short length (.5 cm) of the renal artery was exposed to permit passage of two sutures around the vessel. The femoral arteries and renal artery were ligated and the same diversion system used in the forelimb (Figure 2) was installed. Renal perfusion pressure was obtained by needling the perfusion tubing between the pump and renal artery. A lymph vessel leaving the hilar area of the right kidney was carefully dissected free and cannulated with a fluid filled polyethylene (PE10) cannula. This cannula was passed up the lymph vessel until its tip lay just outside the kidney substance. The distal end of the catheter was connected to a resistance wire pressure transducer. The effects of transient and prolonged square wave changes in renal blood flow and of changes in venous pressure at constant flow upon renal perfusion pressure and lymphatic vessel pressure were studied in this preparation.

The effects of hemorrhage on renal vascular resistance with renal flow held constant was studied in six other animals. A blood pump was interposed between the right femoral and right renal arteries. The perfusion tubing was needled for renal artery pressure and systemic pressure was measured from an aortic cannula. Blood flow to the kidney

was set at a value that gave a renal perfusion pressure approximately equal to aortic pressure. The experimental sequence for the study of hemorrhage was identical to that described for the ileum.

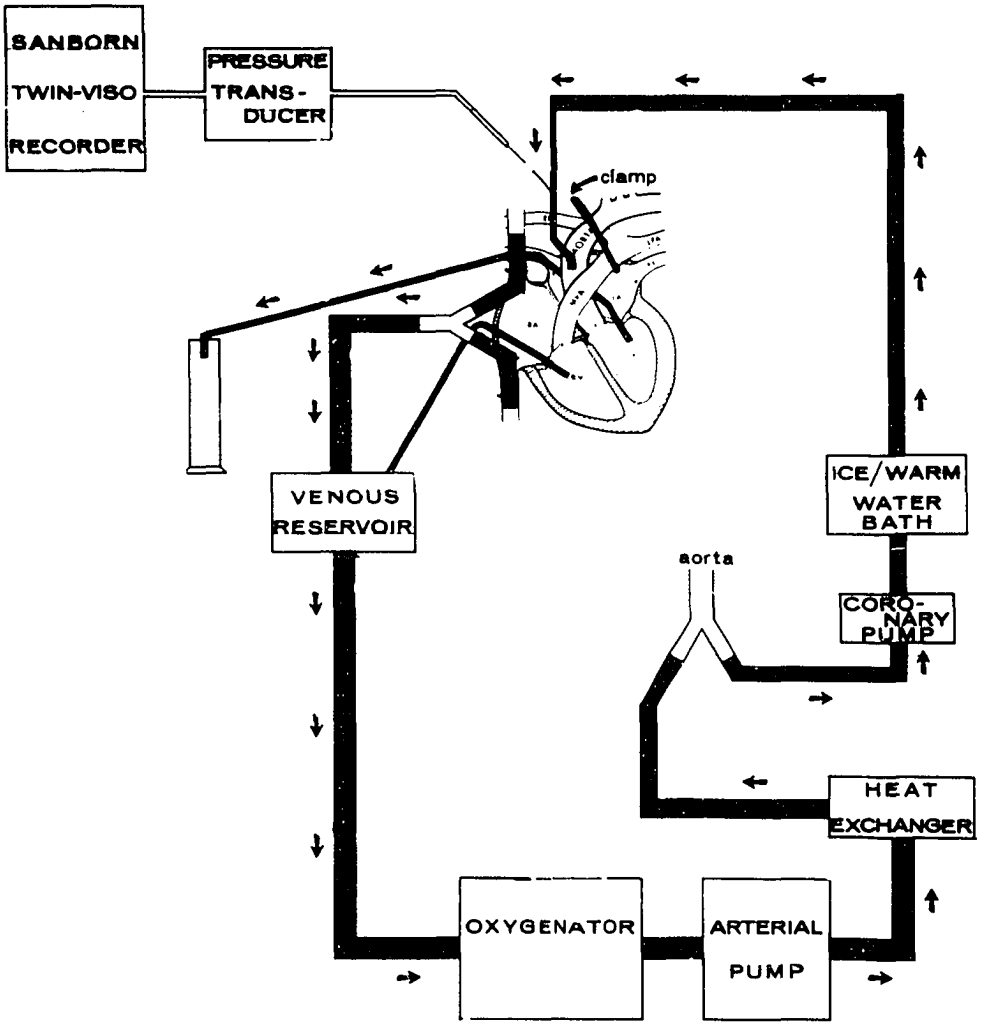
Heart

The relationship of pressure to flow through the entire coronary vascular bed of the dog heart was studied with the heart performing no external work. This was accomplished by shunting the blood around the heart and lungs, clamping the arch of the aorta and perfusing arterial blood at known rates into the ascending aorta. Perfusion pressure was measured at each flow rate. The relationship was examined before and after bilateral vagotomy with the heart beating and fibrillating.

Plastic cannulas were introduced into the superior and inferior vena cava via the right atrium (Figure 4). A rotating disc oxygenator (Kay-Cross disc oxygenator; Pemco, Inc., Cleveland, Ohio) and blood pump (model T-65) were interposed between the cannula and left femoral artery and the body perfused with oxygenated blood at the rate of 50-60 ml/kg/min. Coronary venous blood was collected from the right heart with a cannula threaded through the tricuspid value and the blood returned to the venous limb of the perfusion circuit. Left heart blood was collected with another cannula threaded through the mitral valve.

The coronary vascular bed was perfused with a second pump (model T-6). This was precalibrated to deliver 10 different rates of flow. It was interposed between the right femoral artery and the ascending aorta (Figure 4). After setting the pump in motion, the aorta and pulmonary artery were cross clamped approximately 3 cm from the heart. Hence, coronary perfusion was never interrupted. Perfusion pressure was

Figure 4. Schematic drawing of the cardiac by-pass and coronary perfusion systems. See text for details.


SANBORN
TWIN-VISO
RECORDER
PRESSURE
TRANS-
DUCER
clamp
VENOUS
RESERVOIR
ICE/WARM
WATER
BATH
aorta
CORO-
NARY
PUMP
HEAT
EXCHANGER
OXYGENATOR
ARTERIAL
PUMP

measured with a resistance wire pressure transducer (Figure 4).

The relationship of pressure to flow was studied before and after vagotomy with the heart beating and fibrillating. Both vagi were sectioned high in the neck. Fibrillation was induced by applying a very weak electric shock to the heart. The flow rates studied were 25, 50, 75, 100, 120, 140, 160, 180, 200, and 220 ml/min in that order. Pressures, after stabilizing, were measured at each flow rate. The entire sequence was completed in about two minutes. Since the pressure in the right atrium remained at atmospheric pressure, the resistance to flow through the coronary vascular bed was calculated by dividing perfusion pressure by the rate of blood flow and expressed as millimeters Hg per milliliter per minute.

Flow from the cannula in the left heart chambers did not exceed 10 ml/min in any animal and postmortem tests showed the aortic valve to be competent at pressures well over 300 mm Hg.

Forelimb Assay

In order to study the vasoactivity of venous outflow from regulating organs, a portion of the venous efflux from either the hindlimb, kidney, or coronary vascular bed was perfused at a constant rate through the forelimb of the same dog. After a suitable control period (stable brachial arterial pressure) local regulation was elicited (nerve stimulation, partial or complete occlusion of arterial inflow or outflow, and over perfusion) in the organ supplying venous blood to the forelimb. Brachial arterial pressure was continuously measured.

When the hindlimb was to supply venous blood, the femoral artery and vein were exposed from the saphenous artery to the base of Scarpa's

triangle. The sciatic nerve was isolated high in the hindlimb. Rubber tubing (¼" i.d.), with large bore polyethylene cannulas fitted to each end and a polyethylene T tube in the middle, was spliced into the femoral vein. The vertical branch of the T tube was adapted to smaller polyethylene (PE280) which coursed through a blood pump (model T6SH) before entering the distal segment of the ligated brachial artery (see Forelimb methods). These techniques permitted continuous sampling of hindlimb efflux and also obviated high femoral venous pressure (the femoral venous blood in excess of that going to the forelimb was permitted to drain naturally into the vena cava). This system also permitted comparison of femoral venous blood with vena caval blood. This was accomplished by clamping either above or below the T tube

The effects of faradic stimulation of the sciatic nerve and partial and complete femoral artery occlusion upon brachial perfusion pressure was studied in ten such preparations.

Renal vein blood was also used to provide brachial flow. In these studies, the rotometer was removed from the renal venous outflow system (Kidney methods) and the external circuit was shortened to a minimum length. This greatly reduced the volume in the extra corporal system and reduced circuit time from kidney to limb. The effect of partial and complete renal artery occlusion upon brachial perfusion pressure was investigated with this preparation.

In another group of animals the same venous outflow system was installed between the right renal and jugular veins. In addition, a blood pump was interposed between the right femoral and right renal arteries. The effects of over-perfusion of the kidney, accomplished by

increasing pump flow, upon brachial artery pressure was studied in this preparation.

In the studies in which coronary venous blood was used to supply the forelimb, a specially designed glass cannula was inserted into the coronary sinus via the right atrial appendage. A large bore (3/8" i.d.) rubber tube with a 15 cm length of polyethylene tubing inserted into the distal end was attached to sinus cannula. Two T tubes were interposed into the rubber tube, one for the macro-oxygen electrode, the other for directing blood through the forelimb. The plastic cannula was inserted down the jugular vein until its tip lay in the superior vena cava. The left common coronary artery was dissected free between its ostium and the first bifurcation and encircled with a loose ligature. The effect of partial and complete left common coronary artery occlusion (produced by tightening the arterial ligature) upon brachial arterial pressure was studied in this preparation. The effects of mixed venous blood and coronary sinus blood upon brachial perfusion pressure were also compared in the same animal. This was accomplished by inserting a Y tube upstream to the blood pump, one arm of which was connected to the external sinus circuit and the other arm to a T tube which was spliced into femoral vein. Thus, by clamping one or the other arms of the Y tube or T tube, the forelimb could be perfused with sinus, inferior vena cava, or femoral venous blood.

CHAPTER III

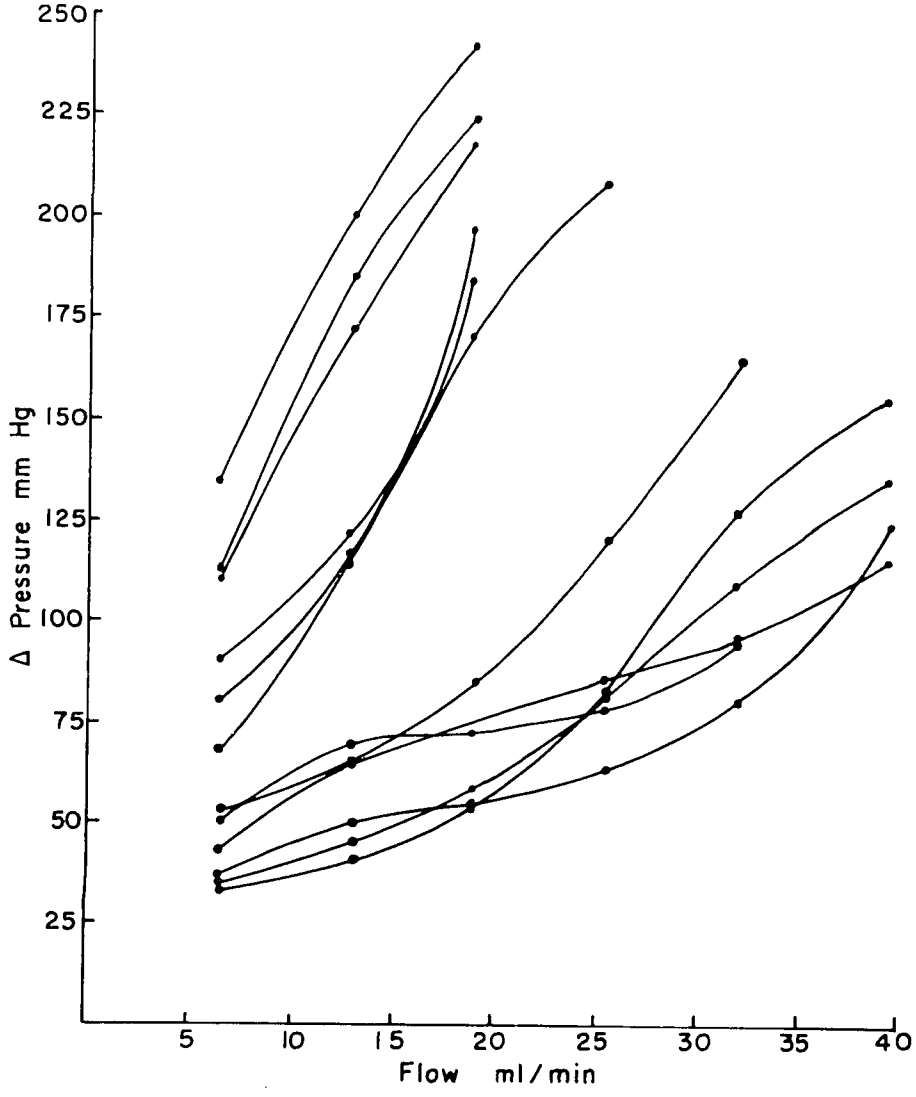
RESULTS

Effect of Change in Perfusion Pressure or Blood Flow Upon Vascular Resistance in Various Systemic Vascular Beds

Ileal Vascular Bed

Figure 5 presents pressure flow relationships in the dog ileum, obtained by increasing flow rate and monitoring steady state perfusion pressure at each increment in flow. In 7 of 12 experiments the ratio of pressure gradient to blood flow increased as a function of flow rate. In the remaining five experiments the ratio of perfusion pressure to flow progressively decreased as a function of flow rate. However, in three of the latter preparations, initial resistance was quite high indicating an inadequate test system. Certainly, in the kidney a high initial resistance often precludes further increase in resistance as flow is increased (29). In many preparations, the activity of the visceral smooth muscle, as determined by lumen pressure, increased at very low flows and, occasionally, at the higher flows. This activity, however, could not be correlated with the changes in resistance to blood flow.

Figure 5. Pressure-flow relationships obtained in twelve pump perfused experiments on a section of dog ileum.


250
225
200
175
150
125
100
75
50
25
Δ Pressure mm Hg
5
10
15
20
25
30
35
40
Flow ml/min

Coronary Vascular Bed

The relationship of steady state perfusion pressure to blood flow rate was examined in 16 beating hearts. As Figure 6 shows, various relationships were observed. Calculated resistance decreased as a function of flow rate in five experiments. The rate of decrease was most rapid over the lower range of flow rates. However, in seven experiments resistance decrease over the lower range of flow rates and increased over the higher range of flow rates. The resistance at a flow rate of 25 ml/min was higher in the former group than in the latter group (1.5 as compared to 0.7 mm Hg/ml/min). In the remaining experiments, resistance did not change greatly as flow was elevated. Thus, on the average, resistance decreased as flow rate was elevated from 25 to 75 ml/min but remained relatively constant over the range 75 to 220 ml/min (Figure 7).

Six hearts were studied following vagotomy (Figure 8). Resistance decreased progressively as flow rate was elevated over the entire range in four experiments. In two experiments, resistance decreased over the lower range of flow rates and remained constant over the range 100 to 220 ml/min. For the entire group, resistance averaged 1.4 mm Hg/ml/min at a flow rate of 25 ml/min. Three of the six hearts were also studied before vagotomy. The pressures at each flow rate were essentially the same under the two conditions in two preparations. In the other, the pressures were slightly lower at each flow rate following vagotomy.

Nine hearts were studied during ventricular fibrillation. As can be seen in Figure 9, various relationships were again observed.

Figure 6. Pressure as a function of blood flow rate in six beating hearts selected for their widely differing resistance to flow.

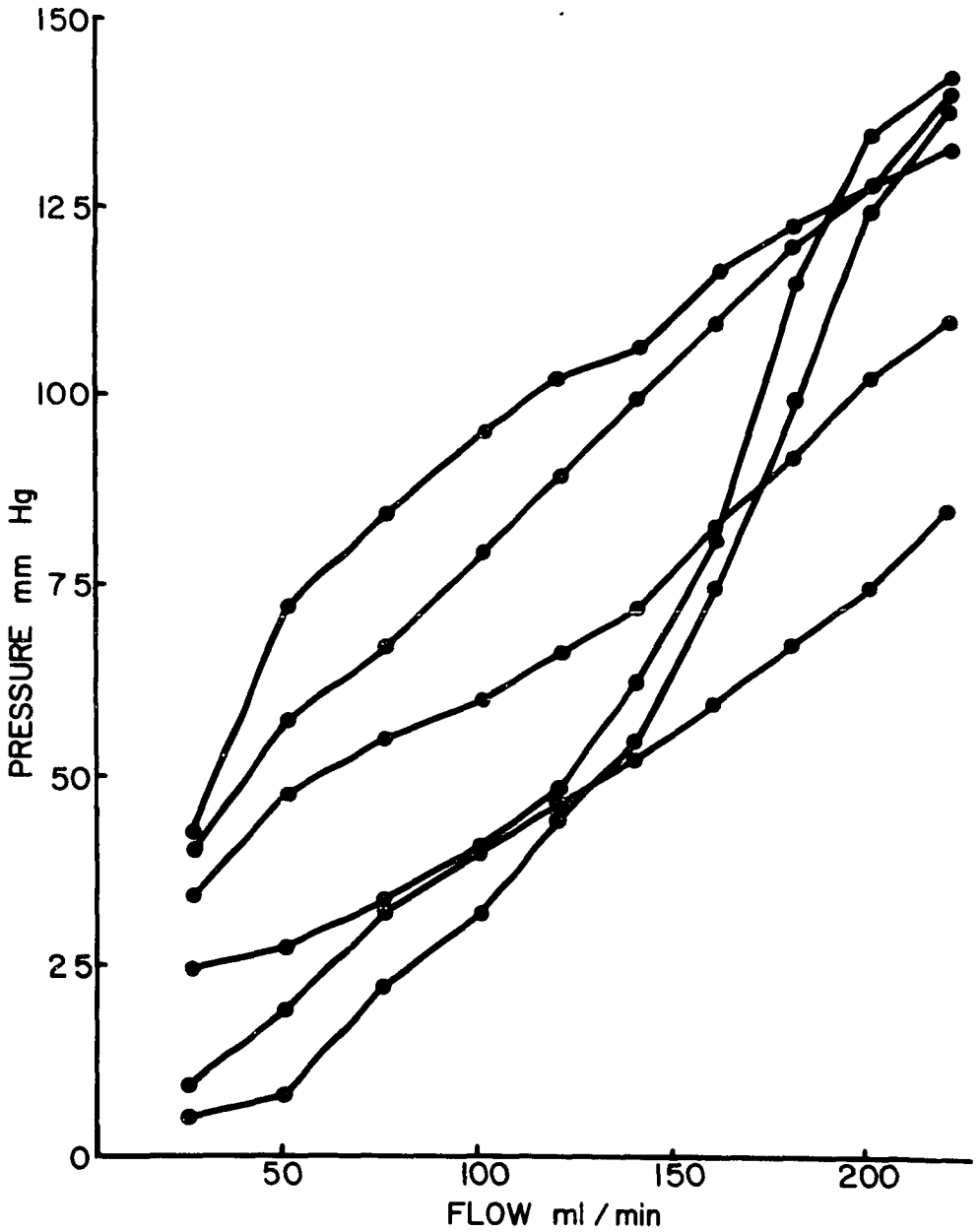

150
125
100
75
50
25
0
PRESSURE mm Hg
50
100
150
200
FLOW ml / min

Figure 7. Pressure and resistance as a function of the rate of blood flow. Average of sixteen beating and nine fibrillating hearts.

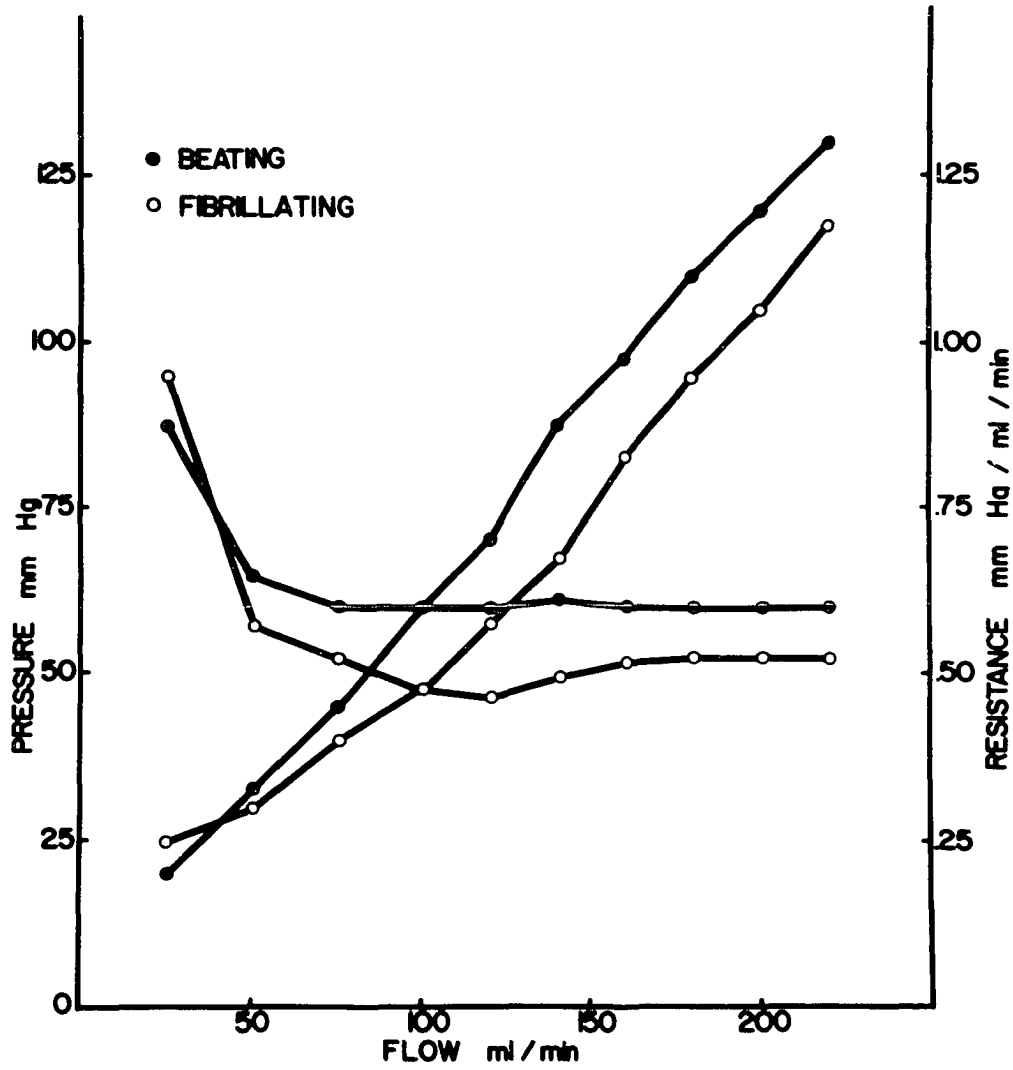

● BEATING
○ FIBRILLATING
125
100
75
50
25
0
PRESSURE mm Hg
1.25
1.00
.75
.50
.25
RESISTANCE mm Hg / ml / min
50
100
150
200
FLOW ml / min

Figure 8. Pressure as a function of blood flow rate in six beating hearts following bilateral vagotomy.

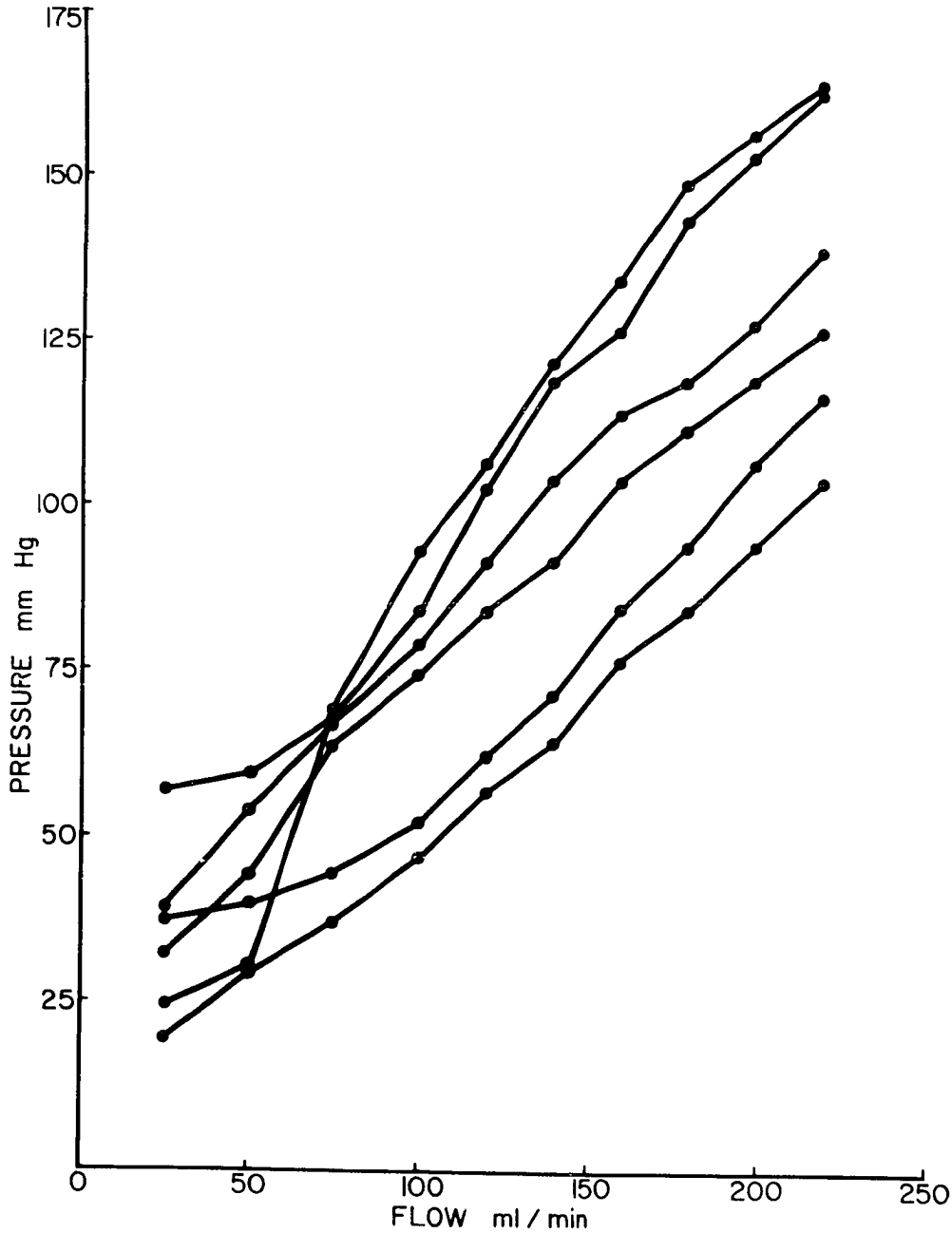
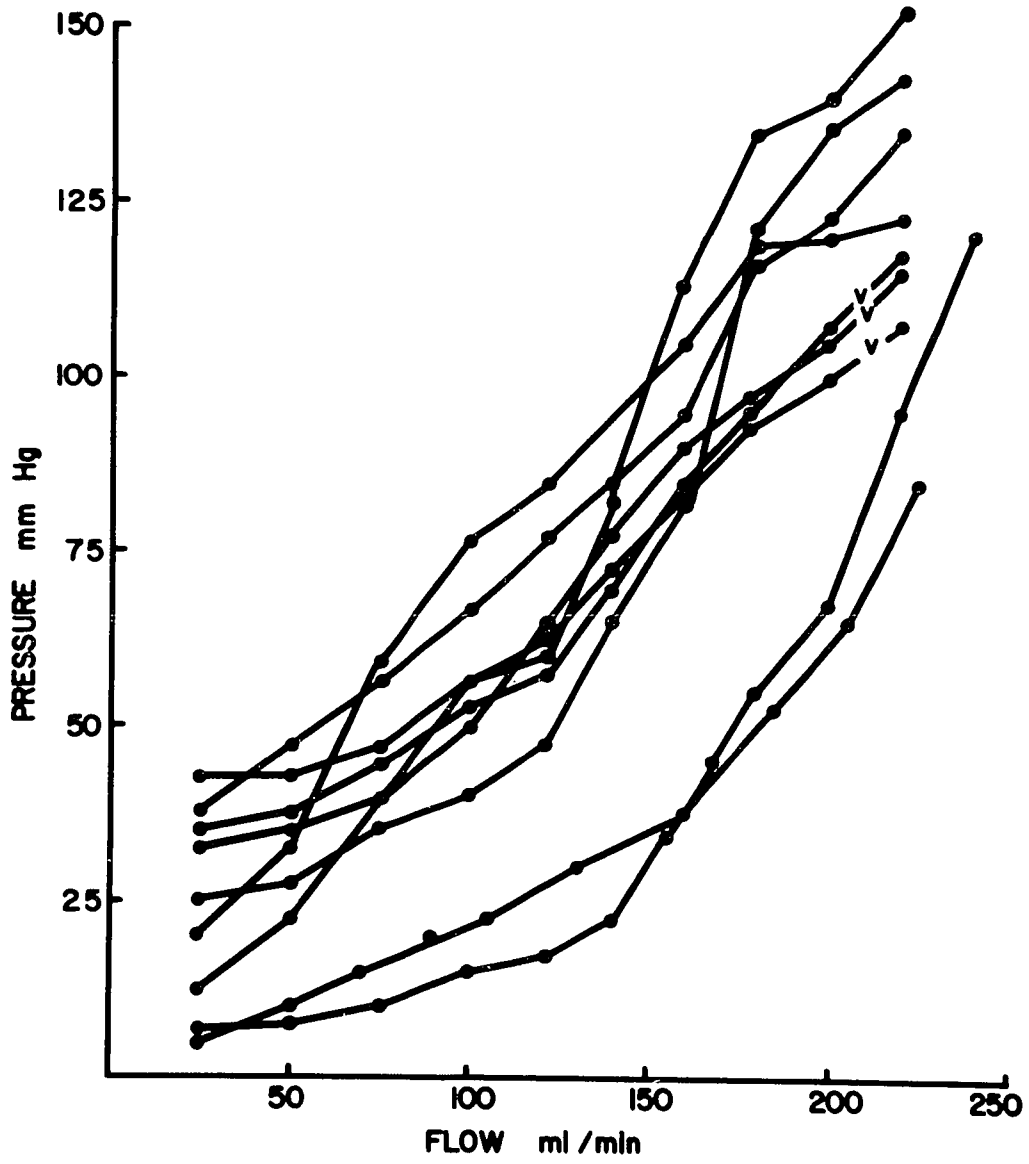

175
150
125
100
75
50
25
PRESSURE mm Hg
0
50
100
150
200
250
FLOW ml / min

Figure 9. Pressure as a function of blood flow rate in nine fibrillating hearts. The letter V indicates those with bilateral vagotomy.


150
125
100
75
50
25
PRESSURE mm Hg
50
100
150
200
250
FLOW ml/min

Resistance decreased as a function of flow rate in one experiment while in four experiments resistance decreased over the lower flows and remained relatively constant over the higher flow rates. Resistance in the latter group averaged 1.2 mm Hg/ml/min at a flow of 25 ml/min. In the remaining four experiments resistance increased as a function of flow rate over the range 120 - 222 ml/min. In this group, resistance averaged 0.8 mm Hg/ml/min at a flow of 25 ml/min. Considering the entire group, average resistance decreased over the range 25-120 ml/min, increased slightly over the range 120-180 ml/min, and did not change over the range 180-220 ml/min (Figure 10).

Forelimb Vascular Bed

Figure 11 presents the typical steady state effects of increasing blood flow by graded increments upon brachial artery, small artery, small vein, and cephalic vein pressures in the dog forelimb. All four pressures rose as a function of flow rate, however, the rise in pressure was not proportional to the rise in flow rate. Thus, resistance to blood flow through the entire bed, as well as through arteries, small vessel and veins, decreased as blood flow was elevated. Tissue pressure, measured in the muscle or subcutaneously, was unaffected by the maneuver.

Figure 12 shows the effect in one experiment of a large, rapid change in limb flow upon brachial artery pressure. The upper panel shows that when limb blood flow was held at a low value for several minutes and then rapidly elevated to a very high value, brachial artery pressure initially rose sharply, transiently fell slightly and then progressively rose until a steady state was reached. However, in the steady

Figure 10. Pressure as a function of flow rate in three hearts before and during ventricular fibrillation. Numbers and letters identify hearts and indicate those with bilateral vagotomy, respectively.

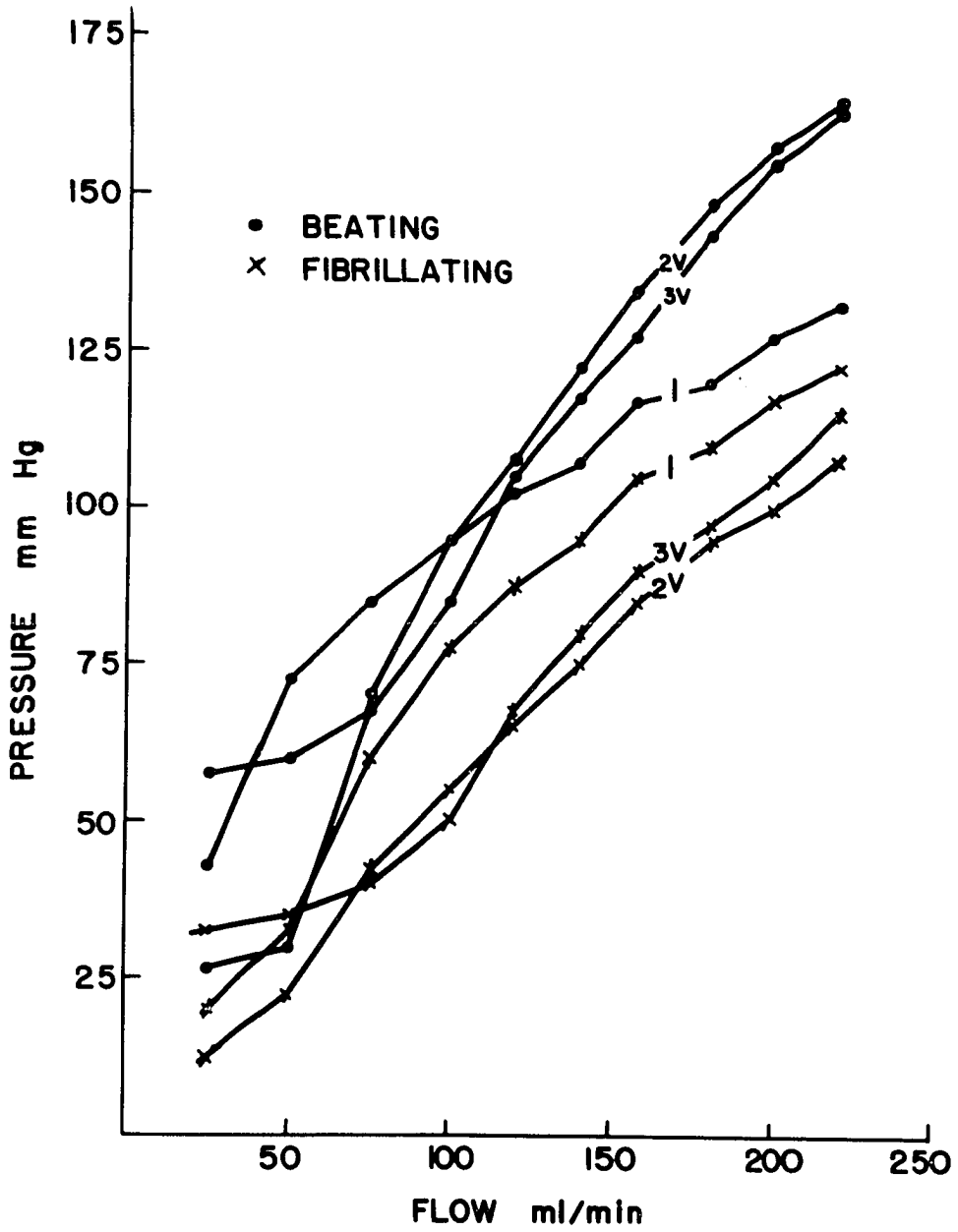

175
150
125
100
75
50
25
PRESSURE mm Hg
BEATING
FIBRILLATING
2V
3V
1
1
3V
2V
50
100
150
200
250
FLOW ml/min

Figure 11. Pressure-flow relationship in a typical forelimb experiment. Numbers refer to resistance through the vascular segments at low, intermediate, and high blood flow.

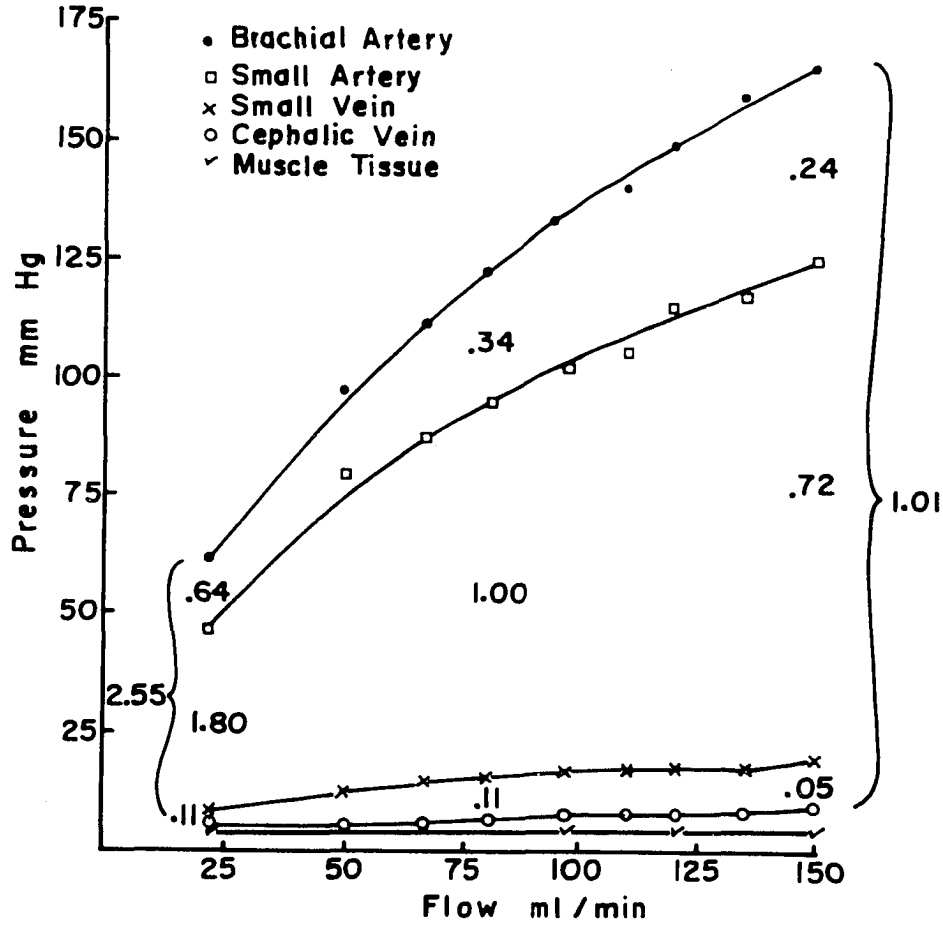
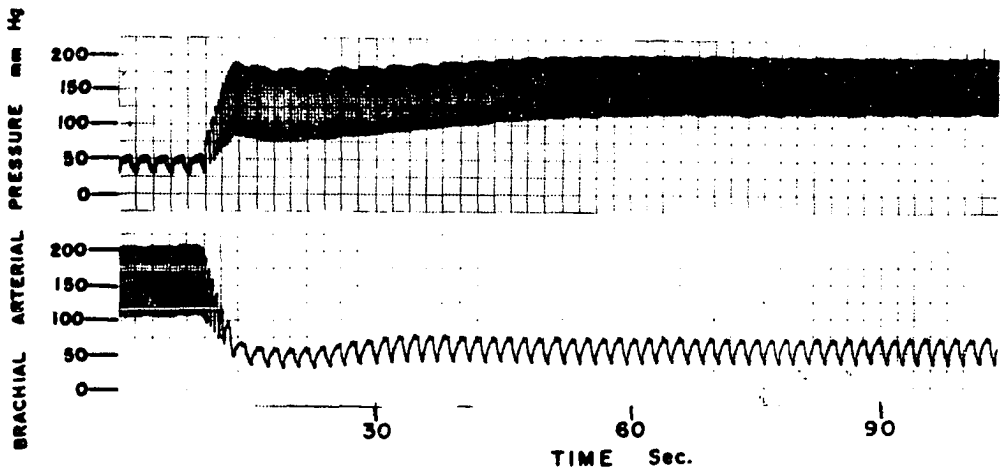

175
150
125
100
75
50
25
Pressure mm Hg
• Brachial Artery
□ Small Artery
× Small Vein
○ Cephalic Vein
✓ Muscle Tissue
.24
.34
.72
1.01
.64
1.00
2.55
1.80
.11
.11
.05
25
50
75
100
125
150
Flow ml / min

Figure 12. Effect in one animal of rapidly increasing (upper panel) and rapidly decreasing (lower panel) forelimb blood flow upon brachial perfusion pressure.

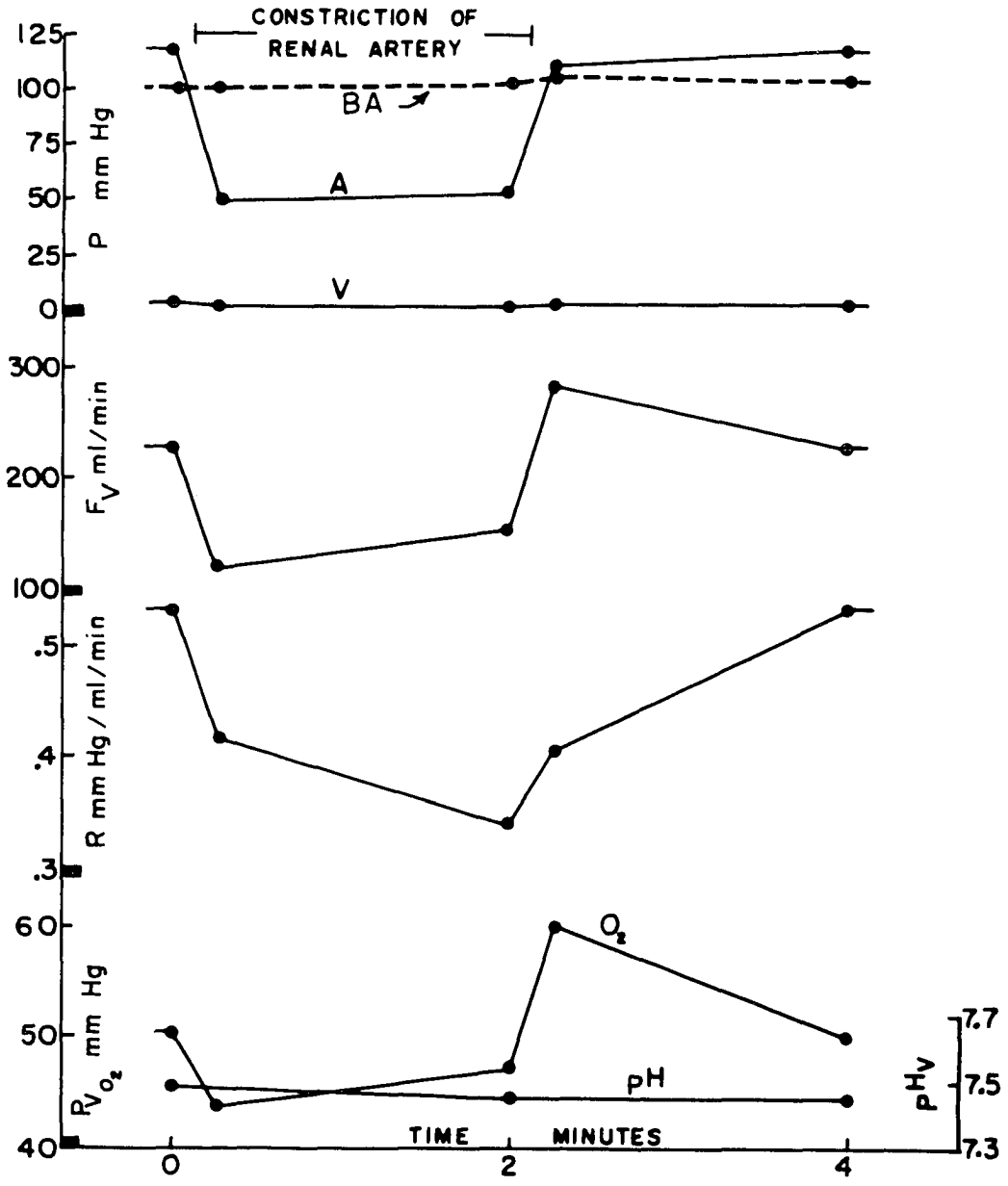

BRACHIAL ARTERIAL PRESSURE mm Hg
200
150
100
50
0
200
150
100
50
0
30
60
90
TIME Sec.

state, resistance to flow was higher at the low flow (1.72 mm Hg/ml/min) than at the high flow (1.22 mm Hg/ml/min). The lower panel (Figure 12) shows the effect of rapidly lowering blood flow to the limb. Brachial pressure dropped precipitously as flow was decreased and then transiently increased before falling to a new steady state. Again, calculated resistance to flow through the limb was higher at the low flow than at the higher flow.

Renal Vascular Bed

Figure 13 presents the average effect in 10 animals of renal artery constriction upon renal venous pressure, renal blood flow, renal vascular resistance, renal venous blood PO_2 tension, and renal venous blood pH. It can be seen that decreasing renal perfusion pressure from 120 mm Hg to 53 mm Hg, by renal artery constricton, had little effect upon renal vein pressure or renal venous blood pH. Renal blood flow immediately fell, partially recovered, and transiently overshot the control values upon release of the occlusion. The renal venous blood PO_2 tension was affected in exactly the manner as the blood flow. Since the fall in pressure was proportionally greater than the fall in blood flow calculated resistance immediately decreased and fell still further as flow partially recovered. Upon release of the occlusion flow transiently overshot the control value. Perfusion pressure returned to control, thus calculated resistance remained below the control value for a time. It can also be seen that diversion of a portion of the renal venous blood (picked up downstream to flowmeter) through the forelimb failed to alter brachial artery (BA, dashed line) pressure. All values returned to control levels within two minutes after release of the renal artery constriction.

Figure 13. Average effects in ten animals of renal artery constriction (A) upon renal venous pressure ($\bar{P}$), renal venous outflow (F_V), calculated renal vascular resistance (R), renal venous oxygen tension (P_{VO_2}), and renal venous blood pH (pH_V). Dashed line shows the effect on brachial perfusion pressure (BA) of a diversion of a portion of the renal venous outflow through the forelimb at constant flow.


CONSTRICTION OF
RENAL ARTERY
125
100
75
50
25
0
P mm Hg
BA
A
V
300
200
100
F_V ml/min
.5
.4
.3
R mm Hg / ml / min
60
50
40
$R_{V_{O_2}}$ mm Hg
O_2
pH
7.7
7.5
7.3
pH$_V$
TIME
MINUTES
0
2
4

Effect of Ischemia Upon Resistance to Blood Flow Through Various Systemic Vascular Beds

Ileal Vascular Bed

The effect of ischemia upon subsequent flow or perfusion pressure was studied in both the natural flow and pump-perfused ileal preparations. In both types of experiments the results were inconsistent. In 10 of 15 trials, in eight animals, measuring natural flow, the volume-rate increased following periods of ischemia of 30 seconds to two minutes. In two experiments the flow following release of occlusion was decreased from control and in three experiments flow was essentially unchanged from control after ischemia. Figure 14 shows another experiment in which blood flow was measured before and after a one-minute arterial occlusion. The pre-occlusion flow rate was 7.09 gm/min and the post-occlusion flow rate was 6.97 gm/min. Figure 15 shows another experiment in which blood flow was sharply elevated from 9.20 to 15.6 gm/min following a one minute ileal artery occlusion.

In the above studies it was noted that during periods of ischemia, the section of ileum under study often became active and the average lumen pressure rose. Figure 16 clearly demonstrates this response in a pump-perfused preparation. An increase in motility and average lumen pressure can be seen during the 10 second, 30 second, one minute, and two minute periods of no perfusion. The perfusion pressure returned to control levels very soon after the pump was restarted. Gut activity and average lumen pressure also decreased shortly after flow was re-established. The latter was a consistent finding whenver motility and tonus increased during a period of ischemia.

Figure 14. Effect in one animal of a one minute ileal artery occlusion upon ileal blood flow and on perfusion pressure gradient immediately upon release of occlusion.

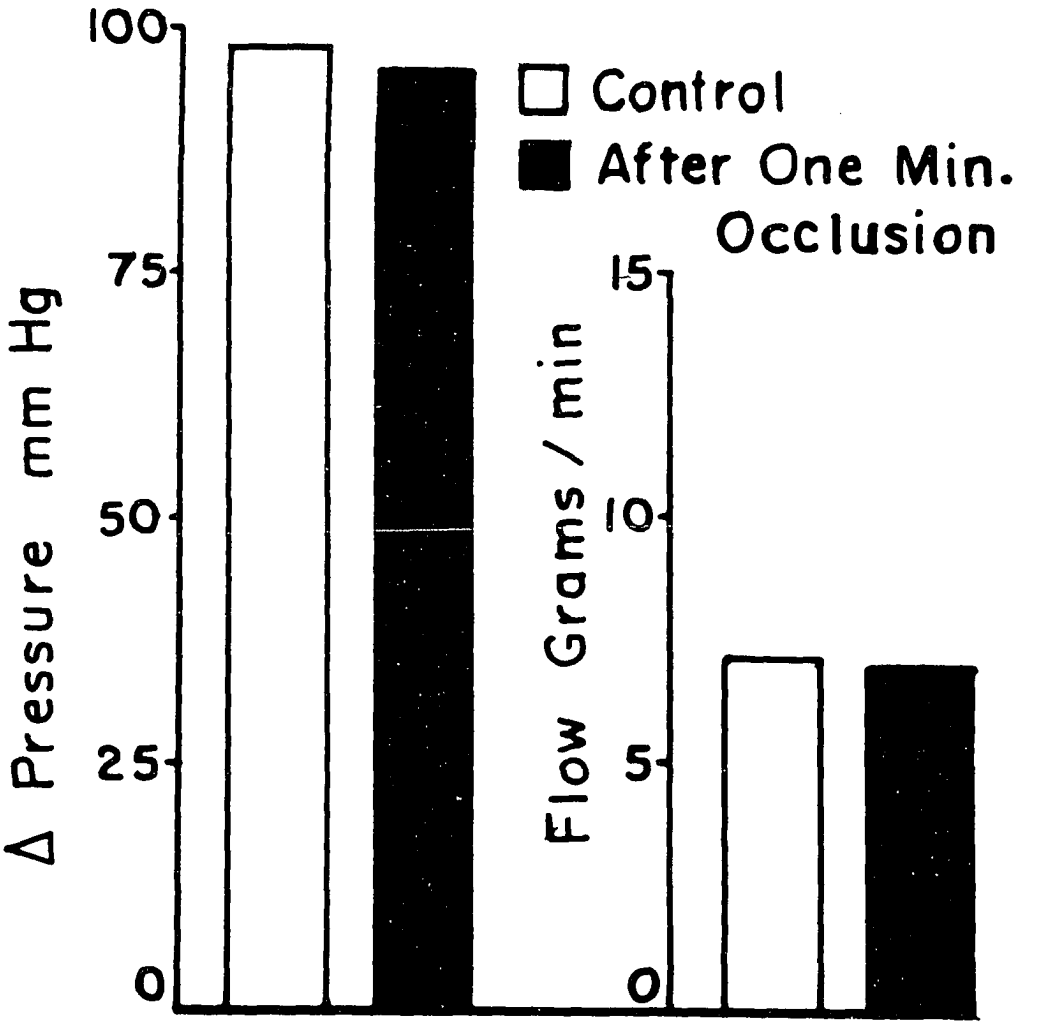

100
75
50
25
0
Δ Pressure mm Hg
Control
After One Min.
Occlusion
15
10
5
0
Flow Grams / min

Figure 15. Same as Figure 14, except ileal lumen pressure is also depicted.

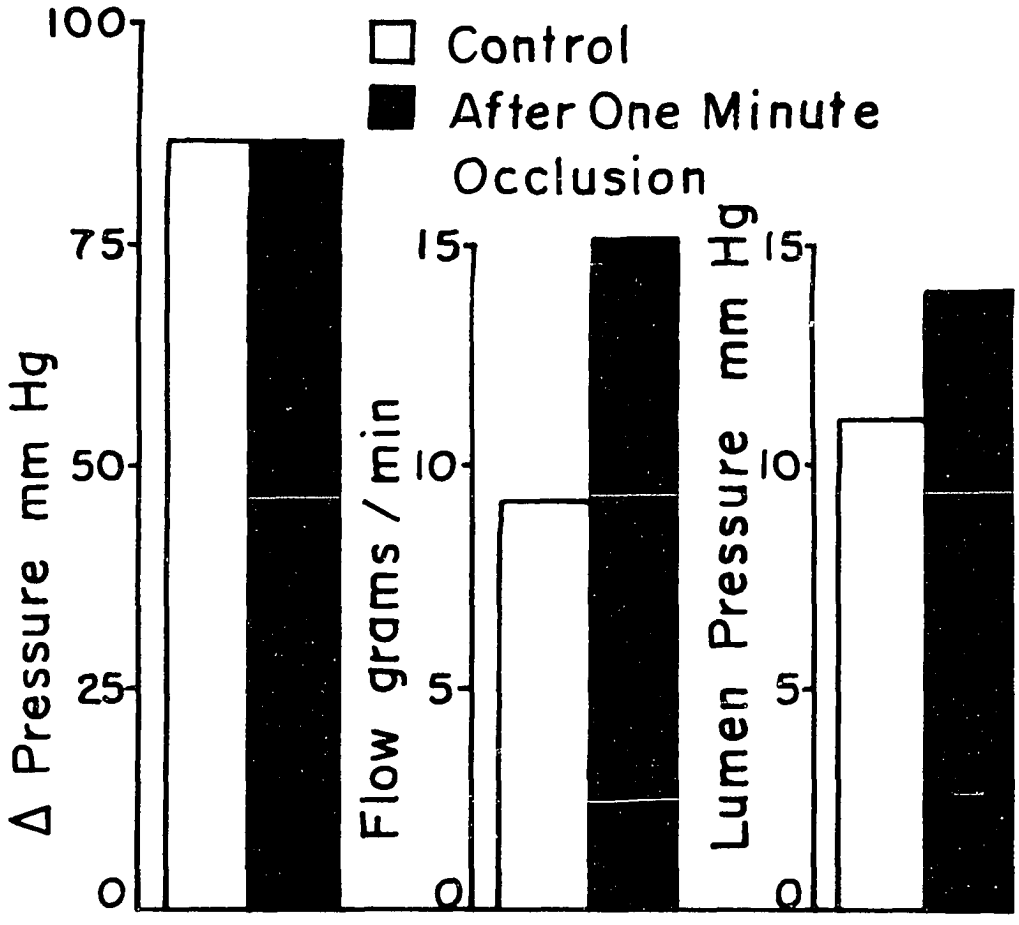

Control
After One Minute Occlusion
Δ Pressure mm Hg
100
75
50
25
0
Flow grams / min
15
10
5
0
Lumen Pressure mm Hg
15
10
5
0

Figure 16. Perfusion pressure (Pa) and ileal lumen pressure (Pl) in one pump perfused preparation before, during and after various intervals of no flow.

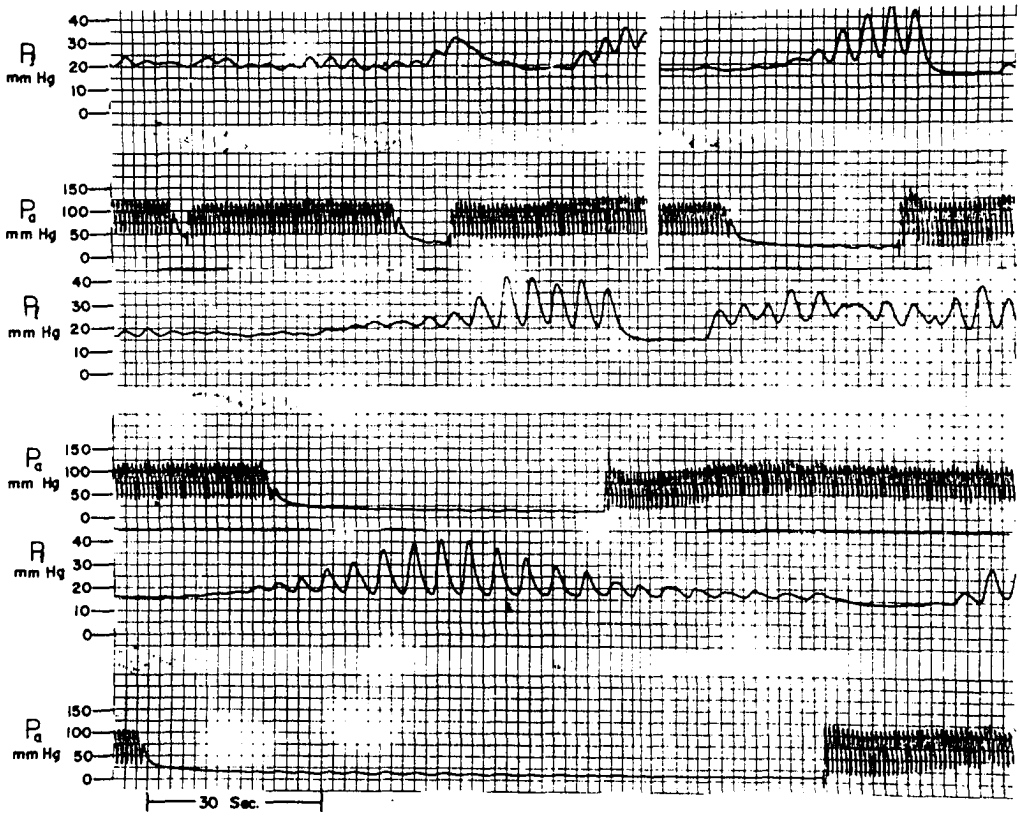

Pf
mm Hg
40
30
20
10
0
Pa
mm Hg
150
100
50
0
Pf
mm Hg
40
30
20
10
0
Pa
mm Hg
150
100
50
0
Pf
mm Hg
40
30
20
10
0
Pa
mm Hg
150
100
50
0
30 Sec.

Figure 17 shows an experiment in which the intestinal muscle did not increase its activity nor did the average lumen pressure rise. In this experiment, in contrast with the results shown in Figure 16, the perfusion pressure after the various periods of ischemia, was much lower than the control value. It is also apparent from the Figure 17 that the magnitude and duration of the hypotension was a function of the length of ischemia.

These two experiments represent the extremes of the responses seen. The usual response was an increase in intestinal activity which was not sufficient to completely abolish the reactive dilation.

Forelimb Vascular Bed

Table I summarizes the effects of various periods of ischemia upon the post-ischemic perfusion pressure response in non-congested and congested forelimbs, both innervated and denervated. In the non-congested limb, the magnitude and duration of the response increased as a function of the length of ischemia. The amount of the reactive response (as measured by either the difference between the brachial artery pressure immediately before and after restarting flow or by the total response expressed in area) was completely abolished (20 and 30 second periods)or greatly attenuated (60 second period) when intraluminal pressure was partially maintained during the period of ischemia. The magnitude of the reactive response in the denervated limbs was less than in the innervated limbs.

Figure 18 shows the results obtained in a typical innervated forelimb. The upper panel shows the effect of a 30 second period of flow interruption with the veins occluded. Sudden interruption of flow

Figure 17. Perfusion pressure (Pa) and ileal lumen pressure (Pl) in one pump perfused preparation before, during and after various intervals of no flow.


30
20
10
0
mm Hg
150
100
50
0
30 Sec.

EFFECT OF ISCHEMIA AND ISCHEMIA PLUS CONGESTION UPON SUBSEQUENT PERFUSION PRESSURE IN THE INNERVATED AND DENERVATED FORELIMB

	Non-Congested					Congested				
Time	n	BA[1]	BA[2]	BA[3]	A[4]	n	BA[1]	BA[2]	BA[3]	A[4]
sec		mm Hg	mm Hg	mm Hg	sq mm		mm Hg	mm Hg	mm Hg	sq mm
					Innervated					
20	10	115	37	96	-105	10	115	67	125	- 1
30	27	124	27	97	-234	36	129	59	138	+ 2
60	4	141	41	114	-393	4	140	70	152	-45
					Denervated					
20	6	98	32	75	- 48	6	98	68	115	+13
30	6	104	26	83	- 87	6	102	58	110	+ 2
60	3	136	32	108	-185	3	134	59	134	-13

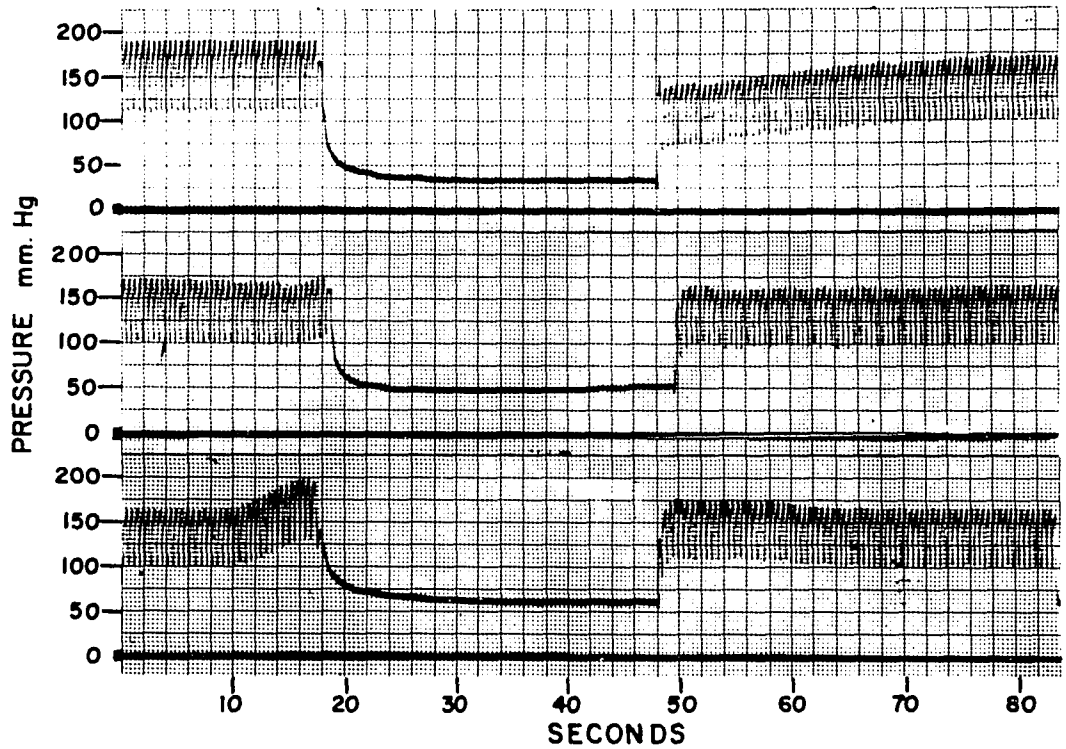
[1]Brachial arterial pressure with flow of 76 ml/min.

[2]Brachial arterial pressure with flow interrupted.

[3]Brachial arterial pressure immediately after restarting flow.

[4]Response expressed as area.

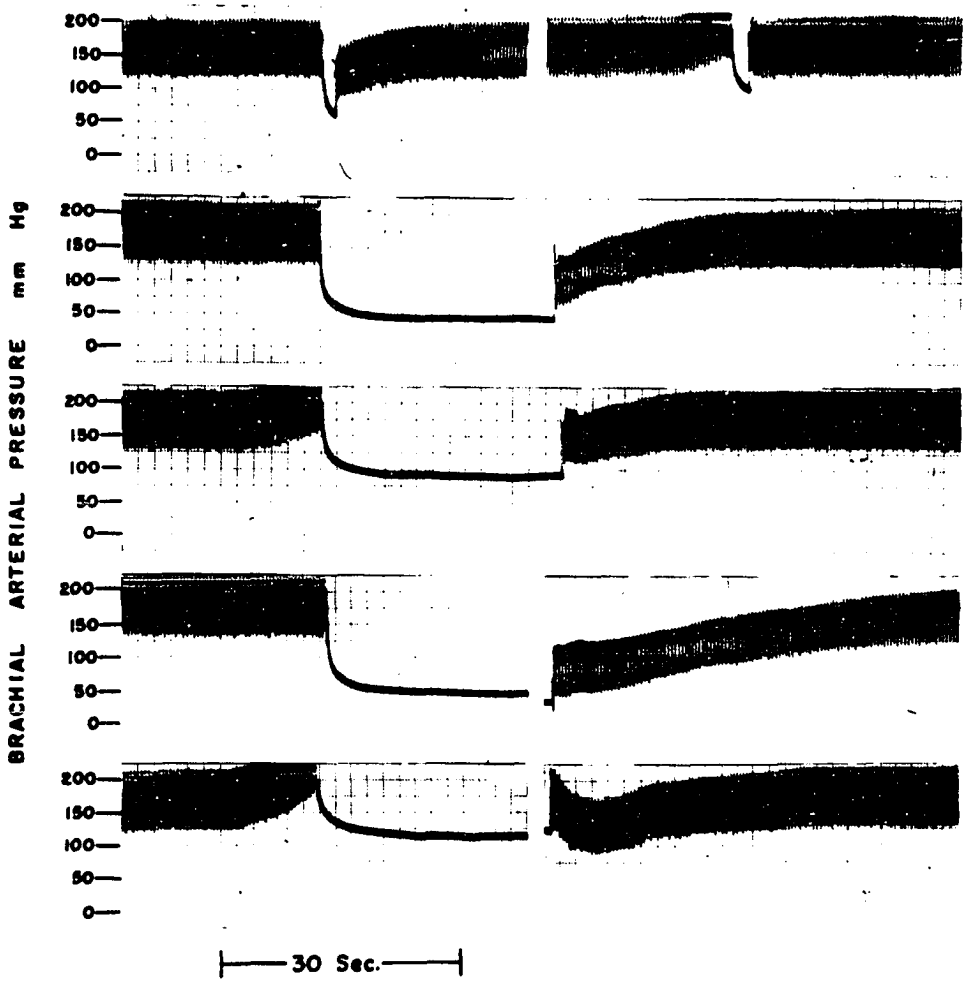
Figure 18. Effect upon brachial perfusion pressure of interrupting arterial inflow for 30 seconds (upper panel). The second and third trials were with the vascular bed packed, at two different levels, with blood. Packing was accomplished by occluding the venous outflow shortly before stopping inflow. See text for details.


PRESSURE mm. Hg
200
150
100
50
0
200
150
100
50
0
200
150
100
50
0
10
20
30
40
50
60
70
80
SECONDS

caused the perfusion pressure to fall from a mean of 150 mm Hg to 33 mm Hg. Immediately upon re-establishing flow at the same rate perfusion pressure was only 100 mm Hg and then gradually returned to control. The second panel demonstrates the same maneuver in the presence of a slight increase in the intraluminal pressure during the period of occlusion. In this trial, the veins were occluded four seconds prior to interruption of flow, thus trapping 5 ml of blood in the forelimb. As a result, intraluminal pressure fell to only 47 mm Hg, 14 mm Hg higher than the previous trial, and upon simultaneously releasing the veins and re-establishing flow, the brachial pressure was essentially the same as before stopping the pump. The lower panel demonstrates the effect of a greater degree of vascular packing. This time the veins were occluded six seconds before interrupting flow, trapping 7.6 ml of blood in the vascular bed. As a result, intraluminal pressure fell to only 60 mm Hg, 27 mm Hg more than control, and upon simultaneously releasing venous occlusion and re-establishing flow the brachial perfusion pressure was actually 10 mm Hg higher than control.

Figure 19 shows this response in another typical experiment. However, in this experiment, the diversion system, as described in the 'Methods' (Figure 3), was used to minimize any possible artifact produced by the blood that had remained static in the pump head during the period of occlusion. The upper panel in Figure 19 shows the effect of a very brief period of ischemia. When brachial artery inflow was stopped for two seconds, by diverting all of the blood into the femoral artery, perfusion pressure gradually returned to the control value in about 16 seconds. The magnitude and duration of the post-ischemic

Figure 19. Effect upon brachial perfusion pressure of stopping flow for 2 seconds (upper panel), 30 seconds (2nd and 3rd panels), and 120 seconds (4th and 5th panels). The second, fourth, and sixth trials were with the vascular bed packed with blood. The diversion systems (Figure 3) was utilized to interrupt flow to the forelimb.


BRACHIAL ARTERIAL PRESSURE mm Hg
200
150
100
50
0
30 Sec.

hypotension progressed with the duration of the ischemia (panels 2 and 4, Figure 19). When venous outflow was interrupted several seconds before interrupting arterial inflow, thus packing the vascular bed with blood, the post-ischemic hypotension was completely abolished in the two second trial (upper right panel, Figure 19) but only partially abolished in the 30 second (panel 3, Figure 19) and two minute trials (panel 5, Figure 19).

Effect of Elevation of Venous Pressure Upon Resistance to Blood Flow Through Various Systemic Vascular Beds

Ileal Vascular Bed

Elevation of venous pressure during natural perfusion of the ileal section had, on the average, little effect upon resistance to flow. The average effect is graphically shown in Figure 20. Elevation of venous pressure from 7 to 21 mm Hg caused a reduction in the pressure gradient from 76 to 62 mm Hg and in the venous outflow from 15.5 to 12.3 gm/min. Therefore, calculated resistance remained essentially unchanged (going from 6.28 to 6.10 mm Hg/gm/min). In 6 of 13 experiments resistance increased upon elevation of venous pressure (Figure 21). In 5 of 13 experiments resistance decreased upon elevation of venous pressure (Figure 22). In the two remaining experiments, resistance was not affected.

The findings were similar in the pump-perfused preparation. Figure 23 shows that, on the average, elevation of venous pressure from 11 to 28 mm Hg, at constant flow, produced an almost equal rise in perfusion pressure (from 113 to 134 mm Hg). Average calculated resistance remained essentially unchanged, increasing in 5 of 10 experiments, decreasing in 2 of 10, and not changing in 3 of 10 experiments.

Figure 20. Average effect in 13 animals of elevation of venous pressure upon ileal perfusion pressure, ileal blood flow, and calculated ileal vascular resistance.

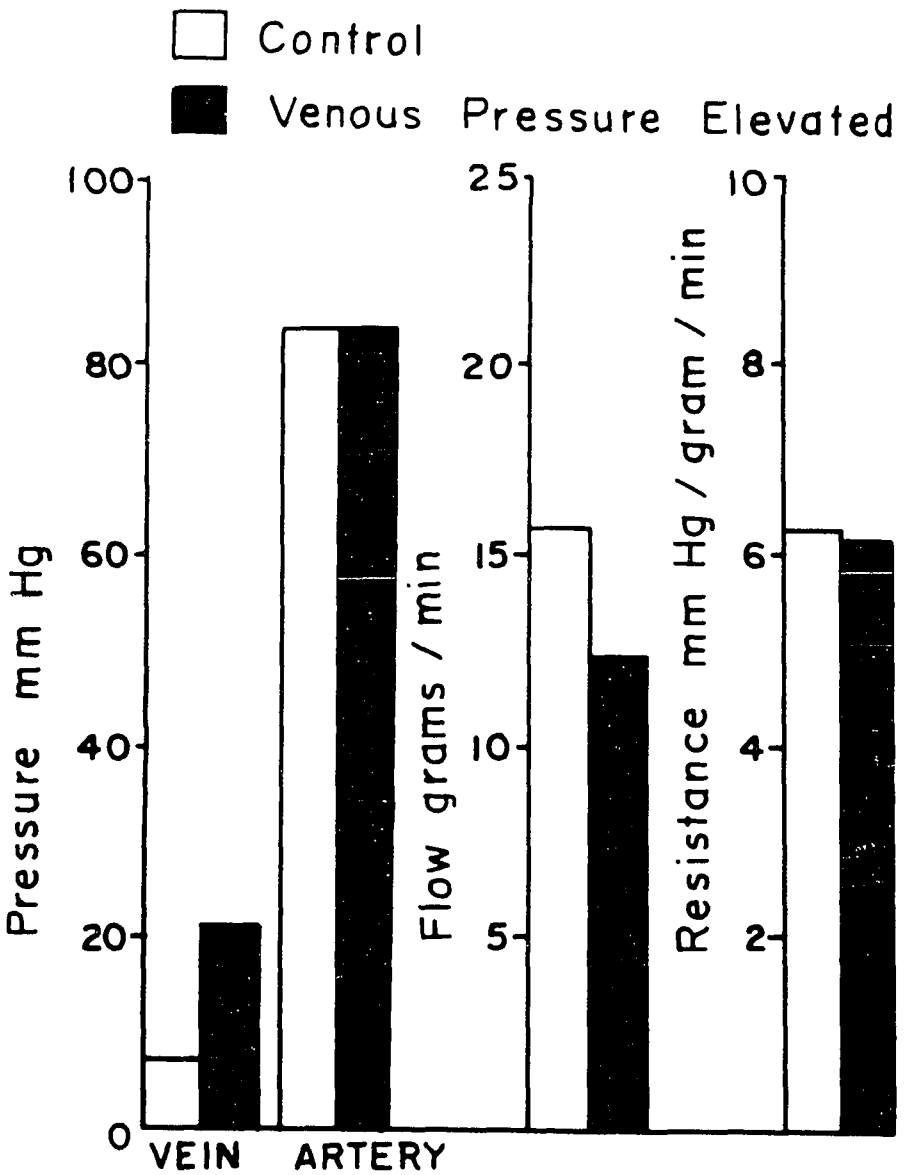

Control
Venous Pressure Elevated
Pressure mm Hg
100
80
60
40
20
0
Flow grams / min
25
20
15
10
5
Resistance mm Hg / gram / min
10
8
6
4
2
VEIN
ARTERY

Figure 21. Effect in one animal of elevation of venous pressure upon ileal perfusion pressure, ileal blood flow, and calculated ileal vascular resistance.

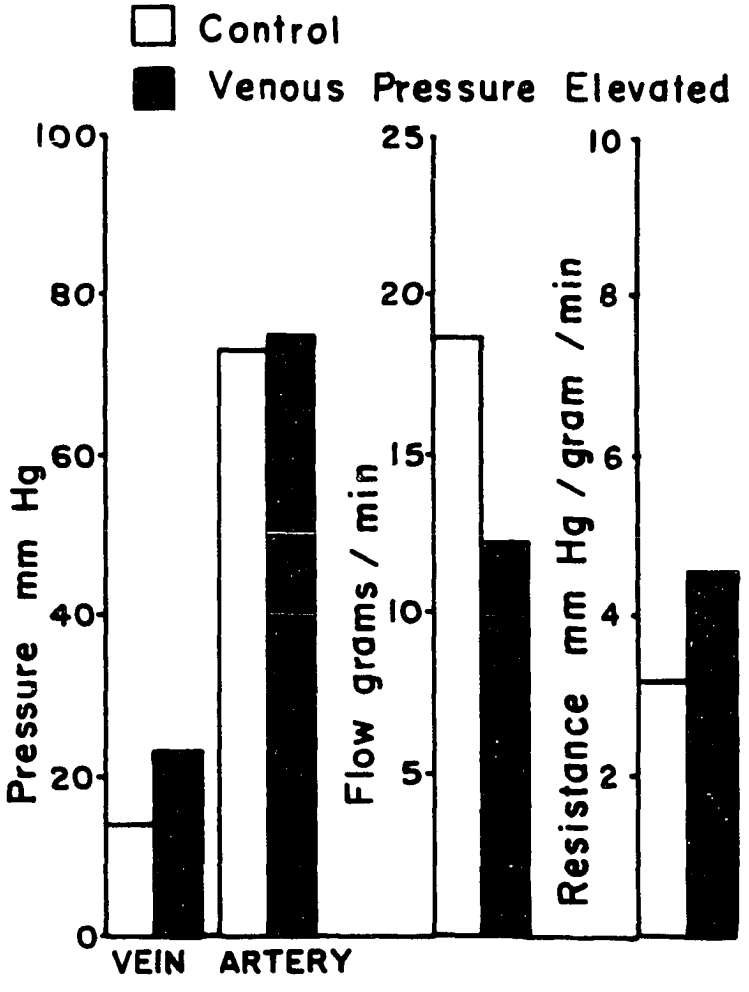

Control
Venous Pressure Elevated
Pressure mm Hg
100
80
60
40
20
0
VEIN
ARTERY
Flow grams / min
25
20
15
10
5
Resistance mm Hg / gram / min
10
8
6
4
2

Figure 22. Same as Figure 21, except in another animal.

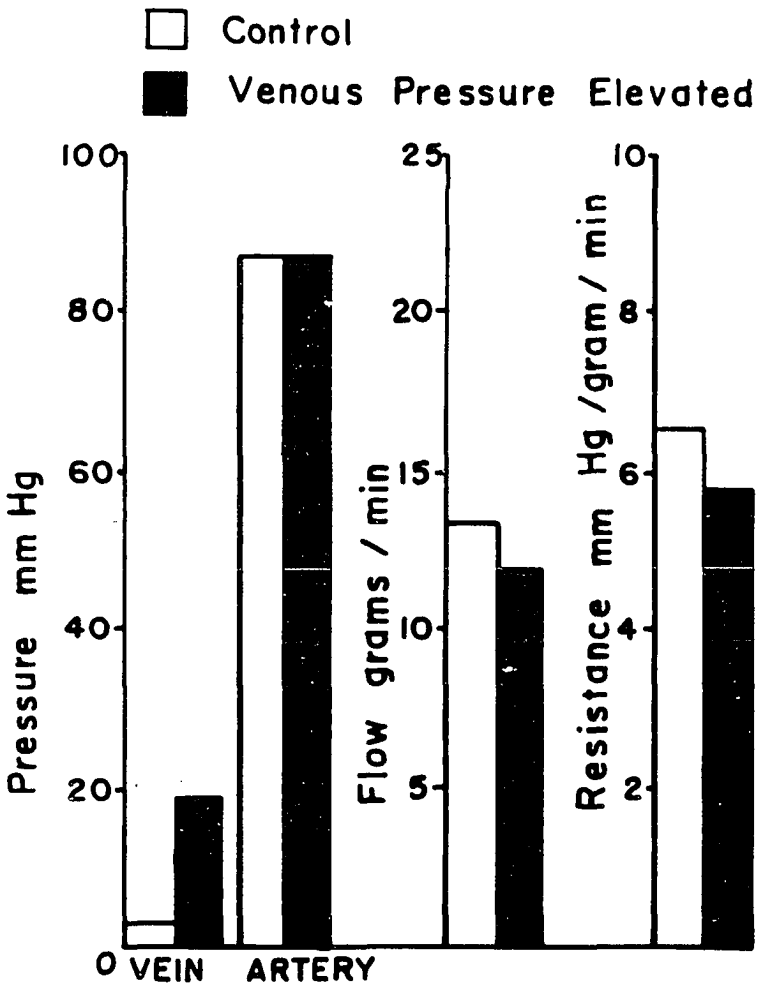
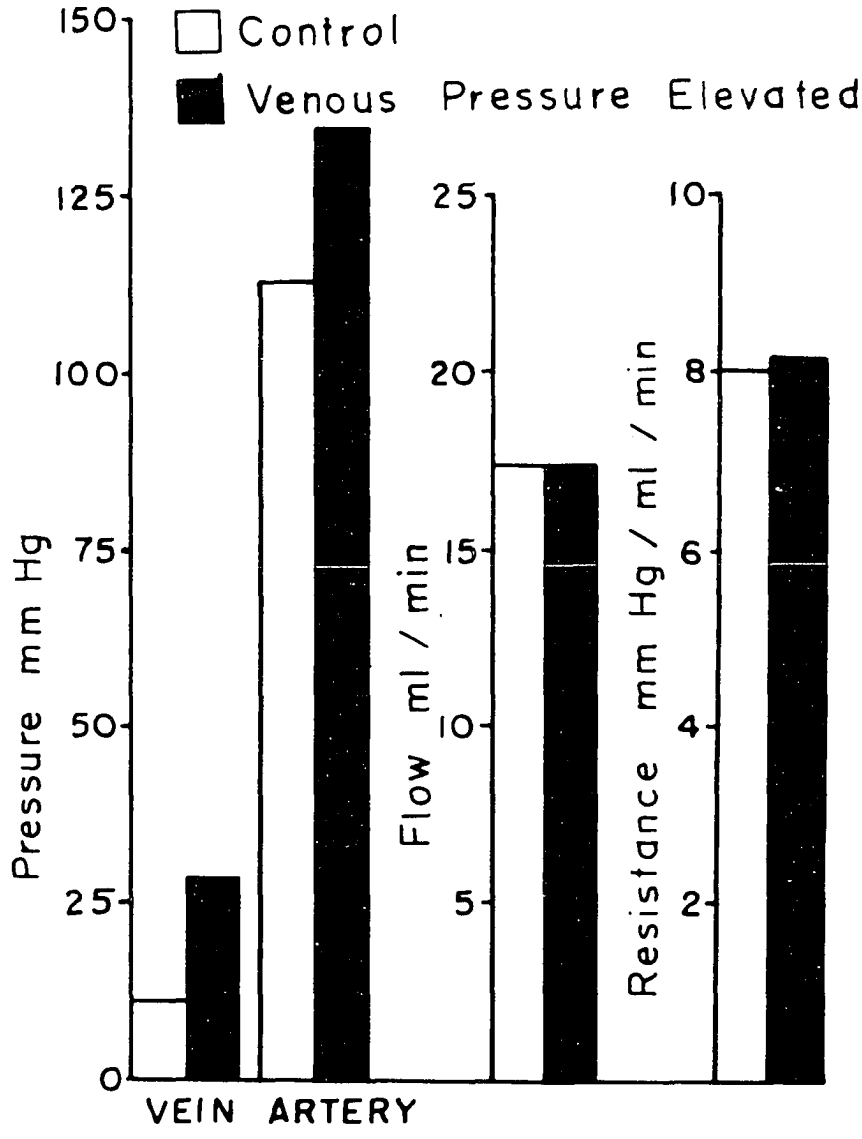

Control
Venous Pressure Elevated
Pressure mm Hg
100
80
60
40
20
0
VEIN
ARTERY
Flow grams / min
25
20
15
10
5
Resistance mm Hg / gram / min
10
8
6
4
2

Figure 23. Average effect in ten animals of elevation of venous pressure, at constant blood flow upon ileal perfusion pressure and calculated vascular resistance.


Control
Venous Pressure Elevated
150
125
100
75
50
25
0
Pressure mm Hg
25
20
15
10
5
Flow ml / min
10
8
6
4
2
Resistance mm Hg / ml / min
VEIN
ARTERY

Renal Vascular Bed

Figure 24 presents the average effects in 10 experiments upon aortic pressure, renal blood flow, renal vascular resistance, and renal venous blood PO_2 of elevating renal venous pressure from 6 to 28 mm Hg. This maneuver had no effect upon aortic pressure and produced only a very slight decrease in renal venous blood oxygen tension (going from 61 to 60 mm Hg). Average renal blood flow was reduced from a control value of 223 to 195 ml/min. However, because the perfusion pressure gradient fell proportionately more (98 mm Hg to 77 mm Hg) than blood flow, calculated resistance fell during the procedure. Restoration of venous pressure to the control value produced an immediate reversal, toward control, of the other parameters.

Forelimb Vascular Bed

Table II presents the effects, in 21 experiments, of elevation of venous pressure upon the innervated forelimb vascular bed of the dog perfused at a constant flow. On the average, elevation of forelimb venous pressure by 25 mm Hg produced a rise in small vein pressure of 24 mm Hg, an increase in small artery pressure of 26 mm Hg and an increase in brachial pressure of 25 mm Hg. Therefore, at constant flow, resistance to flow through the entire vascular bed, as well as through the arteries, remained constant. Small vessel resistance increased slightly, while resistance to flow through the veins was slightly decreased. The maneuver was repeated in 17 of the above animals after denervation of the forelimb and resistance to flow through all the vascular segments was affected irregularly.

Figure 24. Average effects in ten animals of elevation of renal venous pressure (V) upon aortic pressure (A), renal venous outflow (F_V), calculated renal vascular resistance (R), and renal venous blood oxygen tension (P_{VO_2}). Only steady state values are presented.

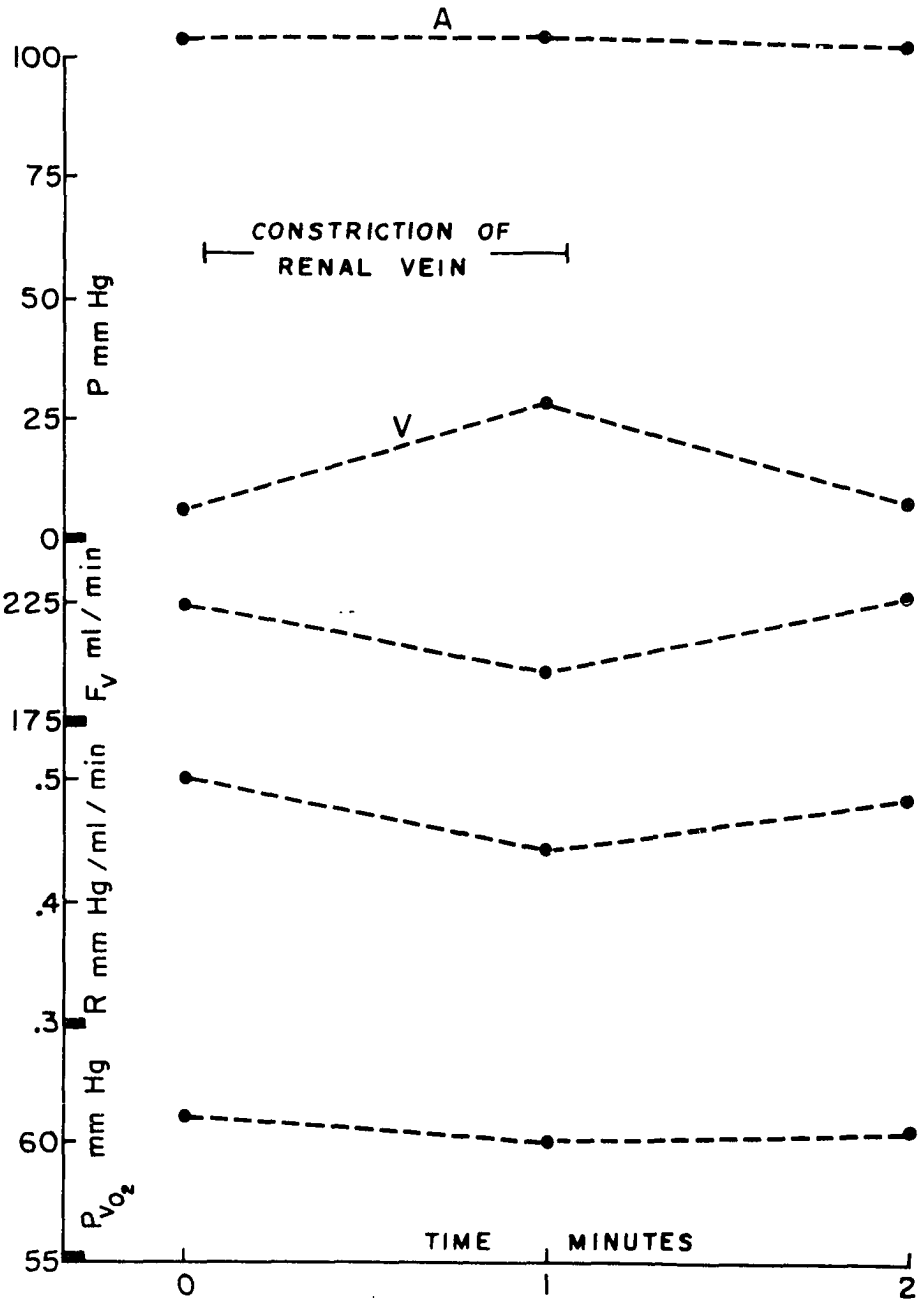

A
100
75
CONSTRICTION OF
RENAL VEIN
50
P mm Hg
25
V
0
225
F_V ml / min
175
.5
R mm Hg / ml / min
.4
.3
mm Hg
60
P_{VO_2}
55
TIME
MINUTES
0
1
2

TABLE II

EFFECT OF ELEVATION OF VENOUS PRESSURE AT CONSTANT FLOW UPON BRACHIAL ARTERY, SMALL ARTERY, SMALL VEIN AND CEPHALIC VEIN PRESSURES IN THE INNERVATED DOG FORELIMB

	Control				Elevated Vein Pressure			
Blood Flow ml/min	P_{CV}	P_{SV}	P_{SA}	P_{BA}	P_{CV}	P_{SV}	P_{SA}	P_{BA}
100	10.5	13.5	87	103	26.5	28.5	117	135
100	9.0	17.5	74	109	15.0	22.5	78	114
100	12.0	15.0	53	82	25.0	28.0	64	93
150	8.5	13.5	68	93	29.0	32.0	83	117
100	4.0	6.0	115	138	34.0	35.0	135	158
76	8.5	10.5	150	175	36.0	38.0	175	220
76	16.0	18.0	88	130	42.0	43.0	113	153
76	7.0	9.0	115	150	40.0	41.0	160	190
76	9.5	12.0	85	106	37.0	38.5	114	136
76	7.0	8.0	85	109	28.5	30.0	127	146
76	6.5	9.5	74	104	38.5	42.0	112	140
76	5.5	8.5	111	133	38.0	40.5	145	167
76	6.0	9.0	93	125	35.0	37.0	125	154
100	12.5	15.0	111	146	34.0	36.0	130	162
76	9.5	14.0	55	105	31.5	35.0	73	120
76	7.0	9.0	88	115	33.0	34.0	123	143
76	10.0	12.0	73	120	38.5	40.0	90	138
76	12.0	16.0	123	168	36.0	39.0	140	183
76	16.0	17.0	80	103	37.0	38.0	100	125
76	4.0	6.0	115	138	34.0	35.0	135	158
76	4.0	5.5	95	138	36.0	37.0	160	188
Average	8.8	11.7	93	124	33.6	35.7	119	149

P_{CV} = Cephalic Vein Pressure

P_{SV} = Small Vein Pressure

P_{SA} = Small Artery Pressure

P_{BA} = Brachial Artery Pressure

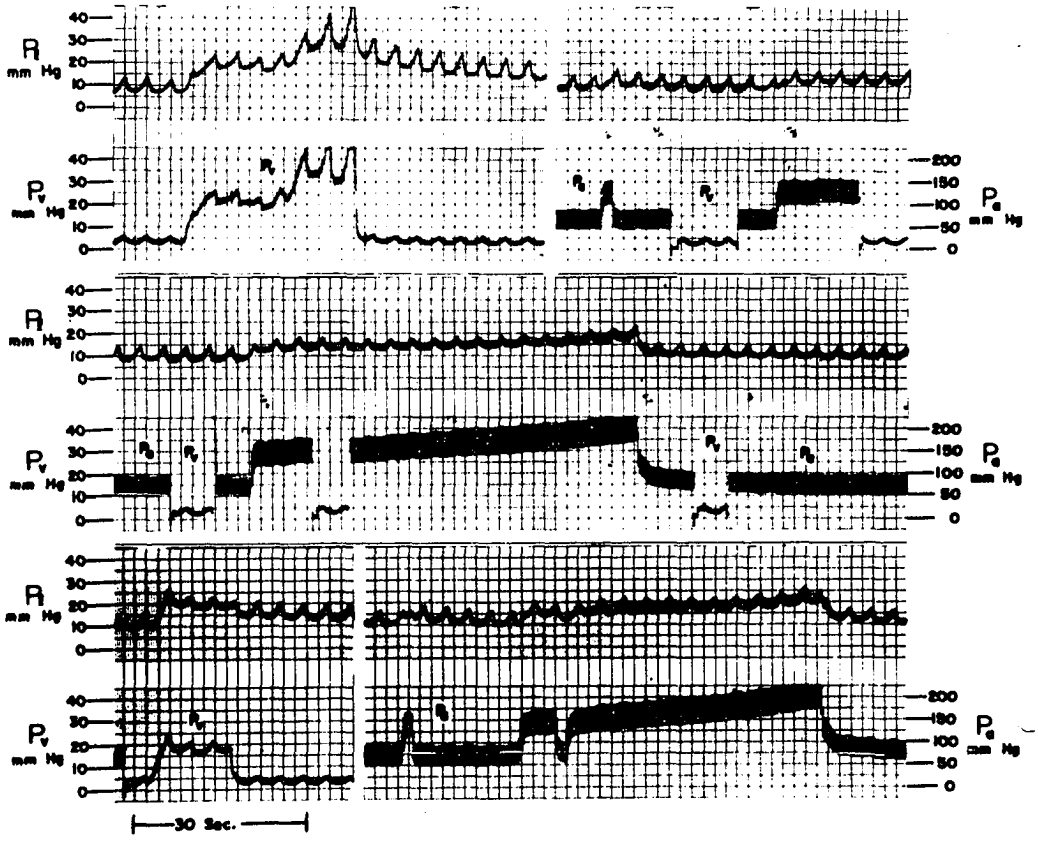
Mechanisms of Local Regulation of Blood Flow

These experiments were designed to yield information relevant to the four mechanisms postulated to explain local regulation of blood flow. Renal lymphatic pressure, forelimb muscle tissue pressure, and ileal lumen pressure were used to assess the role of interstitial pressure in local control of blood flow in the kidney, forelimb, and intestine, respectively. Square wave changes in blood flow were used to assess the role of transmural pressure in local regulation in the limb and kidney. The role of oxygen tension was assessed by comparing the magnitude of renal autoregulation at normal and high arterial oxygen tensions. Diversion of venous blood from an organ undergoing local regulation through an assay organ was used to gain information relevant to the metabolite theory.

Effect of Rapid and Square Wave Changes in Blood Flow Upon Renal and Lymphatic Vessel Pressures and Upon Forelimb Perfusion Pressure

Figure 25 (upper left panel) shows that elevation of renal venous pressure by venous constriction produced an almost equal rise in lymphatic vessel pressure. Upon release of venous constriction lymph pressure fell slowly to control whereas venous pressure immediately fell to control. When renal blood flow was elevated from 57 to 114 ml/min for two seconds (upper right panel) mean arterial pressure rose from 65 to 125 mm Hg and promptly returned to a mean of 65 mm Hg. Lymphatic pressure was hardly affected by the maneuver. When flow was elevated to 114 ml/min and left at that value (upper right panel), renal perfusion pressure rose to 130 mm Hg and lymphatic pressure increased only 2 mm Hg.

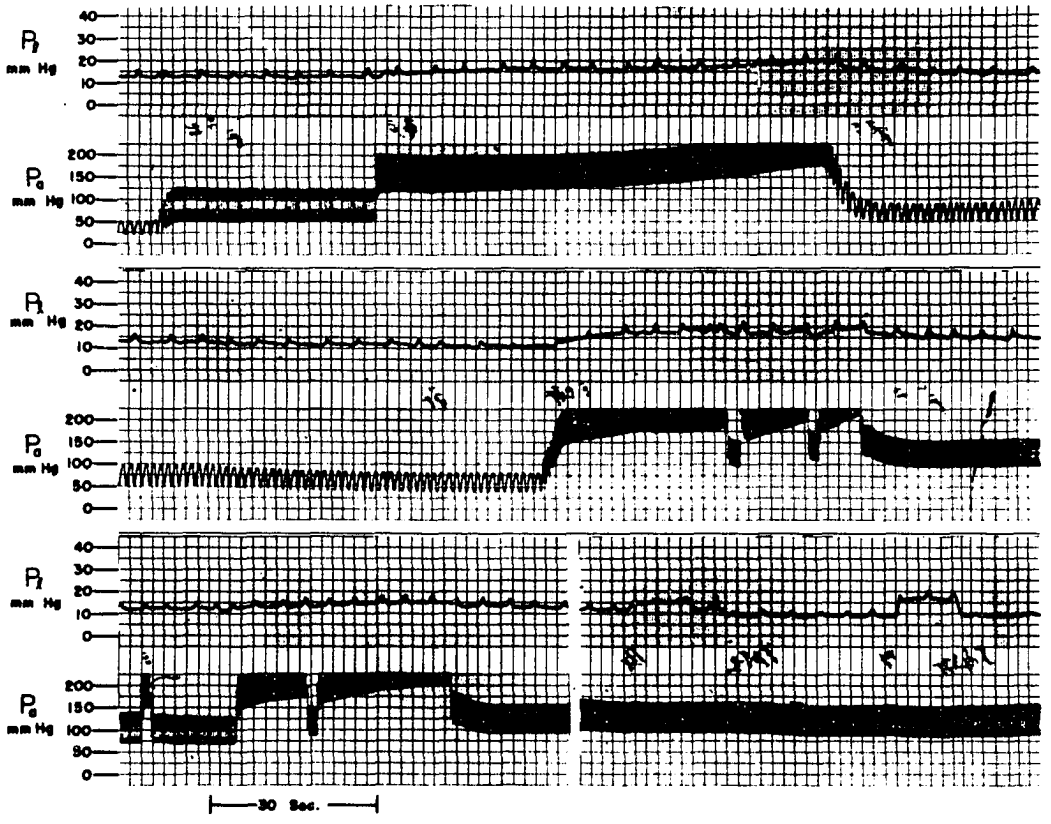
Figure 25. Effects of elevation of renal venous pressure (P_V) at constant blood flow upon hilar lymph vessel pressure (Pl) and of square wave changes in blood flow upon hilar lymph vessel pressure and perfusion pressure (Pa). In each panel, lymph vessel pressure is above and renal venous or perfusion pressure is below. See text for details.


Pa
mm Hg
Pv
mm Hg
40
30
20
10
0
200
150
100
50
0
30 Sec.

Flow elevation of a greater magnitude, 67 to 135 ml/min (middle panel), produced a rise in renal arterial pressure from 75 to 140 mm Hg, not quite in proportion to flow, indicating a slight fall in resistance. Lymphatic pressure rose only 3 mm Hg. Even though flow was held constant at 135 ml/min, perfusion pressure progressively rose (autoregulation) until resistance greatly exceeded the value at the lower flow rate. At the highest perfusion pressure mean lymphatic pressure exceeded the control value by only 9 mm Hg, but there was clearly an increase in lymphatic pulse pressure. Return of flow to 67 ml/min was associated with an immediate fall in lymphatic pressure to control. The rise in lymphatic pulse pressure suggests the lymph vessel remained patent during the flow shifts, and the quick return of lymphatic pressure to control indicates the maneuver was associated with only small changes in interstitial volume. The lower two panels again demonstrate the effects of changes in venous and arterial pressure upon lymphatic pressure.

Figure 26, from another experiment, shows that a square wave elevation of flow from 58 to 116 ml/min (upper panel) produced an immediate rise in perfusion pressure from 85 to 157 mm Hg. Lymphatic vessel pressure rose by only 2 mm Hg. At the new flow perfusion pressure gradually rose to a high level, indicating an increase in resistance, but the lymphatic vessel pressure rose only an additional 5 mm Hg. When flow was rapidly decreased to a low value (upper panel), perfusion pressure, after an initial fall, transiently rose and then progressively fell (middle panel) to a new steady state. The gradual fall in pressure indicates a fall in resistance, a change which occurred in the presence of a 2 mm Hg fall in lymphatic pressure. Flow was then increased rapidly

Figure 26. Effects of change in renal blood flow and external compression (3rd panel, right side) at constant flow, upon hilar lymph vessel pressure and perfusion pressure. In each panel, lymph pressure is above and perfusion pressure is below. See text.


P_f
mm Hg
40
30
20
10
0
P_a
mm Hg
200
150
100
50
0
30 Sec.

to 133 ml/min. Mean perfusion pressure rose to 185 mm Hg and then progressively rose even higher. Lymphatic pressure rose only 6 mm Hg and was little affected by square wave halving of blood flow. The same maneuver was repeated with the same results (lower left panel). Slight external pressure applied on the surface of kidney raised lymphatic pressure (lower right hand panel). This manuever was often used to test the patency of the lymphatic cannula.

Figure 27 is a continuation of the same experiment and again demonstrates the effect of elevation venous pressure on lymph vessel pressure (upper left panel). A square wave doubling of renal flow for two seconds (upper right panel) was associated with an immediate increase in perfusion pressure which did not return quite to the control immediately upon reduction of flow. The maneuver hardly affected lymphatic pressure. When flow was doubled and left at the high value (middle panel) perfusion pressure gradually increased, again indicating an increase in resistance. Lymphatic was increased by only 6 mm Hg. Elevation of venous pressure (lower panel) by 15 mm Hg produced a 20 mm Hg increase in perfusion pressure, indicating a rise in resistance to flow through the kidney. Lymph pressure rose 9 mm Hg. This maneuver produced greater increases in renal resistance in other experiments.

Figure 28 shows that a two second square wave doubling of renal blood flow from 46 to 92 ml/min (upper left panel) produced an immediate rise in perfusion pressure which was partially maintained for 14 seconds after flow was returned to 46 ml/min. There was no change in lymph vessel pressure during the maneuver. This type of response was seen in several other preparations. The middle panel shows the effects of

Figure 27. Continuation of the experiment shown in Figure 26, showing the effects of elevation of renal venous pressure at constant flow and of square-wave changes in blood flow upon hilar lymph vessel pressure and perfusion pressure. See text.

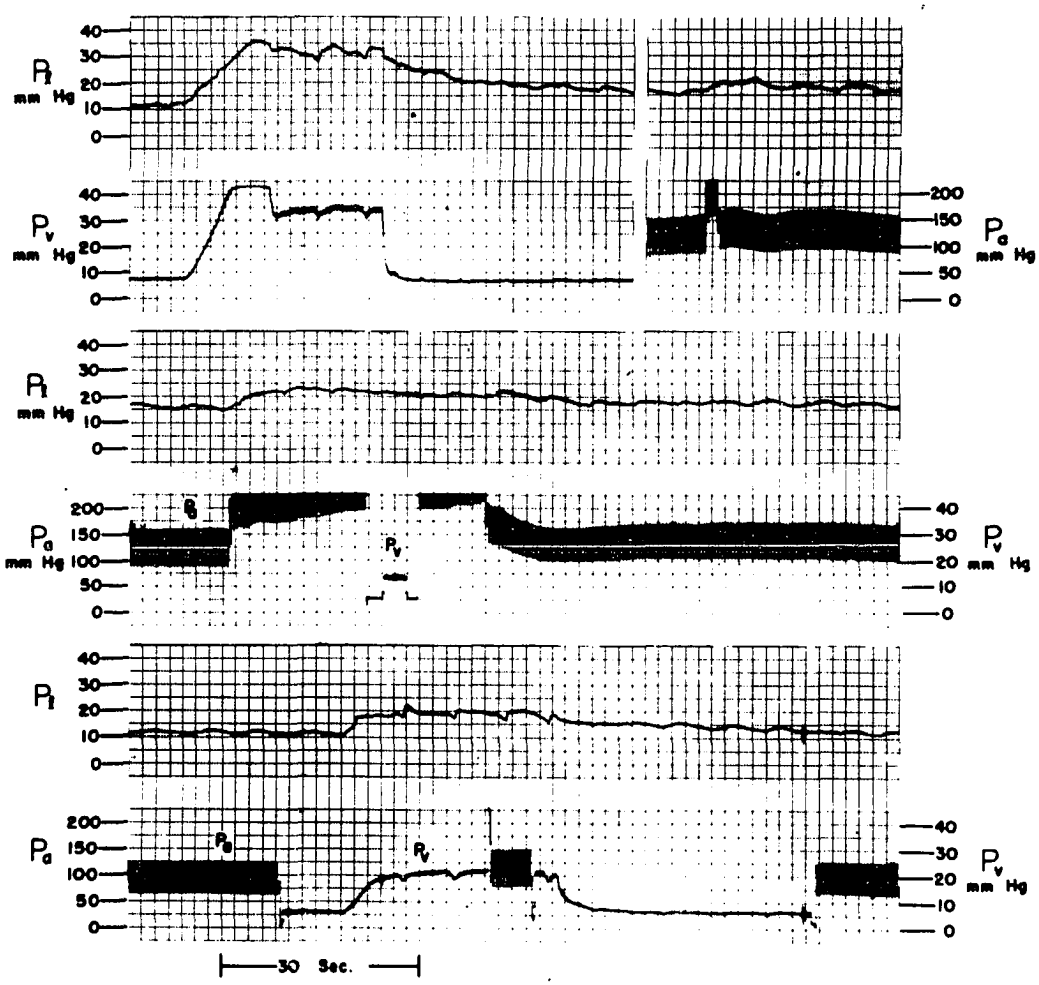
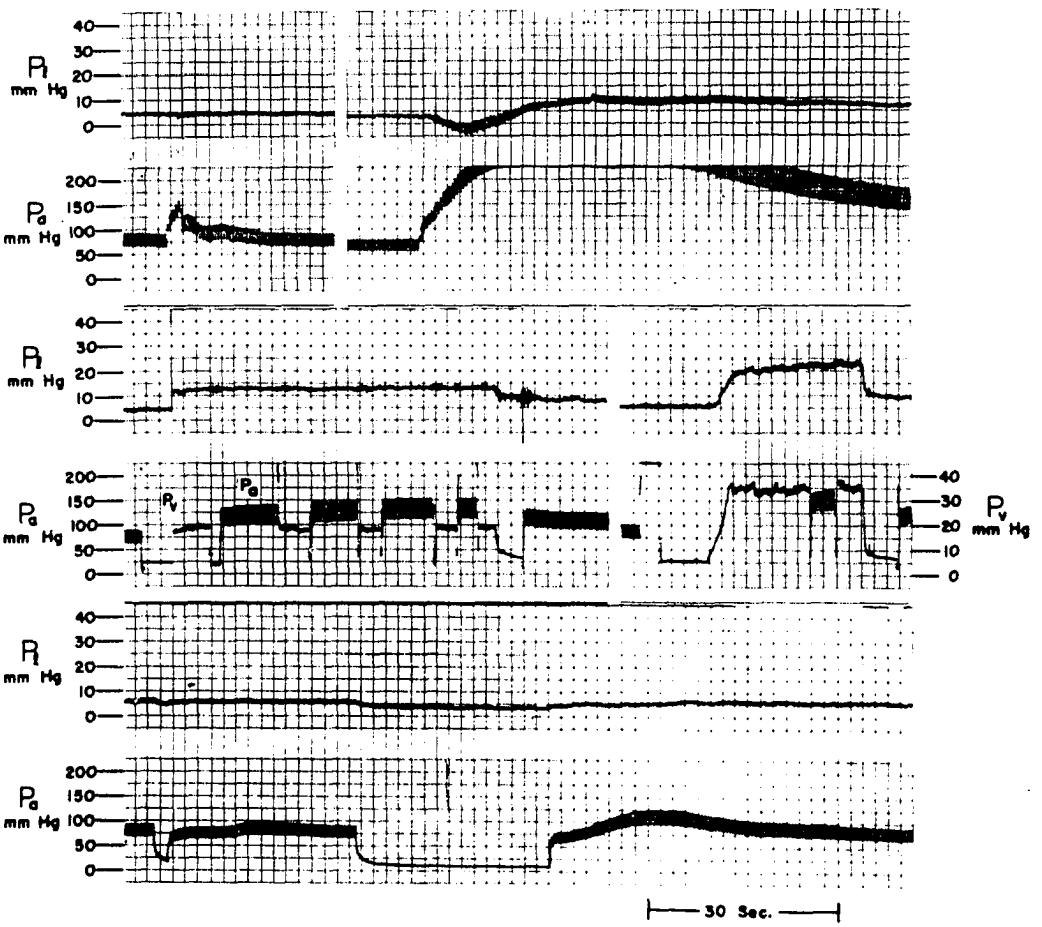

P_t mm Hg
40
30
20
10
0
P_v mm Hg
200
150
100
50
P_a mm Hg
P_a
P_v
30 Sec.

Figure 28. Effect of transient and prolonged (square-wave) changes in flow upon lymphatic vessel pressure, renal vein pressure, and perfusion pressure. Middle panel shows effect of venous pressure elevation upon lymphatic pressure and perfusion pressure. Lower panel shows effects of interruption of renal inflow for 2 seconds and 30 seconds upon lymph vessel pressure and perfusion pressure. See text.


P_f mm Hg
40
30
20
10
0
P_a mm Hg
200
150
100
50
0
P_f mm Hg
40
30
20
10
0
P_a mm Hg
200
150
100
50
0
P_v
P_e
40
30
20
10
0
P_v mm Hg
P_f mm Hg
40
30
20
10
0
P_a mm Hg
200
150
100
50
0
30 Sec.

elevation of renal venous pressure at constant flow upon lymphatic vessel and perfusion pressure. In both trials elevation of venous pressure produced a greater than proportionate increase in perfusion pressure, indicating a rise in resistance. When arterial inflow to the kidney was interrupted for 30 seconds (lower panel), perfusion pressure immediately upon re-establishment of flow was lower than the pre-occlusion level and progressively increased to control. However, unlike the response in the limb, the pressure continued to climb until resistance was much higher than the control. Lymph pressure fell only 2 mm Hg during the period of ischemia, and returned to control upon re-institution of blood flow.

Figure 29 shows a 30 second period of renal ischemia (upper panel) in another experiment. Perfusion pressure immediately upon re-establishment of flow was lower than control and progressively returned only to the control level. Lymphatic pressure increased slightly during the ischemic period. This was not a typical response, usually lymphatic pressure fell slightly during ischemia. The middle panel shows the effect of 1 μg of epinephrine injected as a bolus into the renal perfusion system. Perfusion pressure rose to over 200 mm Hg but lymphatic pressure was increased by only 4 mm Hg. The lower left panel depicts the effects produced by close arterial injection of 2.5 μg acetylcholine. Again, there was no relation between perfusion pressure and lymphatic pressure.

Figure 30 shows the relationships in five kidneys of lymphatic pressure to venous pressure and to arterial pressure. On the average, a one mm Hg rise in mean perfusion pressure produced by increasing flow,

Figure 29. Effect of interruption of blood flow (upper panel), injection of 1 μg epinephrine(middle panel), injection of 2.5 μg acetylcholine (lower panel, left) and venous pressure elevation (lower panel, right) upon renal perfusion pressure (Pa), lymph vessel pressure (Pl) and renal venous pressure (Pv). See text.

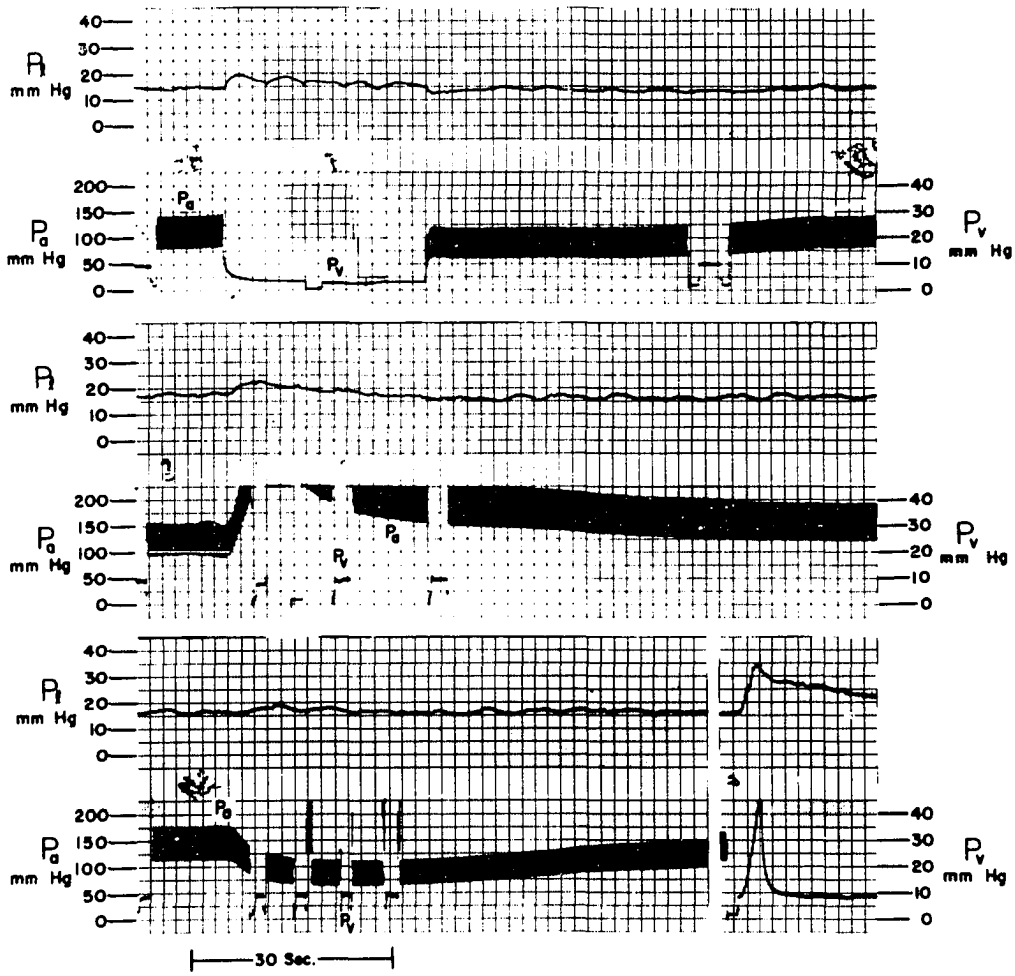
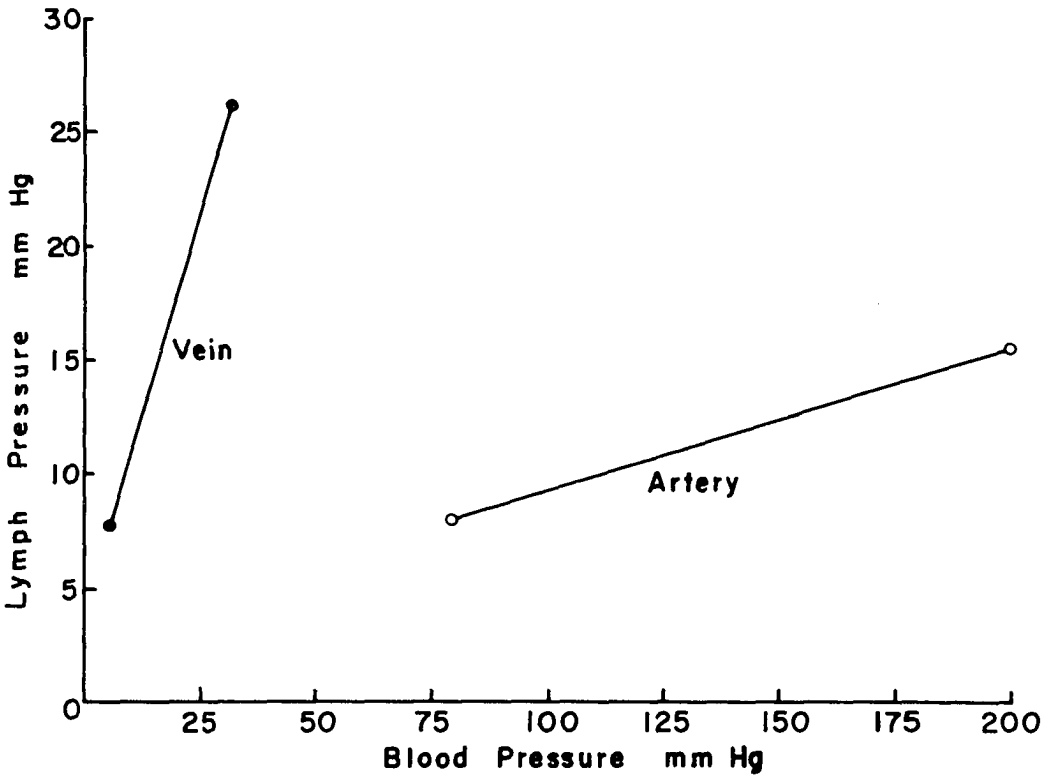

P_f mm Hg
40
30
20
10
0
P_a mm Hg
200
150
100
50
0
P_a
P_v
P_v mm Hg
40
30
20
10
0
30 Sec.

Figure 30. Relationship of lymphatic vessel pressure to renal artery pressure and to renal vein pressure. Each value is the average of five animals.


30
25
20
15
10
5
0
Lymph Pressure mm Hg
Vein
Artery
25
50
75
100
125
150
175
200
Blood Pressure mm Hg

raised lymphatic vessel pressure by 0.07 mm Hg. A one mm Hg rise in venous pressure produced an increase in lymphatic vessel pressure of 0.6 mm Hg. Hence, over the ranges studied, venous pressure had ten times the effect of arterial pressure.

The effects of square wave changes in blood flow upon the forelimb vasculature are shown in Figure 31. With a clamp at B (Figure 3) forelimb flow was halved by simultaneously clamping at A and C. This trapped a column of blood in the pump head and subjected it to the repeated action of the pump fingers. This maneuver produced a vasoactive substance which upon release dilated the forelimb vasculature (Figure 31, upper panels). (This same substance produced renal vascular constriction) The artifact was circumvented by simultaneously adjusting clamps at points A and D (described in 'Methods'). The effect of a square wave doubling of flow to the forelimb is shown in Figure 31 (lower left panel). Perfusion pressure immediately fell and upon restablishment of flow pressure gradually returned to control.

A square wave halving of flow rate produced a large rapid fall in perfusion pressure followed by a small slow rise in pressure (Figure 32, upper panel). The small slow rise in pressure was minimal or absent if flow was halved after being at the original value for only one or two seconds (Figure 32, middle left panel). After flow had been at the lower value for a period of time, return of flow to the original value produced a sharp rise in pressure to a level slightly in excess of the control value followed by a gradual fall to the control value (Figure 5, upper panel). Conversely, return of flow to the original value after flow had been halved for only one or two seconds produced a gradual

Figure 31. Effect upon perfusion pressure of prolonged and transient square-wave changes in flow rate produced by two different methods. Demonstration of a vasodilator substance in damaged blood. Upper panel left. With A, C, and B, clamped (Figure 3) and pump operating on the column of blood between A and C, A and C were simultaneously unclamped. Upper panel right with B clamped, A and C were simultaneously clamped and, after four seconds, unclamped. Lower panel left. Site A unclamped and site B clamped simultaneously, thus diverting flow away from femoral artery and into forelimb. Lower panel right. Site A clamped and site B unclamped and, after two seconds, A unclamped and B clamped.

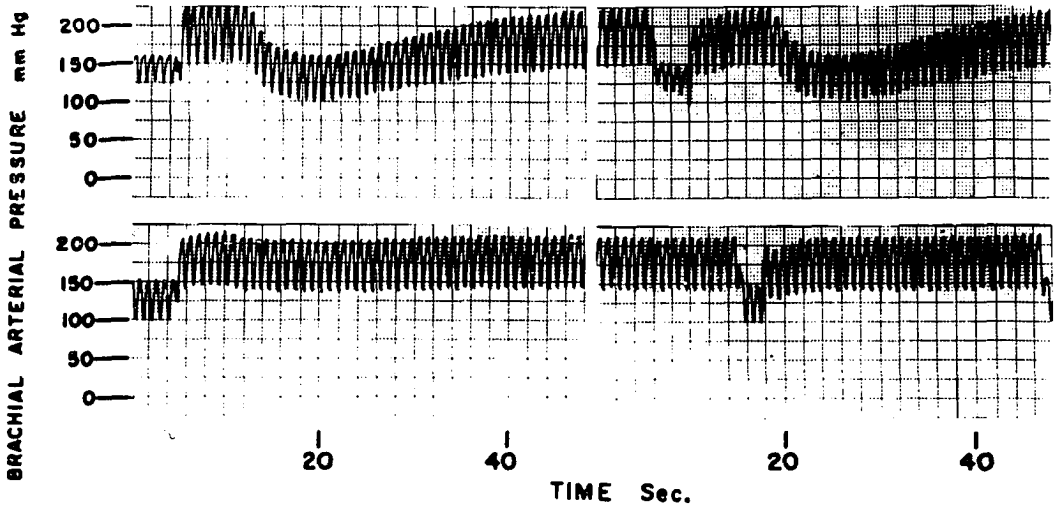
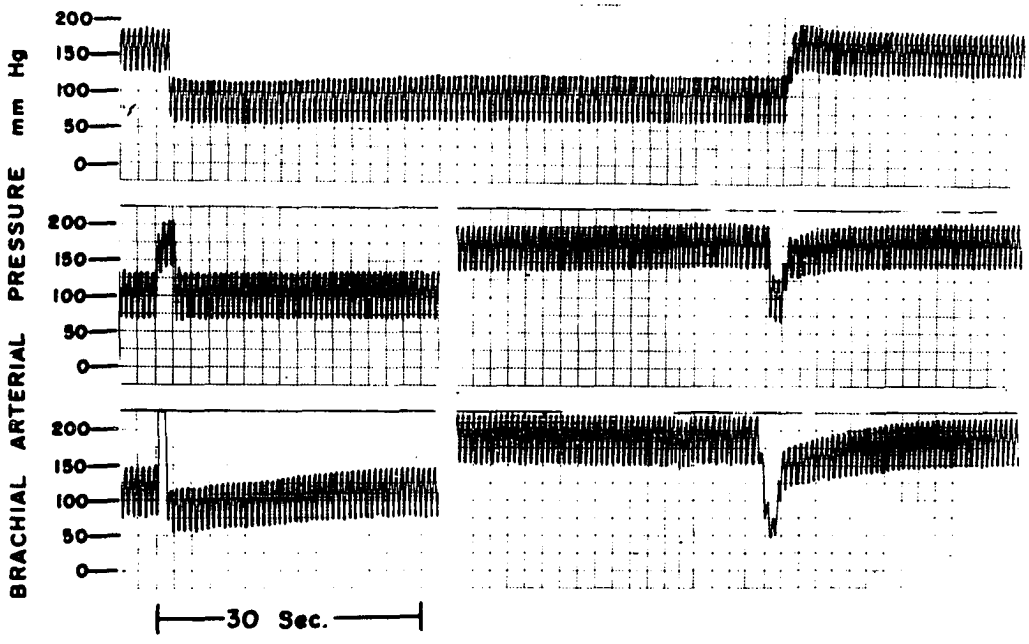

BRACHIAL ARTERIAL PRESSURE mm Hg
200
150
100
50
0
200
150
100
50
0
20
40
20
40
TIME Sec.

Figure 32. Effect upon perfusion pressure of prolonged and transient square wave changes in flow rate produced by two different methods. Upper two panels. The diversion method described in Figures 3 and 31. Lower panel. Injection and withdrawal of blood with a syringe and large bore needle from the perfusion system between pump and limb. See text


BRACHIAL ARTERIAL PRESSURE mm Hg
200
150
100
50
0
30 Sec.

increase in pressure which did not overshoot the control value (Figure 32, middle right panel).

Figure 32 (lower left panel) shows the effect of rapid injection of blood from a syringe into the perfusion tubing. Pressure immediately rose with the injection, fell well below control, and then gradually returned to control.

The lower right panel shows the effect of rapid withdrawal of blood from the perfusion tubing. Perfusion pressure fell as blood was withdrawn and then gradually returned to the control.

Effect of Oxygen Tension Upon the Response of the Renal Vascular Beds To Altered Perfusion Pressure and Upon Renal Vascular Resistance

The effect of O_2 tension upon renal autoregulation was studied in a series of ten animals. Figure 33 shows the effect of renal artery constriction on renal venous pressure, renal blood flow, renal vascular resistance and renal venous O_2 tension. The same animals were then ventilated with 100% O_2 just prior to constriction of the renal artery (Figure 34). Renal blood flow fell but the fall in pressure was out of proportion to the fall in flow. Calculated resistance therefore decreased. Ventilation with 100% O_2 completely prevented the fall in renal venous PO_2. Indeed, the O_2 tension rose well above the control value during the maneuver. Hence, ventilation with oxygen failed to alter the response.

Figure 35 shows the effect (average of ten animals) of ventilation with 100% oxygen on the same variables without renal artery constriction. The only parameter that was measurably affected was renal venous blood oxygen tension which rose to over 130 mm Hg.

Figure 33. Average effect in ten animals of renal artery constriction (Pa) upon renal venous pressure (Pv) calculated renal vascular resistance (R), renal venous blood oxygen tension (P_{vO_2}) and renal venous blood pH (pH_v). Steady state values given for all values except P_{vO_2}.

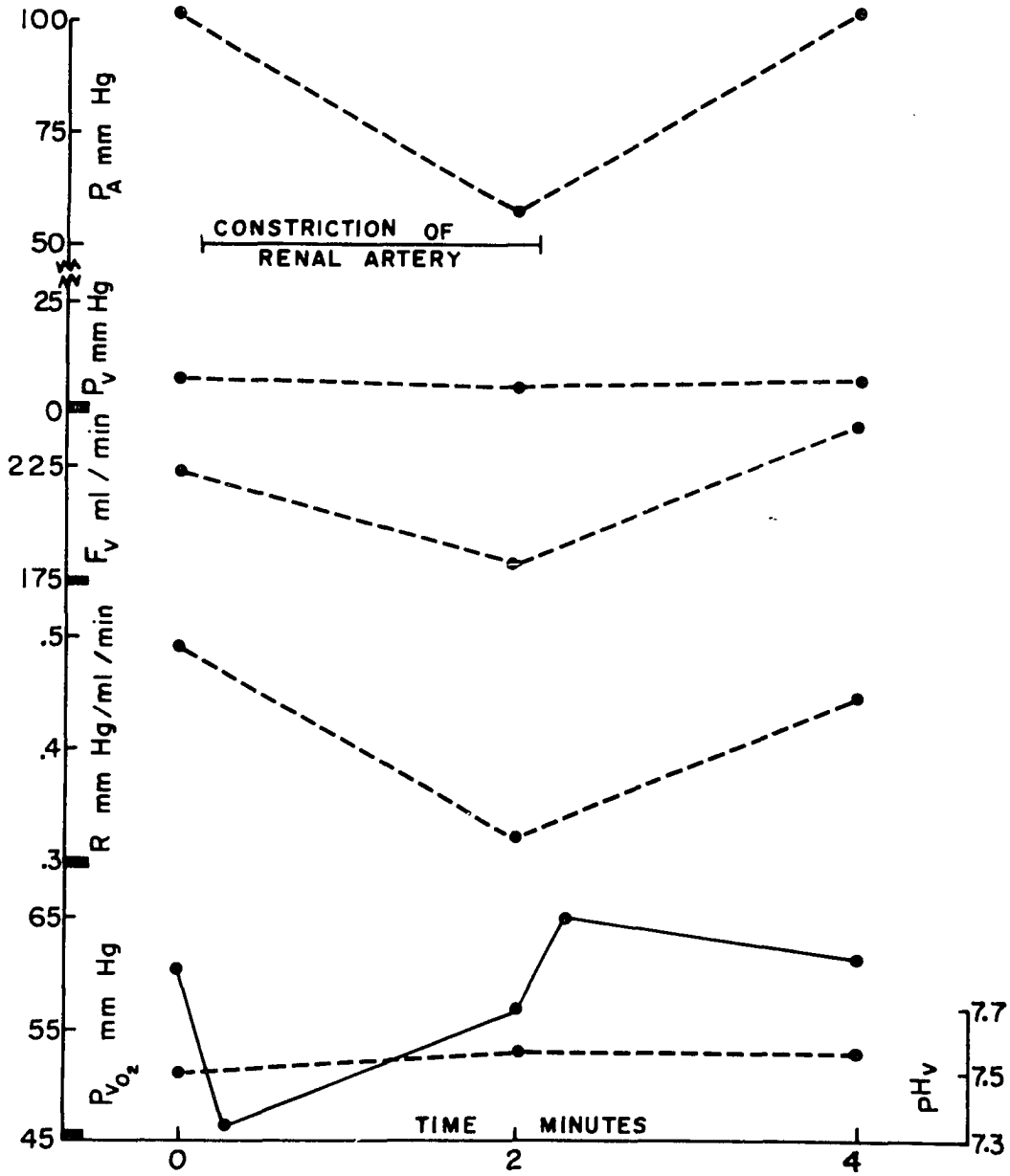

100
75
50
25
0
225
175
.5
.4
.3
65
55
45
P_A mm Hg
P_V mm Hg
F_V ml / min
R mm Hg/ml /min
P_{VO_2} mm Hg
CONSTRICTION OF
RENAL ARTERY
TIME MINUTES
0
2
4
7.7
7.5
7.3
pH_V

Figure 34. Same as Figure 33, except ventilation with 100% oxygen was instituted shortly before the renal artery constriction.

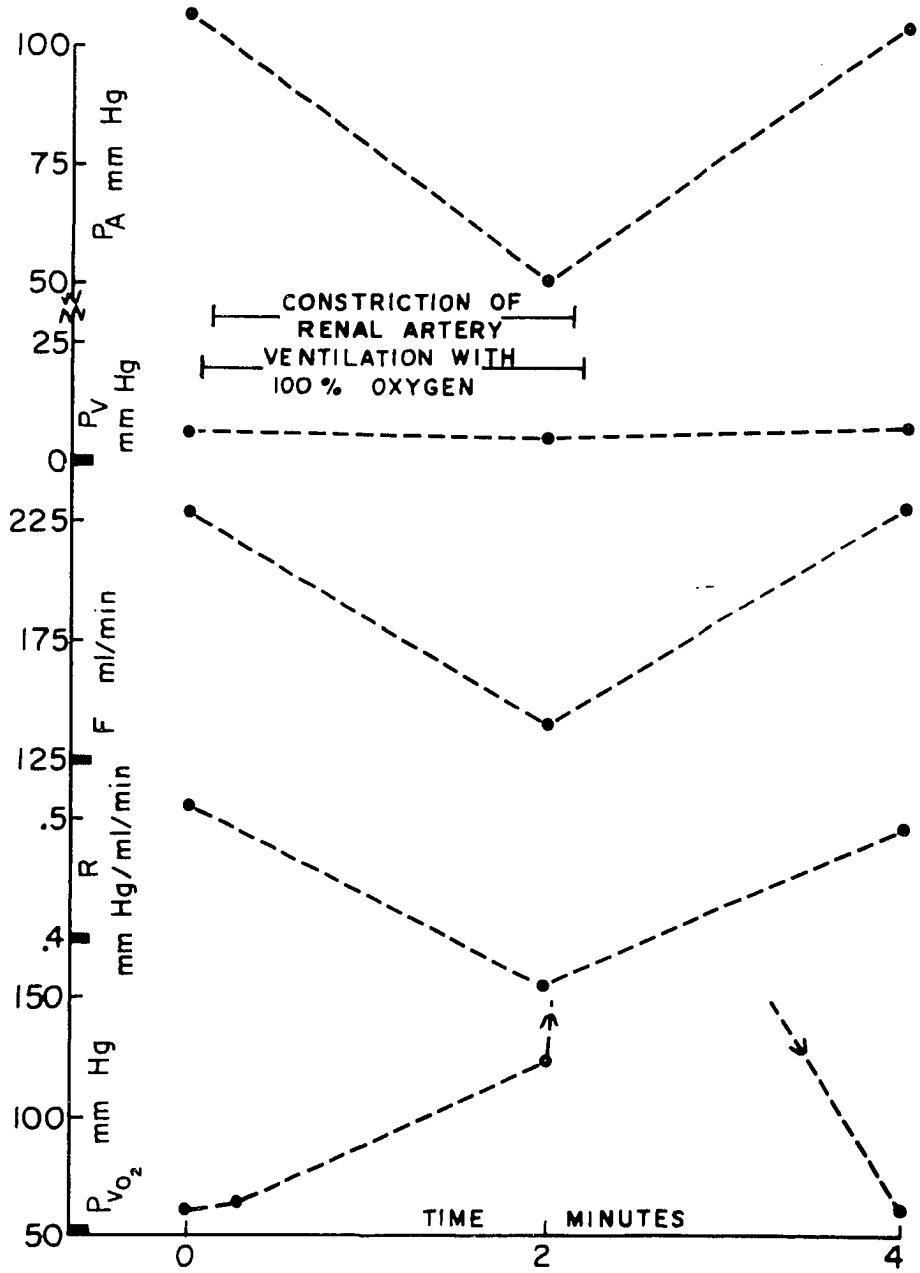
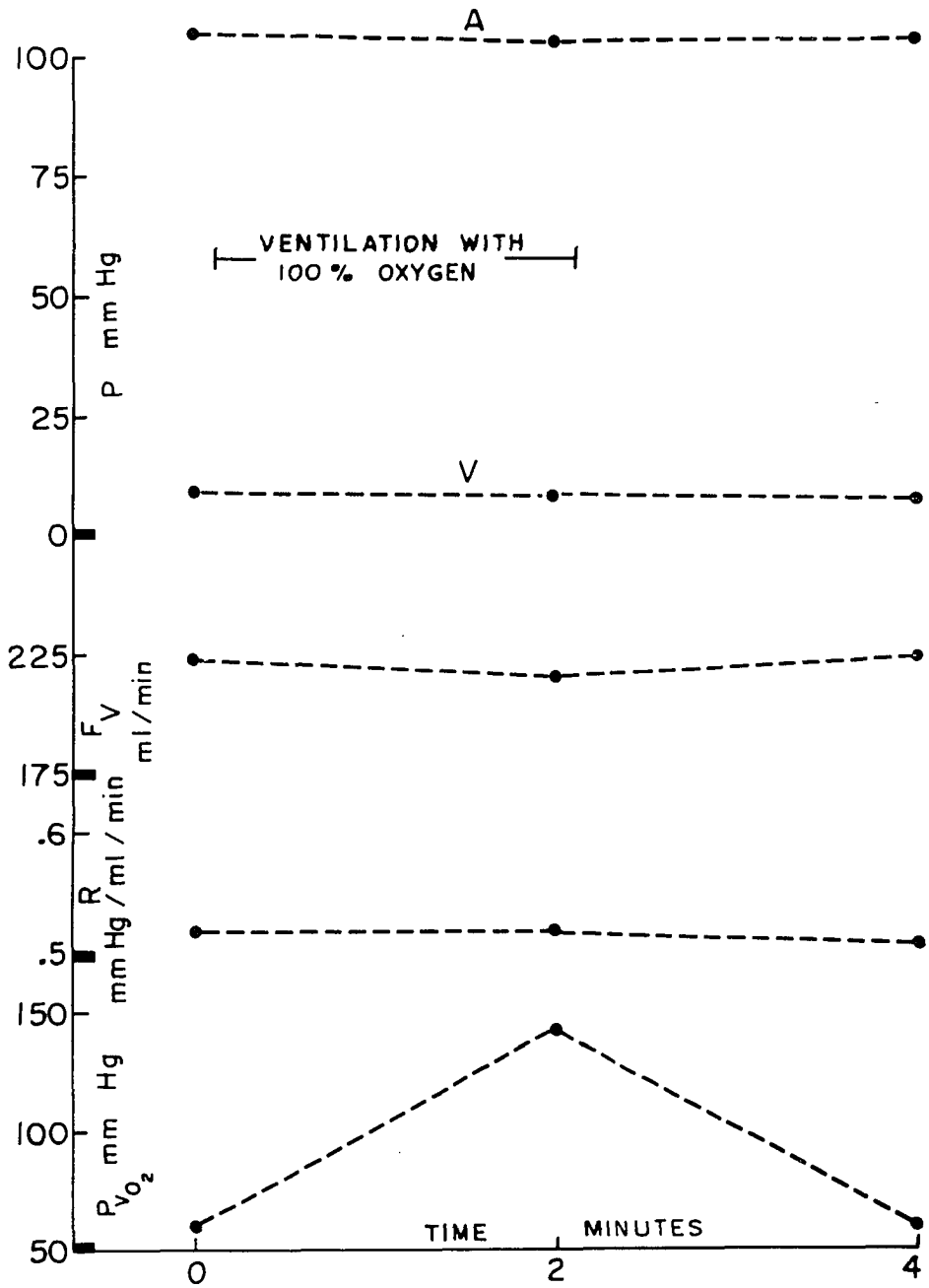

100
75
50
25
0
225
175
125
.5
.4
150
100
50
P_A mm Hg
P_V mm Hg
F ml/min
R mm Hg/ml/min
P_{VO_2} mm Hg
CONSTRICTION OF RENAL ARTERY
VENTILATION WITH 100 % OXYGEN
TIME MINUTES
0
2
4

Figure 35. Average effect in ten animals of ventilation with 100% oxygen upon aortic pressure (a), renal venous pressure (v), renal venous outflow (F_V), calculated renal vascular resistance (R), and renal venous oxygen tension (P_{VO_2}). The experiments were performed on the same animals as in Figures 33 and 34.


A
100
75
VENTILATION WITH
100 % OXYGEN
50
P mm Hg
25
V
0
225
175
F_V
ml/min
.6
R
mm Hg / ml / min
.5
150
mm Hg
100
P_{VO_2}
50
TIME
MINUTES
0
2
4

Effect of Alteration in Perfusion Pressure or Metabolism Upon The Vasoactivity of Venous Blood

A portion of the venous blood from an organ undergoing local regulation was directed through the forelimb of the same animal (at constant flow) in order to ascertain if the vasoactive properties of the venous blood was in anyway altered during the local regulatory responses. An earlier study (Figure 13) failed to demonstrate that renal venous blood vasoactivity was altered during renal artery constriction. This could mean either that there was no increase in vasoactivity, or if there was an increase it was masked by the extensive extracorporal circuit used in that study. Therefore, the circuit was reduced by removing the flow meter and shortening all extracorporal tubing to a minimum. This greatly reduced transit time and volume from renal vein to forelimb.

Figure 36 (upper panel) shows that, utilizing the new circuit, reduction of renal artery perfusion pressure from 110 to 48 mm Hg was associated with a fall in brachial artery pressure of 10 mm Hg. The delay in onset of the brachial dilation was the time necessary for the venous blood to reach the limb. Renal venous blood oxygen tension also fell slightly. This fall is of the same magnitude that occurred in earlier experiments (Figure 13) in which there was no change in brachial pressure.

Figure 37 shows the same brachial artery response following release of complete renal artery occlusion of 60, 10 and 30 seconds. In this preparation, occlusion of these durations were always associated with renal reactive hyperemia as is evidenced in this Figure by the rise in venous oxygen tension following release of occlusion. The

Figure 36. Effect of renal artery constriction (P_{RA}) upon renal venous blood oxygen tension (P_{RVO_2}) and the effect of the renal venous blood upon brachial artery pressure (P_{BA}). In these experiments a portion of the renal venous outflow was continuously diverted at a constant rate through the forelimb. See text for complete explanation. In each panel renal artery pressure is above, renal venous oxygen tension in the middle, and brachial artery pressure below.

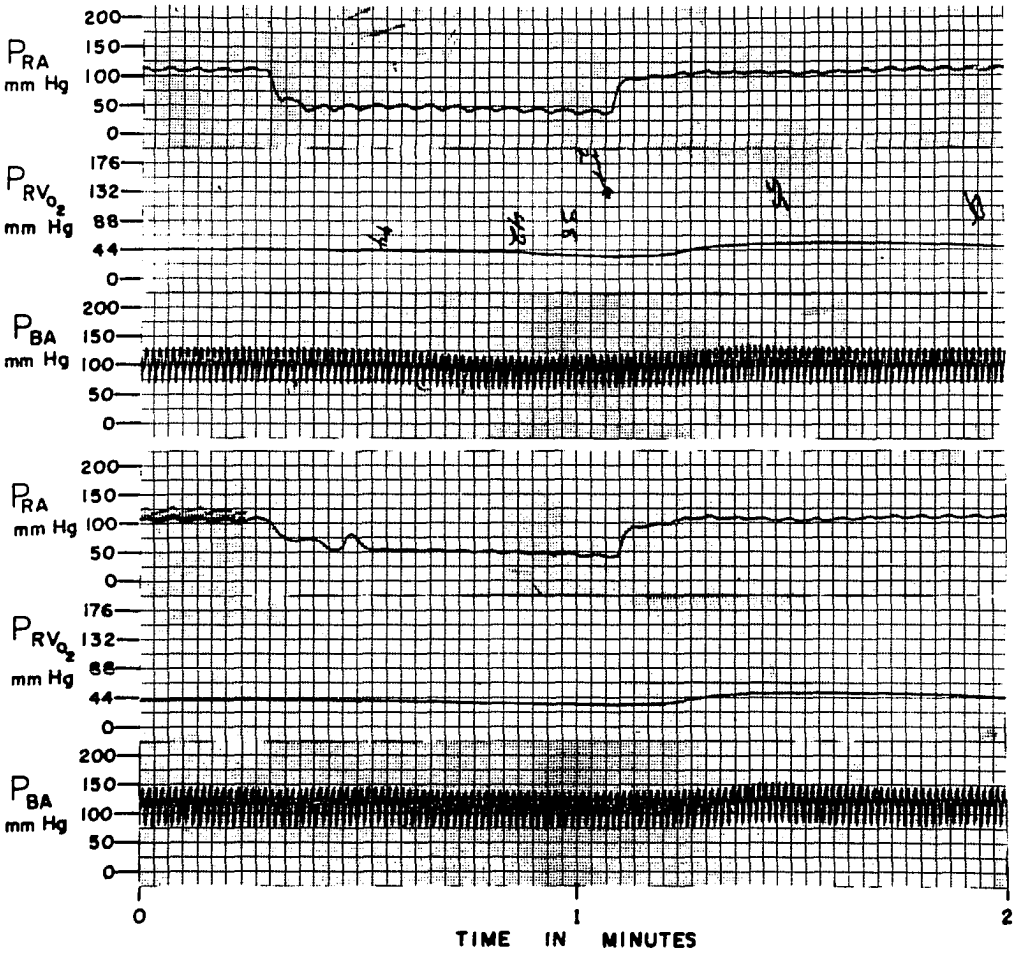
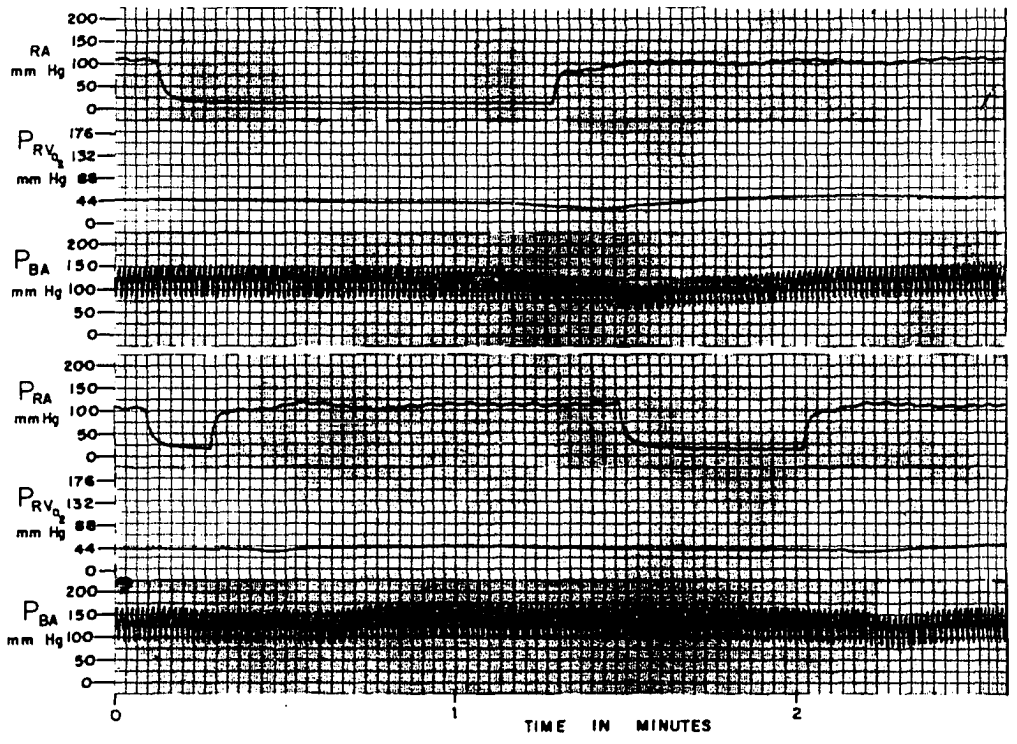

P_{RA} mm Hg
200
150
100
50
0
$P_{RV_{O_2}}$ mm Hg
176
132
88
44
0
P_{BA} mm Hg
200
150
100
50
0
P_{RA} mm Hg
200
150
100
50
0
$P_{RV_{O_2}}$ mm Hg
176
132
88
44
0
P_{BA} mm Hg
200
150
100
50
0
0
1
2
TIME IN MINUTES

Figure 37. Same as Figure 36, except the renal artery was completely occluded for 60 seconds (upper panel), 10 seconds and 30 seconds (lower panel).


RA
mm Hg
200
150
100
50
0
$P_{RV_{O_2}}$
mm Hg
176
132
88
44
0
P_{BA}
mm Hg
200
150
100
50
0
P_{RA}
mm Hg
200
150
100
50
0
$P_{RV_{O_2}}$
mm Hg
176
132
88
44
0
P_{BA}
mm Hg
200
150
100
50
0
0
1
2
TIME IN MINUTES

response of the forelimb shown in Figures 36 and 37 was not altered when the animals were ventilated with 100% oxygen, thus preventing a fall in renal venous oxygen tension below the control. In an attempt to determine the cause of this vasodilation, the concentration of H^+, K^+, Na^+, and osmolarity were determined on the renal venous blood of 15 animals before, during and after the maneuver. These concentrations were not changed significantly. Nor were the responses altered by infusion of atropine, diphenhydramine or phentolamine into the brachial artery at rates which were sufficiently rapid to block the response of the forelimb vascular bed to challenging arterial injections of acetylcholine, histamine, or epinephrine.

Figure 38 shows the reverse effect, that is brachial artery constriction associated with over perfusion of the renal vascular bed. In this animal a second pump was also interposed between the right femoral and right renal arteries to control renal blood flow. Blood flow to the kidney was rapidly elevated to a new steady state (first arrow) and this quickly produced a proportionately greater rise in renal perfusion pressure (autoregulation) and an increase in brachial perfusion pressure. When renal flow was returned (second arrow) to control there was a concomitant fall in brachial pressure. During the autoregulatory period renal venous hematocrit was elevated slightly (2%).

Figure 39 shows the effect on forelimb perfusion pressure of femoral venous blood from a hindlimb undergoing skeletal muscle activity. The sciatic nerve was stimulated at a frequency and voltage which produced obvious skeletal muscle contractions in the lower portion of the hindlimb. Within three minutes after starting stimulation the brachial

Figure 38. Effect of renal venous blood from an autoregulation kidney upon brachial artery pressure (P_{BA}). Utilizing a pump in the renal artery, renal blood flow was quickly elevated to a new steady state (first arrow) with a pump, and then decreased to the initial value (second arrow) while a portion of the renal venous outflow was continuously perfused at a constant rate through the forelimb. See text.

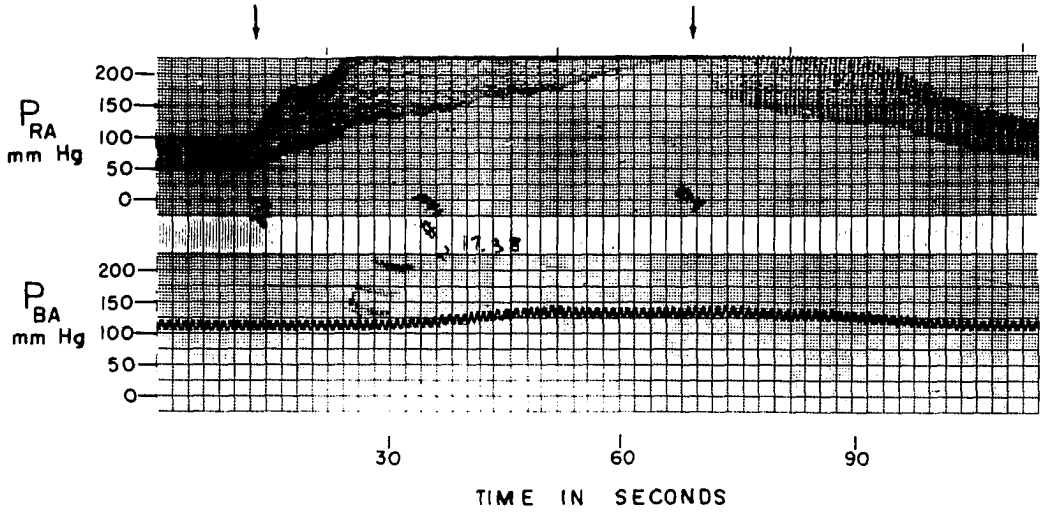
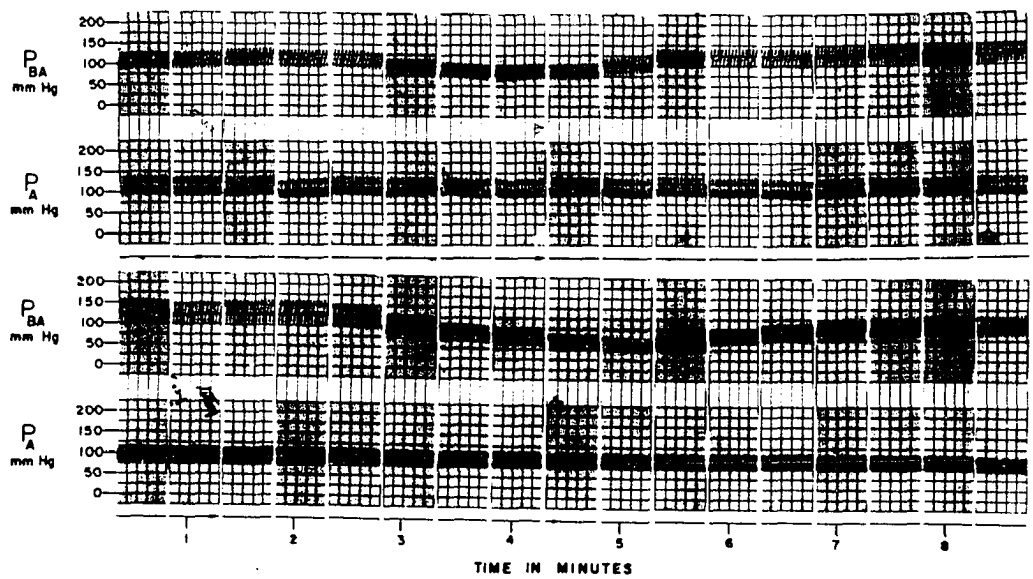

200
150
100
50
0
P_{RA}
mm Hg
200
150
100
50
0
P_{BA}
mm Hg
30
60
90
TIME IN SECONDS

Figure 39. Effect of femoral venous blood upon brachial artery pressure (P_{BA}) before, during and after faradic stimulation of the sciatic nerve. Lower portion of each panel is aortic pressure (P_A). Upper panel. Sciatic stimulation at a voltage and frequency that produced jerky hindlimb contraction, was started at the first heavy mark on the upper abscissa and stopped at the second heavy mark. Femoral venous blood was continuously perfused through the forelimb at a constant rate. Lower panel. Sciatic stimulation, at a voltage and frequency that produced hindlimb tetany, was started at the first heavy mark on the lower abscissa and stopped at the second heavy mark. Again, the forelimb was continuously perfused at a constant rate with femoral venous blood.


P_{BA} mm Hg
P_A mm Hg
P_{BA} mm Hg
P_A mm Hg
200
150
100
50
0
1
2
3
4
5
6
7
8
TIME IN MINUTES

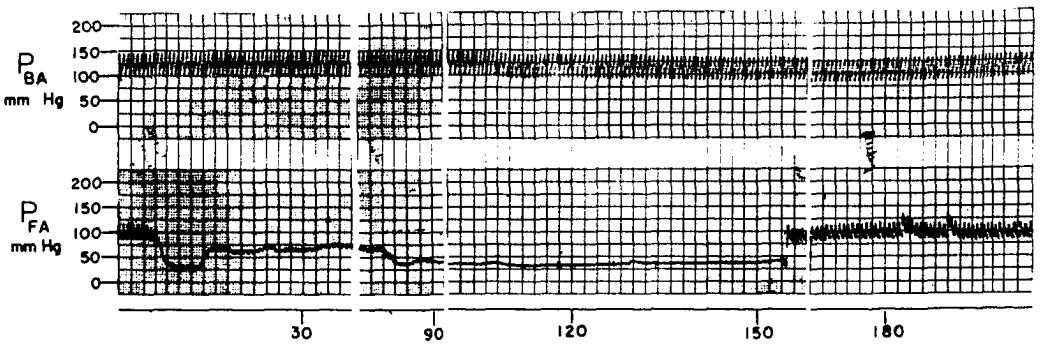
artery perfusion pressure was decreased by approximately 30 mm Hg and upon stopping stimulation gradually returned to above control. The fall in brachial artery pressure was even more evident when the hindlimb musculature was subjected to tetany (lower panel).

Figure 40 shows the effect upon brachial perfusion pressure produced by partial (upper panel) and complete (lower panel) femoral artery occlusion. When femoral artery pressure was dropped from a mean of 100 mm Hg to 30 mm Hg there was an associated decrease in brachial perfusion pressure of approximately 30 mm Hg (upper panel). Femoral artery occlusion (lower panel) which dropped femoral perfusion pressure from 110 mm Hg to 15 mm Hg (hindlimb collateral flow was not eliminated) was also associated with an approximate 30 mm Hg decrease in brachial artery pressure.

Figure 41 (upper panel) shows the effect upon brachial artery pressure of switching from inferior vena caval blood to coronary sinus blood. Blood flow to limb was identical in both cases. It is evident that when blood flow to the limb was changed from vena caval (first arrow) to sinus blood there was a progressive fall in brachial artery pressure which began in approximately 6 to 8 seconds. The delay is that calculated to be the approximate lag time of the system. In the steady state the fall in pressure amounted to 40 mm Hg. Coronary sinus blood was dilator relative to inferior vena caval blood in each of ten experiments. In these same experiments, vena caval blood was also always dilator relative to arterial blood.

Figure 41 (lower panel) shows that coronary sinus blood becomes more dilator following release of left coronary artery occlusion. The

Figure 40. Effect of femoral venous blood before, during and after partial (upper panel) and complete (lower panel) constriction of the femoral artery (P_{FA}) upon brachial artery pressure (P_{BA}). Blood flow through the forelimb was held constant with a pump.


200
150
100
50
0
P_{BA}
mm Hg
200
150
100
50
0
P_{FA}
mm Hg
30
90
120
150
180
TIME IN SECONDS

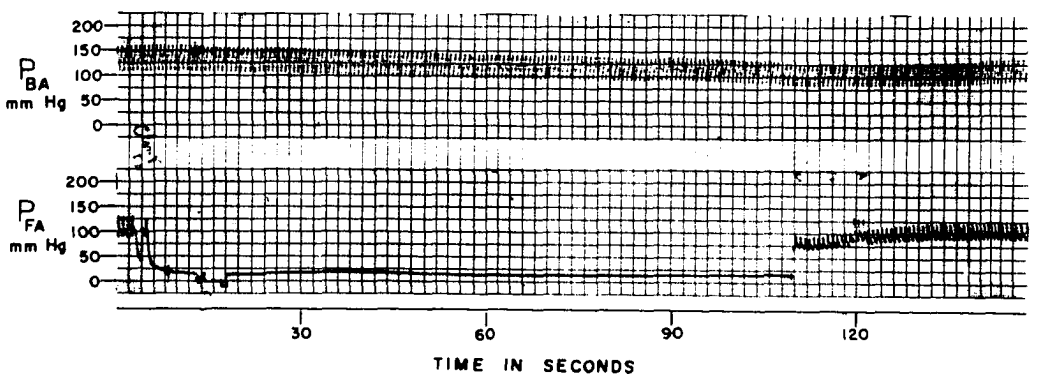
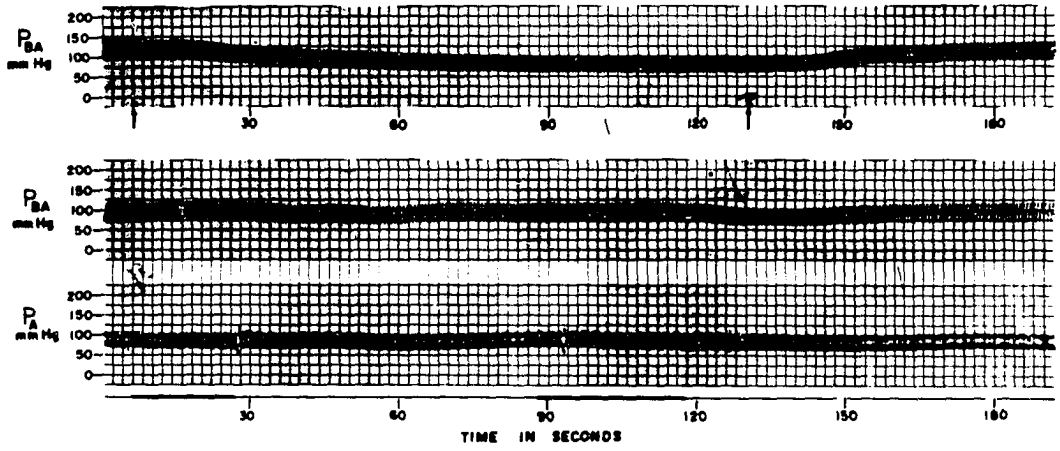

200
150
100
50
0
P_{BA}
mm Hg
200
150
100
50
0
P_{FA}
mm Hg
30
60
90
120
TIME IN SECONDS

Figure 41. Upper panel. Effect upon brachial artery pressure of switching perfusion from inferior vena caval blood to coronary sinus blood (first arrow) and back to inferior vena caval blood (second arrow). Flow rate to the limb was maintained constant throughout the maneuver. Lower panel. Effect of coronary sinus blood on forelimb perfusion pressure, following left common coronary artery occlusions of 20 seconds (first heavy mark on lower abscissa) and 30 seconds (second heavy mark).


P_{BA}
mm Hg
200
150
100
50
0
30
60
90
120
150
180
P_{BA}
mm Hg
P_A
mm Hg
TIME IN SECONDS

left common coronary artery was completely occluded for 20 seconds (period of ischemia indicated by heavy mark on abscissa) and then quickly released. Approximately eight seconds after release there was a slight fall in brachial artery pressure. The fall in brachial artery pressure was greater when the coronary artery occlusion was maintained for 30 seconds (lower panel, second heavy mark on abscissa). Aortic pressure remained relatively constant throughout the sequence. The coronary artery was also occluded for longer periods of time. However, as would be expected, they produced changes in aortic pressure which complicated interpretation of the response seen in the forelimb (carotid sinus reflex).

Effect of Vasoactive Agents Upon The Renal and Ileal Vascular Beds

Figure 42 shows the average effects in eight animals of close arterial injections of adenosine, AMP, ADP, and ATP upon renal artery pressure, renal venous pressure, renal blood flow, calculated renal vascular resistance, and renal venous blood PO_2. All solutions were isosmotic to plasma and the amount of active agent introduced was 6.5 μg in each case. It is apparent that none of the agents affected renal artery or renal vein pressures. Adenosine reduced renal blood flow and increased calculated renal vascular resistance. Adenosine also reduced renal venous blood PO_2. Conversely, ATP increased renal flow, venous blood PO_2, and decreased calculated resistance. The responses to AMP and ADP were irregular.

Figures 43 and 44 show the average effects in six animals of infusion of these same agents into the intestinal vascular bed. In

Figure 42. Average effects in eight animals of intra-renal artery injections of 6.5 μg of adenosine, AMP, ADP, and ATP upon renal artery pressure (RA), renal venous pressure (RV), renal venous outflow (F), calculated renal vascular resistance (R), and renal venous blood oxygen tension (P_{VO_2}).

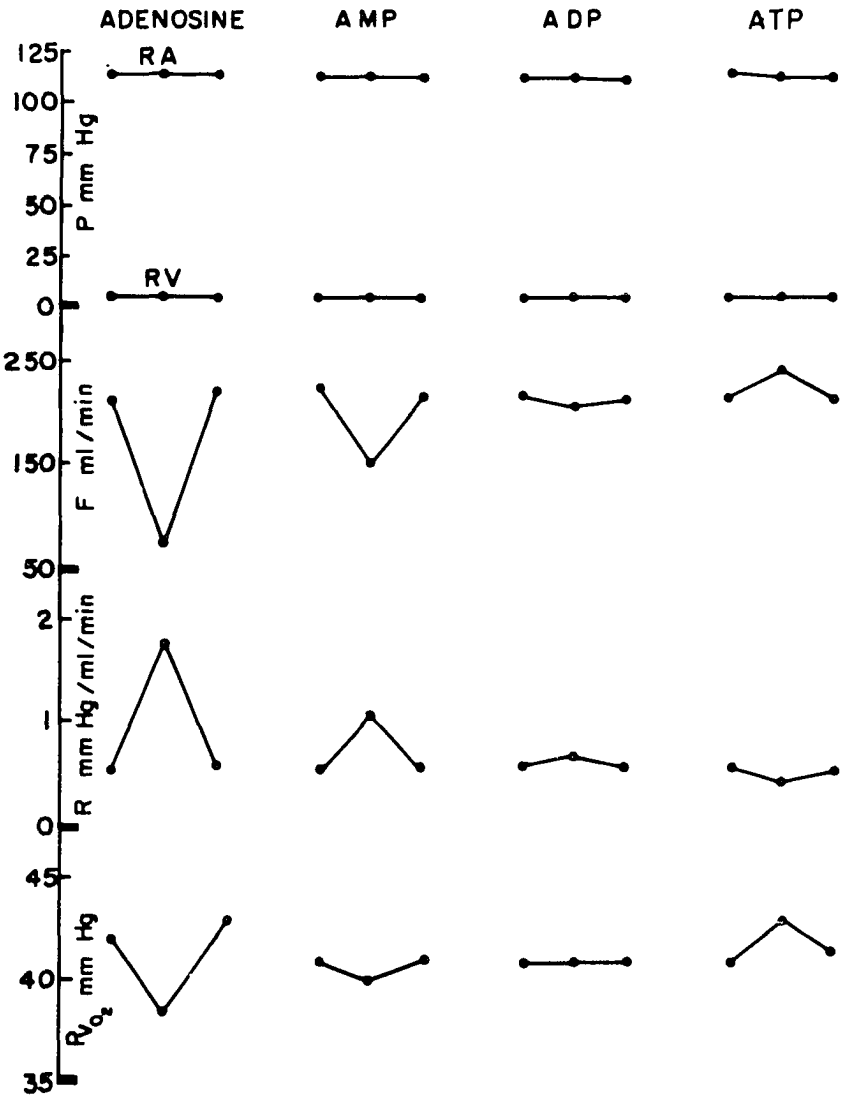

ADENOSINE
AMP
ADP
ATP
125
RA
100
75
50
P mm Hg
25
RV
0
250
150
F ml/min
50
2
1
R mm Hg/ml/min
0
45
40
$R_{V_{O_2}}$ mm Hg
35

Figure 43. Average effects upon ileal lumen pressure, blood flow, venous pressure and aortic pressure of intra-arterial infusion of adenosine and ATP. The dashed lines indicate a return to zero infusion rate. The post-infusion values were measured during the 30 to 90 seconds after stopping the infusion. Blood flow is expressed in terms of grams/minute/gram of tissue (N = 7).

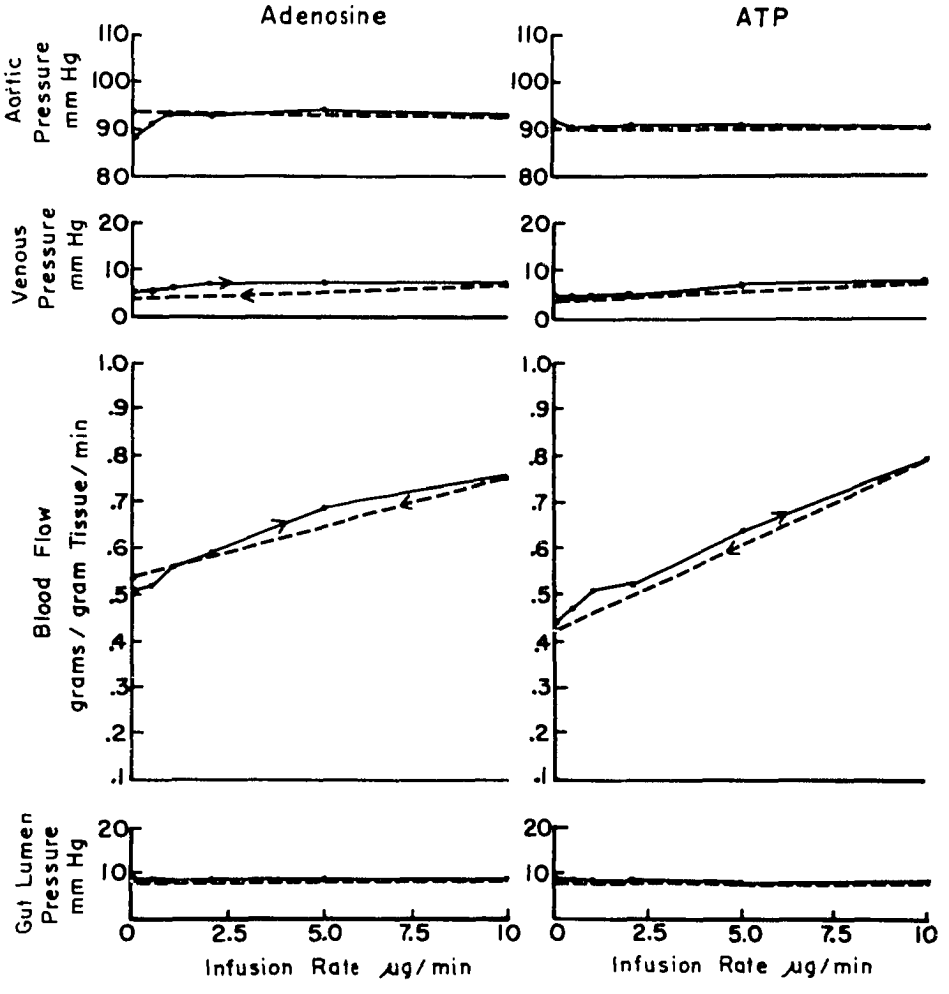
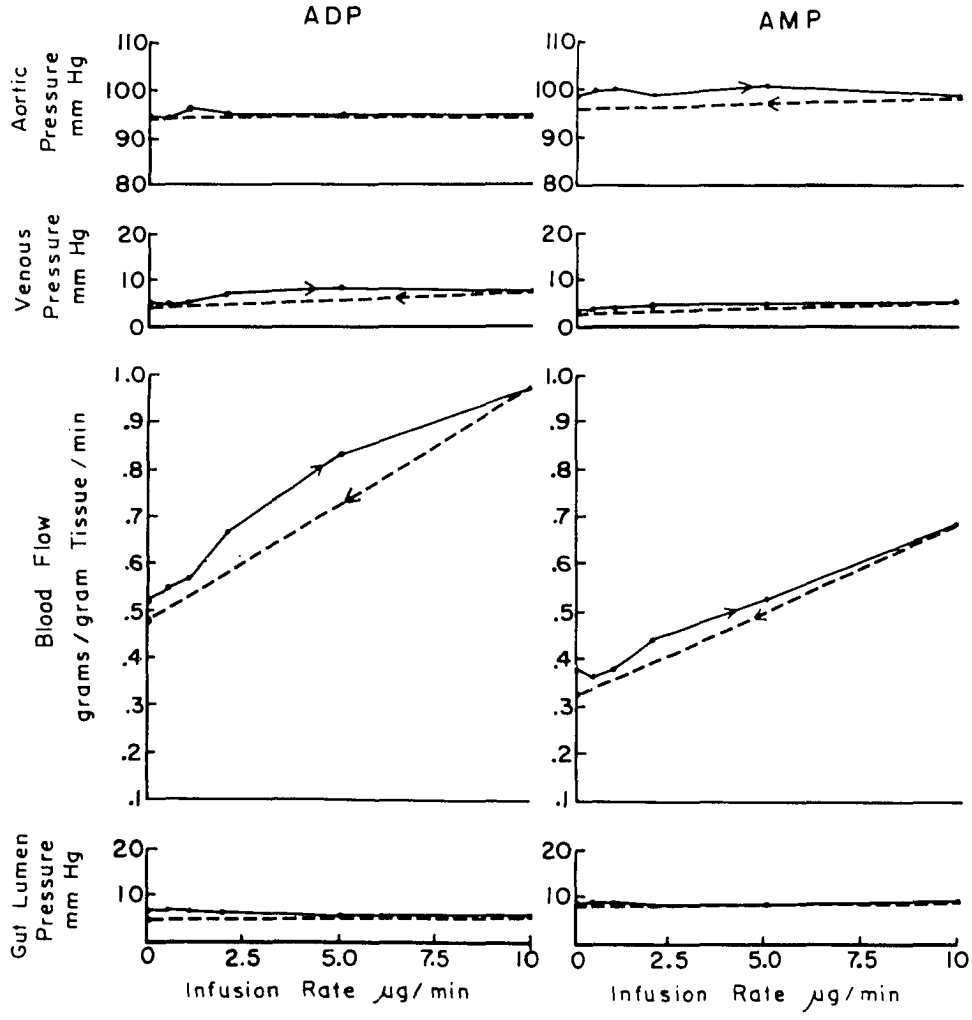

Adenosine
ATP
Aortic Pressure mm Hg
110
100
90
80
Venous Pressure mm Hg
20
10
0
Blood Flow grams / gram Tissue / min
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
Gut Lumen Pressure mm Hg
20
10
0
2.5
5.0
7.5
10
Infusion Rate µg/min

Figure 44. Same as Figure 43, except the agents infused were ADP and AMP (N = 7).


ADP
AMP
Aortic Pressure mm Hg
110
100
90
80
Venous Pressure mm Hg
20
10
0
Blood Flow grams / gram Tissue / min
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
Gut Lumen Pressure mm Hg
0
2.5
5.0
7.5
10
Infusion Rate µg / min

this bed, all the adenyl compounds produced an increase in intestinal blood flow, which was readily apparent over the range of infusion rate from 2.5 to 1.03 μg/min. There was no changes in aortic, venous and gut lumen pressures associated with infusion of any of the agents over the concentrations studied. All parameters studied returned to control values within 90 seconds after stopping the infusion (dashed line).

Figure 45 shows the average effects in 10 animals of intra-arterial infusion of isosmotic solutions of magnesium chloride and calcium chloride in the intestinal preparation. Magnesium chloride increased flow linearly over the infusion rates .05 to 2.1 ml/min without changing lumen pressure. Upon stopping the infusion flow returned to the control level.

Infusion of calcium chloride produced on the average a slight increase in blood flow and little change in luminal pressure. However, responses in different experiments varied. In three experiments blood flow markedly increased with increasing rates of calcium chloride infusion. In two, flow was virtually abolished at the highest rate of calcium chloride infusion and remained low for several minutes. In five experiments flow was elevated slightly (this may have been due to dilution by the infusate).

Figure 46 shows the average effects in ten animals of intra-arterial infusions of potassium chloride and potassium chloride plus atropine in the same preparation. During the infusion of potassium chloride blood flow was first elevated, leveled off and then dropped sharply. The luminal pressure was almost a mirror image of blood flow, decreasing at first, leveling off, and then increasing sharply. Infusion

Figure 45. Same as Figure 43, except the agents infused were magnesium chloride and calcium chloride (N = 10).

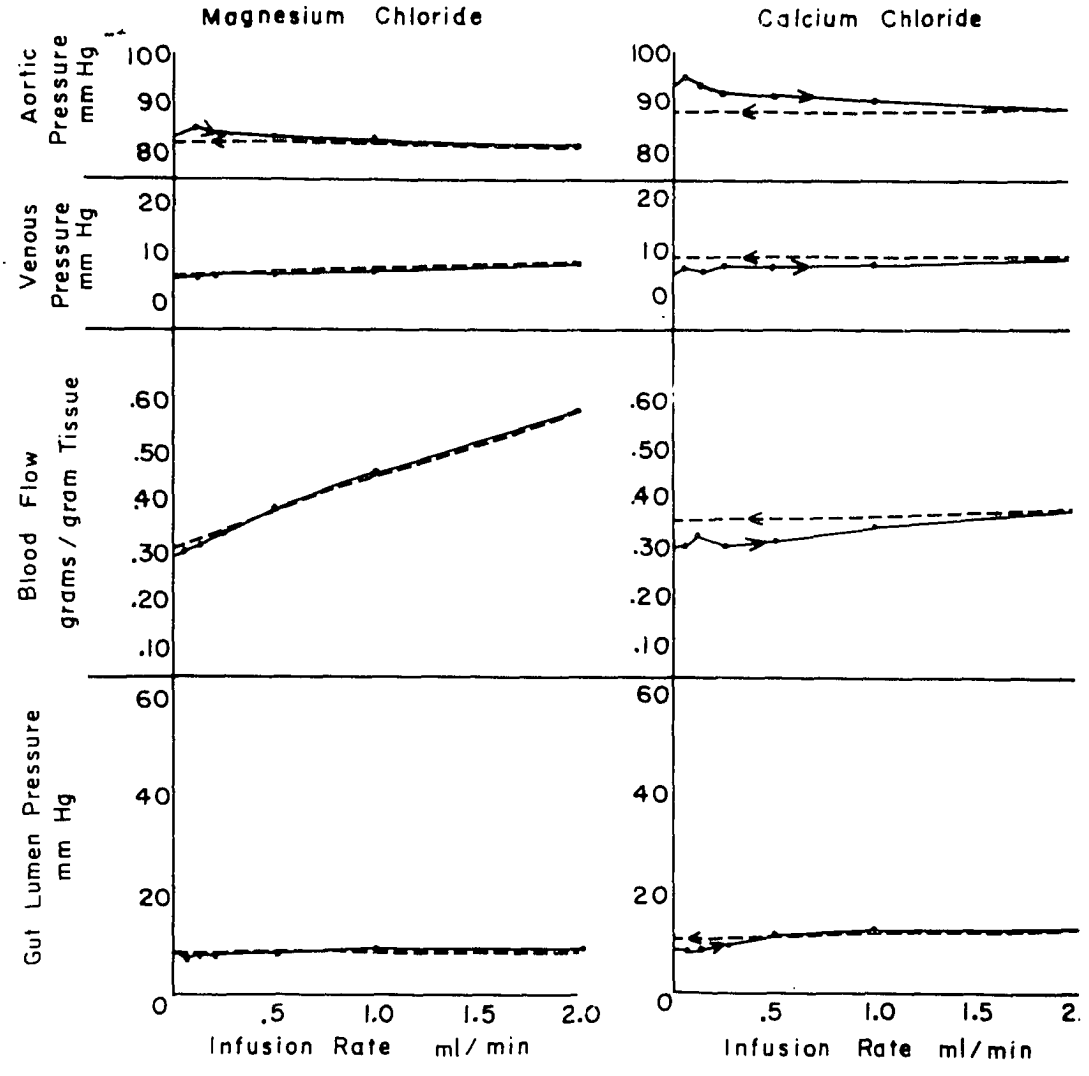
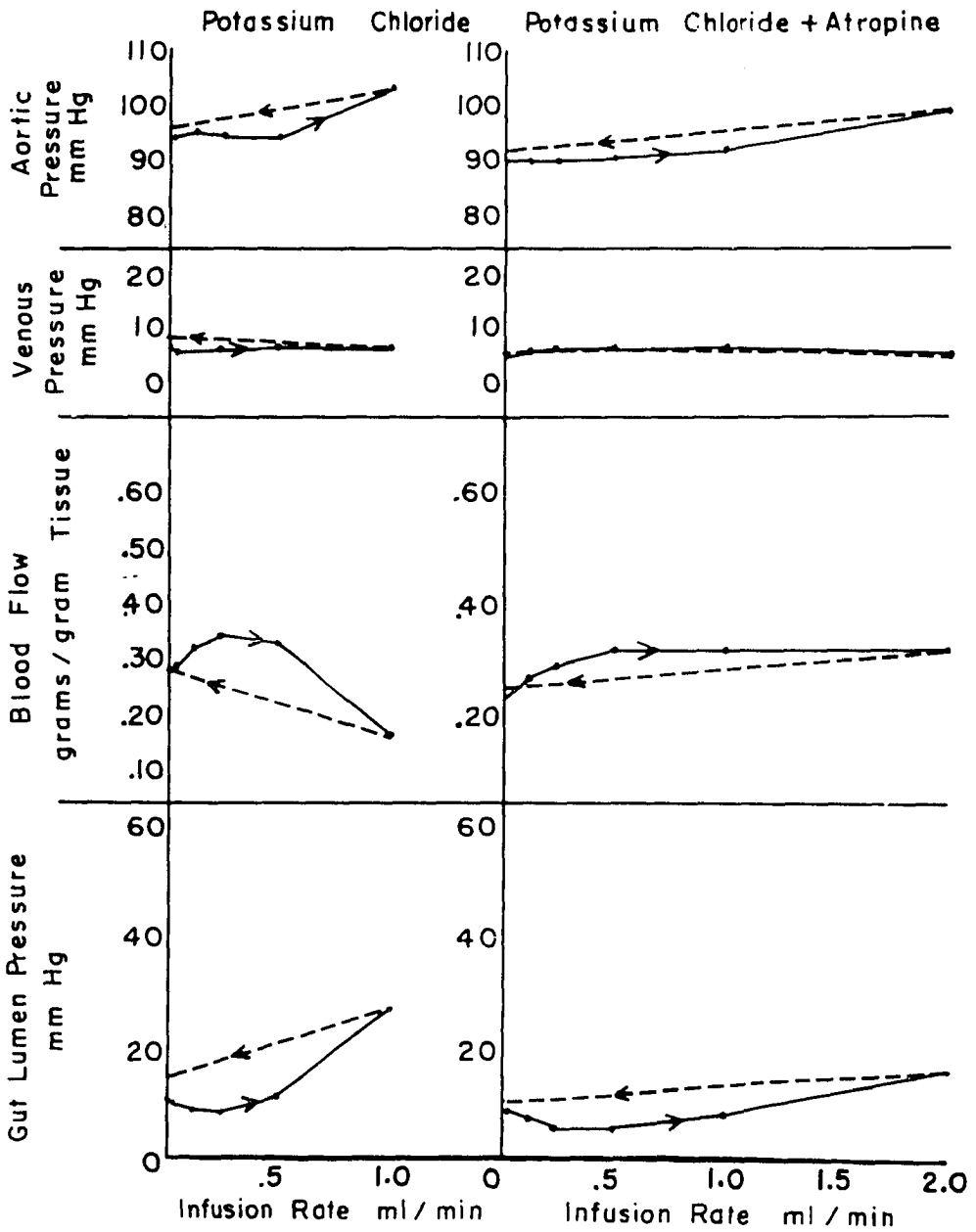

Magnesium Chloride
Calcium Chloride
Aortic Pressure mm Hg
100
90
80
Venous Pressure mm Hg
20
10
0
Blood Flow grams / gram Tissue
.60
.50
.40
.30
.20
.10
Gut Lumen Pressure mm Hg
60
40
20
0
.5
1.0
1.5
2.0
Infusion Rate ml/min

Figure 46. Same as Figure 43, except the agents infused were potassium chloride and potassium chloride plus atropine (N = 10).


Potassium Chloride
Potassium Chloride + Atropine
Aortic Pressure mm Hg
110
100
90
80
Venous Pressure mm Hg
20
10
0
Blood Flow grams / gram Tissue
.60
.50
.40
.30
.20
.10
Gut Lumen Pressure mm Hg
60
40
20
0
.5
1.0
0
.5
1.0
1.5
2.0
Infusion Rate ml / min
Infusion Rate ml / min

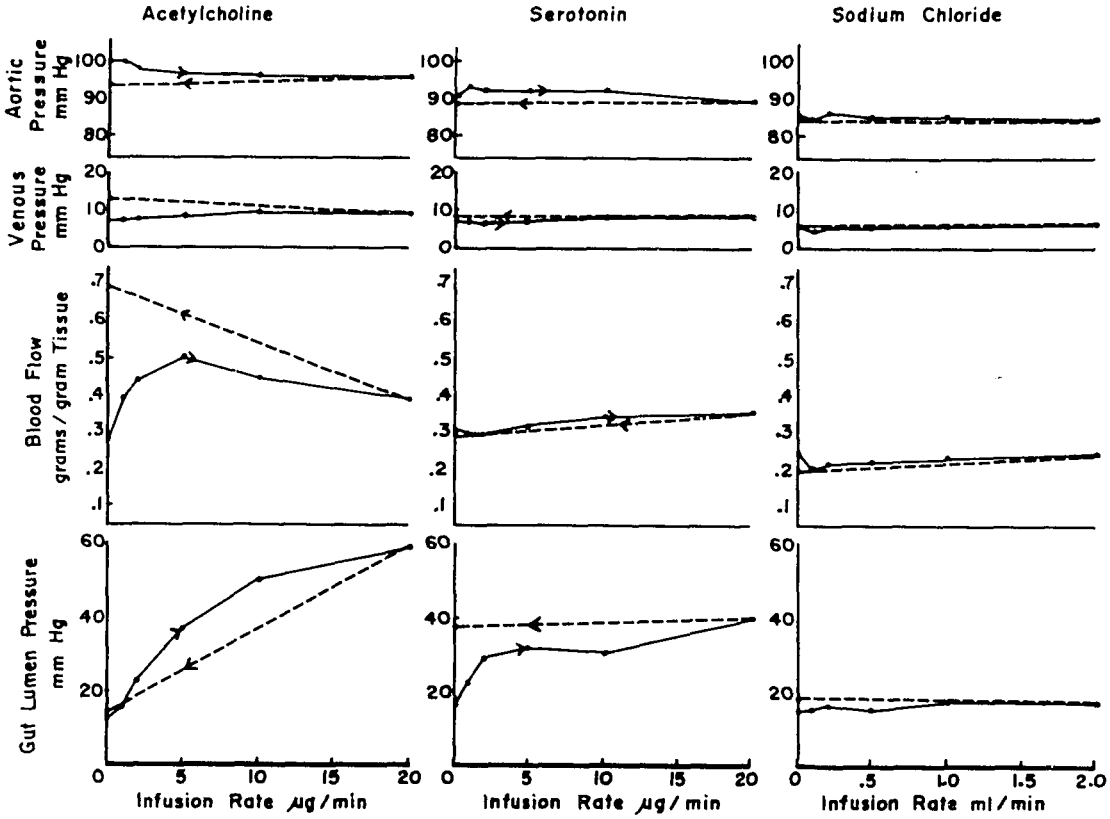
at higher rates usually resulted in flows so low as to be almost unmeasurable.

The infusion of potassium chloride at a rate of 1.0 ml or more per minute always produced a rise in mean aortic pressure. Preliminary studies indicate the pressor response is eliminated by complete denervation of the ileal section.

In an effort to prevent the rise in luminal pressure seen when potassium was infused at high rates, atropine sulfate was infused with the potassium chloride. As shown in Figure 46, the luminal pressure tended to stay much below the pressure recorded when potassium chloride alone was infused. Even when the infusion rate was raised to 2.1 ml/min luminal pressure was considerably lower than when potassium chloride, without atropine, was given at a lower infusion rate. Blood flow was elevated and stayed high even at the highest infusion rate. However, at the highest infusion rate there was still a slight elevation in aortic pressure.

Figure 47 shows the average effects, in ten intestinal preparations, of infusion of acetylcholine, serotonin, and saline upon blood flow, aortic pressure, venous pressure, and luminal pressure. The highest volume infusion rate for both drugs was 2.1 ml/min. Saline infused at the same rates served as a control for all agents used in intestinal studies. Acetylcholine produced a rise in luminal pressure and blood flow up to the infusion rate of 5 μg/min. At higher rates luminal pressure continued to rise but blood flow fell. On stopping the infusion, luminal pressure immediately fell to control while blood flow rose to about two and one-half times the control value.

Figure 47. Same as Figure 43, except the agents infused were acetylcholine, serotonin, and sodium chloride. Acetylcholine and serotonin are in terms of the sale (N = 10).


Acetylcholine
Serotonin
Sodium Chloride
Aortic Pressure mm Hg
100
90
80
Venous Pressure mm Hg
20
10
0
Blood Flow grams / gram Tissue
.7
.6
.5
.4
.3
.2
.1
Gut Lumen Pressure mm Hg
60
40
20
0
5
10
15
20
.5
1.0
1.5
2.0
Infusion Rate µg / min
Infusion Rate µg / min
Infusion Rate ml / min

Serotonin produced an increase in luminal pressure with little change in flow. On stopping the infusion, blood flow fell while luminal pressure remained elevated. Both serotonin and acetylcholine caused rhythmic variations in luminal pressure. Those produced by serotonin continued for several minutes after stopping the infusion of the drug.

Saline had little effect on any of the parameters.

Interaction of Local and Remote Flow Regulating Mechanisms In Hemorrhagic Shock

Figure 48 shows the effect, in one animal, of removal and replacement of 22% of the blood volume on arterial and venous pressures, renal blood flow, and calculated renal vascular resistance. Immediately after hemorrhage renal blood flow fell proportionately more than the pressure gradient indicating a rise in renal vascular resistance. Pressure and flow gradually recovered, the latter proportionately more than the former, during the last 15 minutes of the hypovolemic period, indicating a gradual fall in resistance. On re-infusion of the shed blood, resistance transiently rose and then returned to the control value. This same type of response was seen in all five animals studied.

Figure 49 shows the average effects in six animals of a 25% hemorrhage upon the ileal preparation. Blood flow after hemorrhage was decreased proportionately more than the pressure gradient, indicating a rise in resistance. Blood flow and pressure then began to rise and the rise in flow was out of proportion to the rise in pressure indicating a fall in resistance. Gut lumen pressure fell slightly during the hypovolemic period. One infusion of the shed blood, ileal resistance transiently rose and then began falling toward control.

Figure 48. Effects in one animal of removal and replacement of 22% of the blood volume on aortic pressure, renal vein pressure, renal venous outflow, and renal vascular resistance.

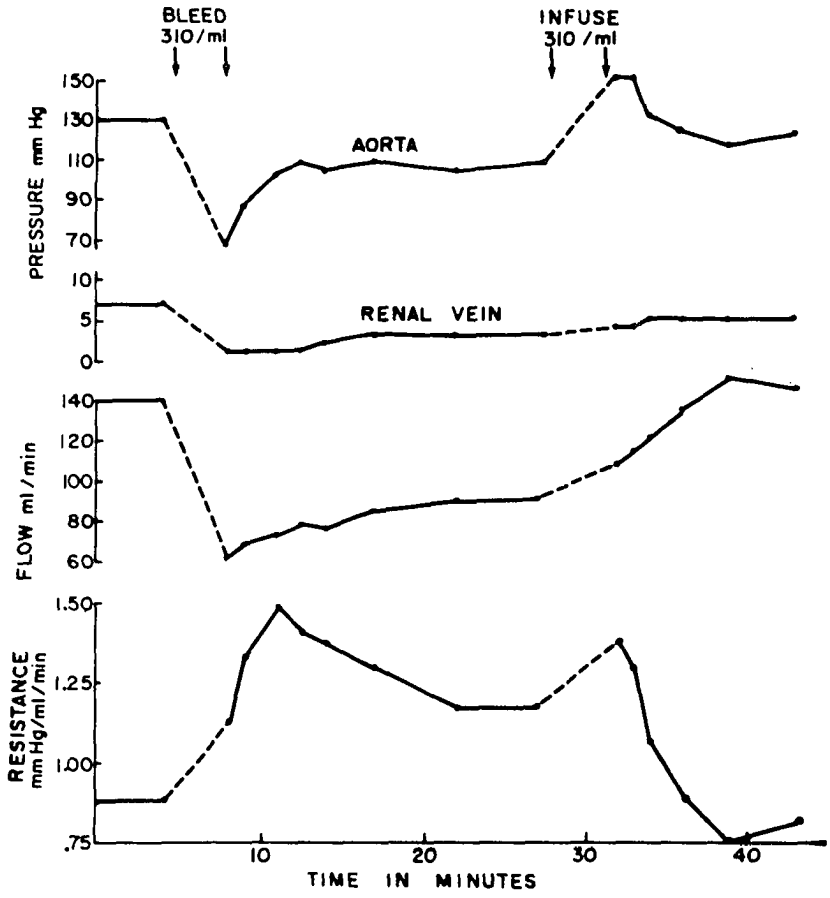

BLEED
310/ml
INFUSE
310 /ml
PRESSURE mm Hg
150
130
110
90
70
AORTA
10
5
0
RENAL VEIN
FLOW ml/min
140
120
100
80
60
RESISTANCE
mm Hg/ml/min
1.50
1.25
1.00
.75
10
20
30
40
TIME IN MINUTES

Figure 49. Average effects in six animals of hemorrhage on aortic pressure, flow through a section of ileum, ileal venous pressure, ileal lumen pressure and ileal vascular resistance.

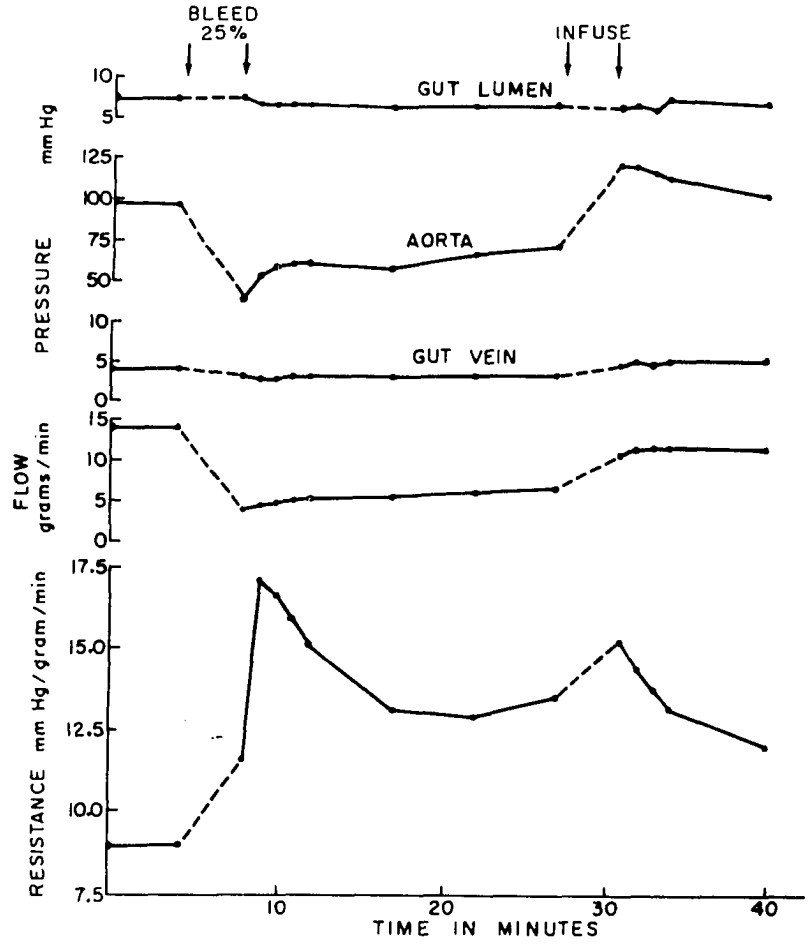

BLEED
25%
INFUSE
GUT LUMEN
AORTA
GUT VEIN
PRESSURE
mm Hg
FLOW
grams/min
RESISTANCE mm Hg/gram/min
TIME IN MINUTES
10
5
125
100
75
50
0
15
17.5
15.0
12.5
10.0
7.5
20
30
40

Figure 50 shows the average effect in seven animals of a 25% bleed out upon renal and intestinal vascular resistance. In these studies blood flow the kidney and ileum was held constant with blood pumps. Resistance in both beds rose quickly upon hemorrhage, the rise in resistance beginning sooner in the kidney. Resistance in both beds then began to fall, however, they never approached control values during the hypovolemic period. Neither did resistances transiently increase upon re-infusion of the shed blood. Hematocrit rose slightly during the bleeding process in 5 of 7 animals. Arterial blood pH during the control period and at the 18th minute of the hypovolemic period was 7.45 and 7.44, respectively.

Figure 51 shows the effects in one animal of removal and replacement of 25% of the blood volume upon forelimb blood flow, pressures, and resistances. Following hemorrhage, blood flow fell proportionately more than brachial artery to cephalic vein pressure gradient indicating a rise in total resistance through the forelimb. This rise in resistance resulted mainly from an increase in resistance through the small vessels and slightly from an increase in the resistances to flow through large veins and large arteries. Within a short time, total resistance began falling toward control,mainly because of a fall in resistance through small vessels. Arterial pressures fell immediately upon bleeding and partially recovered during the hypovolemic period. Venous pressures also fell, cephalic slightly more than small vein, and remained low during the entire hypovolemic period. All pressures returned toward control upon re-infusion of the shed blood. This experiment shows that hemorrhage raises the precapillary and postcapillary resistance but that the increase in small vessel resistance is not well maintained.

Figure 50. Average effects in seven animals of hemorrhage on aortic pressure, renal artery pressure, ileal artery pressure, ileal vein pressure, ileal lumen pressure, arterial blood pH and arterial blood hematocrit with the rate of blood flow the kidney and ileal segment held constant.

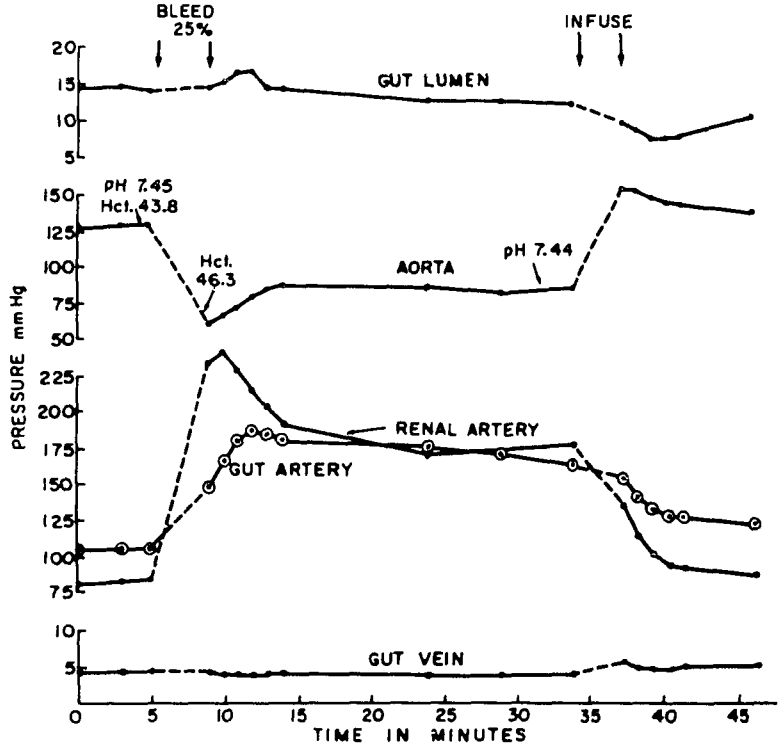

BLEED
25%
INFUSE
GUT LUMEN
pH 7.45
Hct. 43.8
Hct.
46.3
AORTA
pH 7.44
RENAL ARTERY
GUT ARTERY
GUT VEIN
PRESSURE mm Hg
TIME IN MINUTES

Figure 51. Effects in one animal of removal and replacement of 25% of the blood volume on forelimb weight, large and small vessel pressures, venous outflow, and total and segmental resistances.

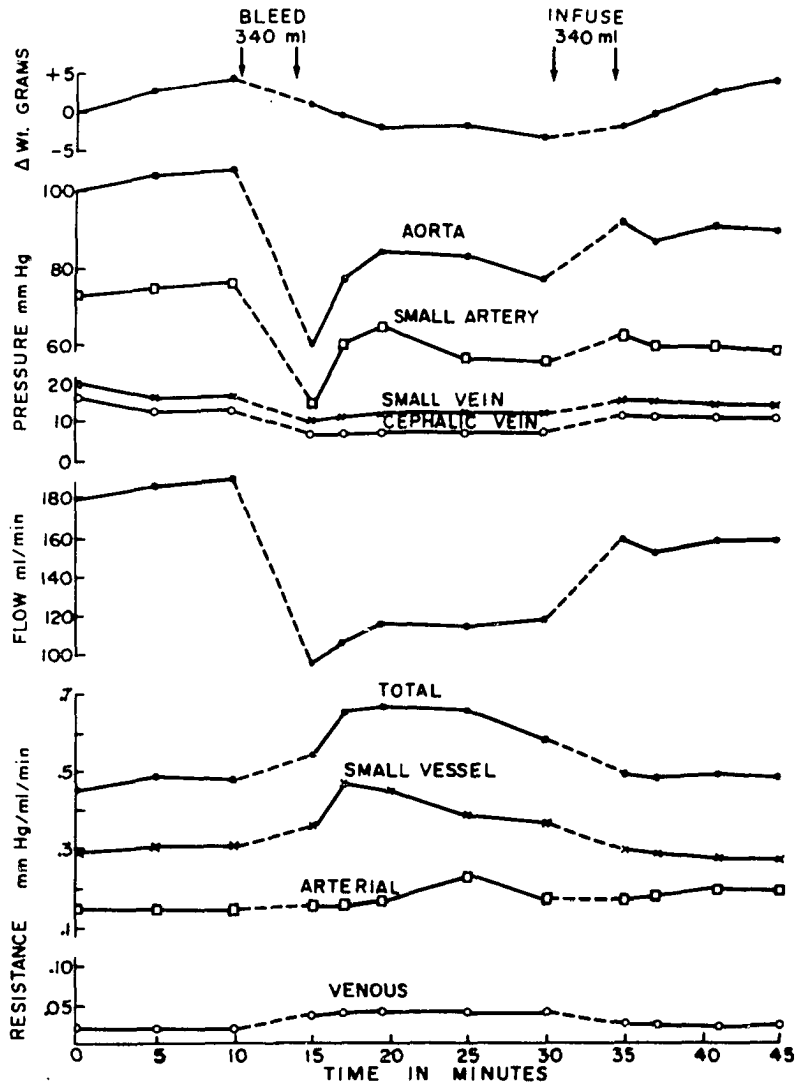
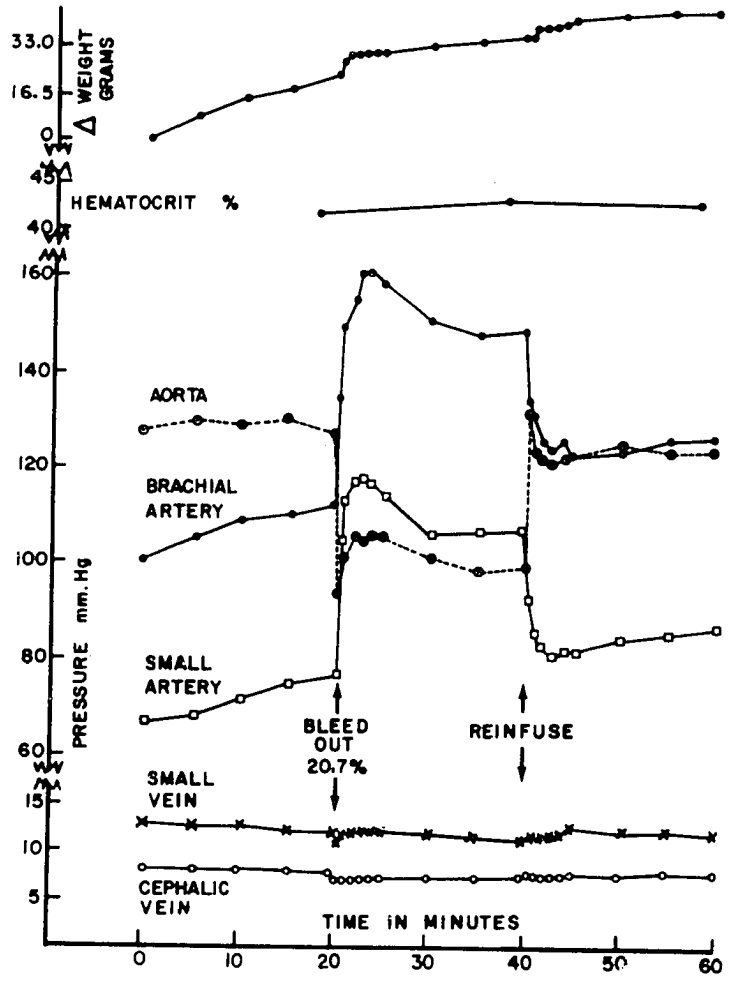

BLEED
340 ml
INFUSE
340 ml
Δ WT. GRAMS
+5
0
-5
PRESSURE mm Hg
100
80
60
20
10
0
AORTA
SMALL ARTERY
SMALL VEIN
CEPHALIC VEIN
FLOW ml/min
180
160
140
120
100
RESISTANCE mm Hg/ml/min
.7
.5
.3
.1
.10
.05
TOTAL
SMALL VESSEL
ARTERIAL
VENOUS
0
5
10
15
20
25
30
35
40
45
TIME IN MINUTES

Figure 52 shows the average effect in eleven animals of hemorrhage upon forelimb pressure with blood flow held constant. As aortic pressure fell, brachial arterial pressure rose while cephalic venous pressure remained essentially unchanged indicating an increase in total resistance to flow through the forelimb due to active vasoconstriction. Similarly, small arterial pressure rose while small venous pressure changed only slightly, indicating a rise in the resistance to flow through small vessels also due to active constriction. These resistances fell slightly during the second five minutes of the hypovolemic period but remained steady at well-elevated values during the last ten minutes of the period. The change in small vessel resistance accounted for most, but not all, of the change in total resistance. During the first minute following hemorrhage, small arterial pressure rose more than brachial arterial pressure, indicating a fall in resistance to flow through large arteries probably due to passive dilation subsequent to rise in arterial transmural pressure. During the remainder of the period the gradient from brachial artery to small artery was larger than control, indicating a rise in resistance through the large arteries due to active vasoconstriction. This finding indicates the active response of large arteries is slower than the active response of small vessels. The pressure gradient from small vein to cephalic vein was unchanged throughout the maneuver, implying an absence of an active response in this segment.

Figure 52. Average effects of hemorrhage upon forelimb large and small vessel pressures, forelimb weight, aortic pressure, and hematocrit with rate of blood flow through the limb held constant in eleven animals.


33.0
16.5
0
Δ WEIGHT GRAMS
45
HEMATOCRIT %
40
160
140
AORTA
120
BRACHIAL ARTERY
100
80
SMALL ARTERY
PRESSURE mm.Hg
BLEED OUT 20.7%
REINFUSE
60
15
SMALL VEIN
10
CEPHALIC VEIN
5
TIME IN MINUTES
0
10
20
30
40
50
60

CHAPTER IV

DISCUSSION

The studies presented were designed to: 1) characterize local regulation of blood flow in several systemic vascular beds, 2) elucidate the mechanisms responsible for local regulation of blood flow, and 3) ascertain if local control of blood flow is an important factor in determining blood flow through organs under conditions that affect the cardiovascular system as a whole. The discussion will, therefore, consider the topics separately.

Local Control of Blood Flow

Autoregulation

These studies demonstrate some degree of autoregulation of blood flow in four systemic vascular beds. Further, they show that the response can be elicited by either a change in perfusion pressure (kidney) or by a change in blood flow (intestine, heart, and forelimb).

Autoregulation of blood flow through the renal vascular bed is probably better documented (25, 29, 30, 32, 34, 40, 42, 48, 56, 58) than in any other organ in the body. It has been demonstrated in intact kidneys (29), isolated kidneys (25), kidney perfused with oxygenated dextran (25), and in decapsulated kidneys (25). In fact, the only means

of eliminating the response appears to be death of the tissue (25, 56). However, to date, the exact mechanism responsible for renal autoregulation is unknown. The response is presented again in the present studies to: 1) show the remarkable degree of efficiency with which it acts in the kidney and 2) to serve as a model for comparison of the autoregulatory response in various organs of the body.

The present studies also indicate the autoregulatory response is operable in the intestinal vascular bed. In most preparations, resistance to blood flow increased as a function of flow rate over the pressure range 50 to 200 mm Hg. Johnson (36) also found that reduction of perfusion pressure to an isolated section of ileum from normal to 40 mm Hg produces a much less than proportional fall in blood flow, and concluded that the autoregulatory response in the intestine is very efficient. Texter et al. (55) found that the resistance through the vascular bed supplied by the superior mesenteric artery, increases as a function of flow rate over the range 90 to 270 ml/min. In contrast, Hinshaw (30) found that intestinal vascular resistance decreases when arterial perfusion pressure is increased over a wide range (80 to 220 mm Hg). However, in 5 of 9 individual experiments presented by Hinshaw, resistance to blood flow through the intestine remained constant over the pressure range 90 to 200 mm Hg. This would indicate that either an active response prevented a further fall in resistance as pressure was increased, or that the vessels reached their maximum diameters at rather low intraluminal pressure. The latter possibility seems extremely unlikely.

Autoregulation of blood flow in the coronary vascular beds is highly variable. Resistance practically always decreases as flow is

elevated from 25 to 75 ml/min. However, resistance may decrease, remain constant, or increase when flow is elevated further. The response seen is often related to the initial level of resistance. More often than not, a high initial resistance precludes further increase in resistance as flow is elevated. This type of response is also seen in the kidney (29). An increasing resistance as a function of flow rate is encountered relatively frequently in fibrillating hearts. In addition, coronary autoregulation is not different after bilateral vagotomy. Others (4) have reported similar findings in beating perfusing hearts.

In the present study, the steady state resistances to blood flow through all vascular segments of dog forelimb decreased as a function of flow rate. Thus, in the steady state this bed responds much like a passive elastic system, increasing its cross sectioned area as a function of intraluminal pressure. Others have reported similar results in the intact (23) and isolated (30) dog forelimb. However, both studies are subject to criticism for neither measured tissue pressure, and forelimb collateral flow was uncontrolled in the former study.

A new finding of the present study is the demonstration of active changes in vessel caliber when forelimb flow is changed rapidly from a low to a high value or the reverse. The former maneuver is associated with a gradual constriction until a steady state is reached, while the latter maneuver is associated with a gradual dilation until a steady state is reached. Thus, while the limb responds passively in the steady state to changes in blood flow, active vasomotion is apparent when large rapid shifts in flow are made and close attention is paid to the transient responses.

Utilizing data from the present study and from an earlier investigation (29) it is possible to make an inter-organ comparison of the autoregulatory response. Such a comparison reveals autoregulation to be extremely efficient in the kidney, only slightly less efficient in the intestine, moderately efficient in the heart and extremely inefficient in the limb. The validity of the comparison is based on the fact that all organs were studied by the same technique and by the same investigator.

It is also evident from these studies that the autoregulatory response can be elicited by either a change in flow or a change in pressure. In 1958, Haddy et al. (25) concluded from a large amount of experimental data, that renal autoregulation was better correlated with a flow linked mechanism than with a pressure linked mechanism. This view, however, is not supported by Folkow (10, 11) and Johnson (36). These investigators maintain that the response is activated by a change in transmural pressure. This question will be discussed in depth in a section to follow.

Reactive Hyperemia

The studies demonstrate reactive hyperemia or reactive dilation in three vascular beds following brief periods of interruption of arterial inflow. Reactive dilation, as measured in the present studies, should qualitatively represent reactive hyperemia when flow is the independent variable. Thus, for this discussion the term, reactive dilation, will be used synonymously with the term, reactive hyperemia.

Reactive dilation is consistently seen in the forelimb following brief periods of ischemia (2 to 120 seconds), and the magnitude and

duration of the response is directly related to the length of time that forelimb flow is interrupted. It is also apparent from these studies that forelimb denervation slightly attenuates the reactive hyperemic response. This is probably related to the fact that denervation produces vascular dilation. Thus, it is reasonable to expect a smaller response in a bed that is already partially dilated.

Reactive hyperemia, monitored on either the arterial or venous side, is not nearly as consistent in the ileum as in the forelimb. Brief periods of flow interruption often caused no change in post-occlusion flow, and in some instances flow was actually decreased from control. However, in the preparations that did exhibit reactive hyperemia the magnitude and duration of the response was directly related to the length of ischemia.

Although renal reactive hyperemia was not thoroughly investigated in the present studies, it is evident that brief periods of renal ischemia are usually followed by reactive dilation. In a few preparations, however, renal ischemia was followed by reactive constriction. In general, these findings are consistent with the studies of Hinshaw (33). He finds in the isolated kidney that brief periods of renal ischemia are followed by reactive hyperemia, while longer periods of ischemia are usually associated with reactive ischemia.

From the present study it is apparent that reactive hyperemia following brief periods of ischemia is consistently seen in the forelimb, usually seen in the kidney, and irregularly seen in the intestine. Further, the magnitude and duration of the response is directly related to the duration of ischemia.

Venous-Arteriolar Response

Elevation of venous pressure, at constant blood flow, consistently elicits a venous-arteriolar response in the intestine, forelimb, and kidney. Though the response is still evident in the naturally perfused intestine, it is apparently absent in the naturally perfused kidney.

On the average, elevation of venous pressure in the pump perfused forelimb is without effect on resistance to flow through the bed. The maneuver is associated with a slight rise in resistance to flow through the small vessel segment, no change in resistance through large arteries,and a slight fall in resistance through large veins. The rise in small vessel resistance, on the average, is exactly balanced by the fall in venous resistance. Haddy and Gilbert (23) have reported similar findings in the pump perfused dog forelimb.

The absence of a fall in total resistance and the finding of a slight rise in small vessel resistance indicate the intervention of some mechanism (active or passive) which prevents the increased intraluminal pressure from passively distending the bed. Thus, an unchanged resistance to flow through a vascular bed following elevation of venous pressure is evidence of a venous-arteriolar response.

It is clear from these studies that the venous-arteriolar response is operable in the intestinal vascular bed. However, it is impossible to determine the site of the response, since the data only permit calculation of total resistance. It is likely that resistance to flow through the large veins fell for they were visibly engorged during the maneuver. This would place response mainly on the arterial side.

Johnson (35) reports similar effects of venous pressure elevation in a completely isolated section of ileum.

These studies, like the studies of Hinshaw (31), provide little evidence for a venous-arteriolar response in the normally perfused kidney. In the present experiments, calculated resistance consistently decreased as a function of venous pressure elevation. However, when venous pressure is elevated in the presence of a constant renal blood flow, resistance either rises, remains unchanged, or increases slightly. Haddy et al. (25) have reported similar findings in a large series of pump perfused kidneys.

It is concluded from these studies that the venous-arteriolar response is very efficient in intestine, moderately efficient in the forelimb, and inefficient in the kidney, at least under conditions of natural perfusion.

Mechanisms of Local Control of Blood Flow

The data presented in this report are relevant to all four postulated theories of local regulation of blood flow. In general, the studies provide strong support for the metabolic theory, moderate support for the myogenic theory, and little support for either the tissue pressure or oxygen theories of local control.

Tissue Pressure

Renal lymphatic pressure was used to gain information relative to changes in renal interstitial pressure during local regulation of blood flow in the kidney. The studies clearly demonstrate that changes in renal perfusion pressure over a wide range have little effect upon renal lymphatic vessel pressure. However, changes in renal venous

pressure produce almost proportional changes in lymphatic vessel pressure. An increase in renal perfusion pressure from 80 to 200 mm Hg, which consistently elicits an autoregulatory response, is associated with an increase in lymphatic pressure of only 7 mm Hg. Renal ischemia produces only small irregular changes in lymphatic vessel pressure. The present data is in accord with a previous study (26) which showed that renal lymph flow rate is little affected by renal perfusion pressure but greatly increased as a function of renal venous pressure.

The above findings are in conflict with the studies of Hinshaw et al. (32). Using either needle pressure or deep renal venous pressure as an index of tissue pressure, these investigators found large changes in both pressures during renal autoregulation and rather marked decreases in deep venous pressure during brief periods of renal ischemia. From these findings they concluded that renal autoregulation and reactive hyperemia are predominantly mediated through passive vasomotion subsequent to changes in tissue pressure.

It is felt that renal lymphatic vessel pressure is a better index of renal tissue pressure than either needle pressure or deep renal vein pressure because: 1) needle pressure could give falsely high values if bleeding occurred around the tip of the needle (5), 2) wedged renal vein pressures may not be a true lateral pressure because of insufficient vein to vein collaterals upstream to the wedge site, 3) even if it is a true lateral pressure, venous pressure is determined by no less than four variables - upstream pressure, downstream pressure, upstream resistance, and downstream resistance. Certainly tissue pressure affects the latter two variables but so do many other factors. Thus,

the best that can be said for either measurement is that tissue pressure is probably not higher than the recorded value but could easily be much lower. Support for the use of lymphatic vessel pressure as an index of renal tissue pressure is: 1) the lymph vessels used for the pressure measurement have been shown to communicate with the renal parenchyma, 2) other studies (26) show they remain patent during increased renal artery perfusion pressure, 3) slight manual compression of the kidney increases lymphatic pressure, 4) it is highly unlikely that lymphatic vessels undergo active vasomotion (since they possess little or no smooth muscle), and 5) control pressures measured from these vessels agree very well with the direct renal tissue pressure measurements of Gottschalk (21).

The conclusions from these findings are that renal autoregulation and renal reactive hyperemia are not mediated by passive changes in resistance produced by an altered interstitial pressure but are due to active changes in vessel caliber. However, changes in renal interstitial pressure may play an important role in the renal vascular bed's response to elevated venous pressure.

From the present studies it seems unlikely that changes in tissue pressure play an important role in the forelimb vascular bed's response to changes in arterial or venous pressure. Tissue pressure, as measured in muscle or subcutaneously, is not immediately affected by large alterations in either perfusion pressure or venous pressure. However, changes in capillary hydrostatic pressure that favor net filtration, if maintained for prolonged periods, might eventually produce passive changes in vascular resistance.

The studies indicate that intestinal flow can be influenced by changes in interstitial pressure mediated through changes in intestinal tonus and activity. Intestinal ischemia is often associated with increases in both mean ileal lumen pressure and ileal activity. This could explain the irregular occurrence of reactive hyperemia seen in the present studies. These studies, like those of Johnson (35, 36) fail to show a change in intestinal tonus during either the autoregulatory or venous arteriolar response. However, the measurement of lumen pressure and gut movement are only crude indicators of extravascular pressure. It is conceivable that a better measurement of extravascular pressure would reveal its role in the above response. It is concluded from these studies and the studies of others (6, 51) that changes in transmural pressure, elicited by change in intestinal motility and tonus, can influence intestinal blood flow.

Oxygen Theory

The present studies reveal a very poor correlation between renal venous oxygen tension and renal resistance. A reduction of perfusion pressure from normal to 50 mm Hg was always associated with a fall in renal resistance and in the steady state with a slight drop in renal venous oxygen tension (-4 mm Hg). However, upon releasing the renal artery constriction, renal venous oxygen tension rose about 10 mm Hg above the control value and at the same time renal resistance was still well below the control value (these changes in venous oxygen tension were also without measurable effect on the assay organ, Figure 13). Further, preventing the fall in venous oxygen tension during renal artery constriction, by ventilation with 100% oxygen, failed to alter the

resistance drop. In all experiments, venous oxygen tension rose as renal resistance fell. Finally, increasing oxygen tension alone by ventilation with 100% oxygen, has no effect upon renal or forelimb resistances. Thus, changes in oxygen tension over the ranges studied are without effect upon the renal or forelimb vascular beds.

These findings are in agreement with the studies of Molnar et al. (41), but are in apparent conflict with studies of Carrier et al. (8). The latter group of investigators found that the resistance to flow through blood vessels decreases as oxygen tension is lowered from 100 to 0 mm Hg. However, the fall in resistance is relatively small until oxygen tension is lowered below the levels encountered in the present study.

It appears, from these studies, that oxygen tension is not an important factor in renal autoregulation, and that oxygen does not play a major role in the transient active vasomotion seen in the forelimb during rapid changes in blood flow. Further, O_2 tension does not play an important role in the venous-arteriolar response when it is studied at constant flow. It is probable that tissue oxygen tension is much lower during periods of interrupted flow than during periods of reduced flow. Thus, the oxygen might have a role in the dilation seen following periods of ischemia.

Myogenic Response

The studies concerning the effect of square wave changes in blood flow upon perfusion pressure in the forelimb and kidney yeild data relevant to the myogenic theory.

In the forelimb a square wave halving of flow produces a large

decrease in pressure which was followed by a small slow rise in pressure. According to the myogenic theory, pressure should fall immediately upon the flow change and then fall further as the smooth muscle in the vessel wall responds actively to the decrease in transmural pressure. A square wave doubling of flow is associated with an immediate rise in pressure followed by a gradual fall in pressure until a steady state is reached. Again, this response is not compatible with the myogenic theory. A transient (2 second) doubling of flow produced an immediate rise in pressure upon elevation of flow and pressure returned to control upon reduction of flow. If the increased pressure, during the period of elevated flow, had elicited an active response, pressure should have been higher than control upon return of flow to the original value. The observed responses are more in accord with elastic, viscous, and inertial properties of vessels and change in vascular volume than with active change produced by the alterations of transmural pressure.

In the kidney, a two second square wave doubling of flow often produced changes in perfusion pressure which could be interpreted as a myogenic response. Pressure remained above control immediately after flow was returned to the original value. A permanent doubling of flow through the kidney was associated with an immediate rise in pressure which is often followed by a further progressive rise in pressure (autoregulation). While the progressive rise in pressure may be interpreted as a Bayliss response, the long time course of the response suggests it may be more related to other mechanisms (washout of vasoactive metabolites).

The effect of congestion upon the forelimb vascular bed's

response to ischemia may also bear on the myogenic theory of local regulation. These studies show that partial maintenance of transmural pressure, accomplished by congesting the bed, during the period of ischemia, attenuates the amount of post-ischemic dilation. In fact, congestion completely abolishes the response following short periods (2 to 10 seconds) of ischemia. Based on similar congestion experiments, Patterson (44) has also suggested a role for transmural pressure in the reactive hyperemic response seen in human forearms. Both of the above findings are in apparent conflict with the effects of square wave changes in blood flow upon forelimb perfusion pressure. However, part of the response following ischemia must represent refilling of the vascular bed, particularly the arterial segment. It is also evident that part of the response is due to active dilation because the magnitude and duration of the response is directly related to the length of the ischemia period. Thus, it is conceivable that congestion affects the response by preventing the volume depletion and has no effect on the reactive component of the response.

Thus, the studies provide little evidence for an active myogenic response to alteration of transmural pressure in the forelimb and only equivocal evidence for such a mechanism in the kidney. In general, the responses observed are better explained by inertial and viscous properties of the blood vessels and by changes in vascular volume than by active responses. However, square-wave changes in blood flow to the kidney often produces changes in perfusion pressure that are identical to those predicted by the myogenic theory.

An incidental finding of interest is that injured blood has

unusual vasoactive properties. Such blood produces vasodilation in the forelimb and constriction in the kidney. The agent or agents responsible for the vasoactivity are unknown. In this regard, red blood cells are known to contain relatively large concentrations of adenosine and it is interesting that adenosine also dilates the forelimb vascular bed and constricts the renal vascular bed.

Metabolic Theory

The studies using the forelimb vascular bed as an assay organ for the vasoactivity of venous blood are relevant to the metabolic theory.

In general, the changes in resistance in the assay organ are directionally the same as the active changes in caliber of the vessels in the regulating organ. Thus, maneuvers that decrease flow through the donor organ decreases resistance through the assay organ. Maneuvers that increase flow through the donor organ increase resistance through the assay organ. On the other hand, increasing the metabolic rate of the donor organ produces a decrease in resistance in the assay organ. In addition, the studies show that venous blood is always dilator to arterial blood and that coronary sinus blood is consistently dilator to caval blood.

The above changes in the vasodilator properties of the venous blood, at least in the kidney, are not related to changes in plasma potassium, sodium, osmolality or oxygen tension or to changes in blood pH. Nor are they related to acetylcholine, histamine or epinephrine.

It appears that the ratio of blood flow to metabolic rate is an important determinant of vascular resistance. A change in the ratio seems to alter the vasodilator activity of venous blood in such a way

that resistance to flow through the assay organ is altered in the same direction as through the regulating organ. It is probable that a change in the ratio alters the tissue concentration of some vasodilator metabolite which in turn alters the contractile state of the vascular smooth muscle and hence resistance. The possibility that the responses seen were partly due to changes in blood viscosity subsequent to changes in capillary hydrostatic pressure in the regulating organ should be investigated more thoroughly. It is possible, for example, that part of the enhanced vasodilator property of renal venous blood following renal ischemia is due to decreased viscosity resulting from an influx of fluid during the period of occlusion. Small changes in hematocrit were observed.

Peculiarities of Individual Vascular Beds

The present data provide new information relevant to the basic mechanisms involved in local regulation of blood flow. Further, they indicate that some of the mechanisms postulated to be important factors (tissue pressure and oxygen tension) in local regulation may not be operative at all or only play a minimal role in the responses. Although strong support is provided by these studies for the metabolite theory of local regulation the necessity for involvement of other mechanisms is also evident. Certainly, functional and anatomical peculiarities from one vascular bed to another influence the various local responses. For example, increasing blood flow to the coronary vascular bed, as might occur with elevation of aortic pressure, may increase myocardial contractile strength (1) and thus myocardial metabolism. If the increase in metabolism is proportional to the increase in flow the

vasodilator metabolite concentration would be unaltered which would tend to minimize the autoregulatory response. Of course, depending upon the change in the metabolism to perfusion ratio, any degree of coronary autoregulation could be obtained. This may partly explain the highly variable autoregulatory response seen in the coronary bed in the present study.

One of the most interesting and most difficult responses to explain is the venous-arteriolar response. This response was first described by Gaskell and Burton (17) and was attributed to a "veni-vasomotor" reflex of local origin. Haddy and Gilbert (23) subsequently investigated the response in the forelimb of the pump perfused dog. They concluded the response is mediated over nervous pathways which are probably not local in distribution. The latter interpretation was based on the finding that blocking the forelimb nerves with procaine apparently eliminated the response. Haddy, Scott, Fleishman, and Emanuel (26) examined the response in the renal vascular bed of the pump perfused dog and concluded that the response in the kidney is mediated in part by a non-local reflex and in part by passive vasoconstriction induced by an increase in interstitial pressure. Johnson (35) examined the effects of elevated venous pressure in a completely isolated section of the ileum and found resistance to flow consistently increased as a function of venous pressure elevation. The response was not affected by various sympathetic and parasympathetic blocking agents. From these findings he concluded that the response is mediated by changes in transmural pressure (Bayliss) and has no nervous component, at least in the intestine. Hinshaw (31) re-investigated the effects of venous

pressure elevation upon renal vascular resistance in the naturally perfused kidney and found that resistance decreases as a function of venous pressure elevation. He concluded that the fall in resistance is mediated mainly through a fall in venous resistance subsequent to passive distention of intra-renal veins. Thus, the presence or absence of the response in the renal bed apparently depends on the techniques used to examine the response. The present studies and the studies of Johnson indicate the response in the intestine occurs in both the pump perfused and naturally perfused intestine. It is also probable that the response in the limb is not dependent on a constant blood flow (17). Further, the present studies as well as the studies of Johnson, indicate that the response is not mediated through a nervous mechanism, at least in the forelimb and intestine. Thus, in the intestine and forelimb an increase in venous pressure at constant flow or constant perfusion pressure elicits a response that prevents a passive fall in resistance. That the response is active rather than passive is indicated by the present finding that forelimb tissue pressure and gut lumen pressure are unaffected by the maneuver. Elevation of venous pressure at constant perfusion pressure should decrease the ratio of blood flow to metabolic rate, hence produce dilation rather than constriction. Thus, it would appear the active constriction is initiated by the increase in transmural pressure (myogenic response) as postulated by Johnson. However, this is not compatible with the finding in this study that square wave changes in blood flow do not appear to elicit a myogenic response in the forelimb.

The response in the kidney seems to be complicated by active and passive changes in resistance. Resistance increases or remains

unchanged after venous pressure elevation in the pump perfused kidney, but the same maneuver produces a fall in resistance in the naturally perfused kidney. Renal tissue pressure increases in both situations. The dilation seen in the naturally perfused kidney could be due to: 1) passive distention of veins and perhaps arteries subsequent to increased transmural pressure, 2) active dilation due to a decrease in the ratio of flow to metabolism, subsequent to the fall in blood flow, 3) active dilation due to a decrease in transmural pressure if intraluminal pressure rises more than extraluminal pressure. Certainly, the dilation is limited by the rise in interstitial pressure and possibly by an active response. The lack of dilation seen in the pump perfused kidney could be due: 1) to an unchanged ratio of flow to metabolism, since flow is constant, 2) active constriction due to increased transmural pressure if intraluminal pressure rises more than extraluminal pressure.

It is apparent from the above discussion that the final explanation of the venous-arteriolar awaits further investigation.

It is clearly evident from these studies that a change in intestinal activity or tonus can greatly modify the reactive hyperemic response in the intestine. Certainly, in vascular beds that have little smooth muscle (lung) the passive effects produced by alterations in arterial or venous pressure will predominate.

From the above discussion it is obvious that any exact theory of local regulation of blood flow might have to be modified when applied to a particular vascular bed. However, from the present data, a general hypothesis of local regulation of blood flow would be that local regulation is primarily mediated by changes in vasoactive metabolite concentrations produced by alteration of the ratio of blood flow to metabolic rate.

A possible abetting mechanism is active changes in vessel caliber mediated through changes in transmural pressure.

Effect of Vasoactive Agents on the Intestinal And Renal Vascular Bed

As indicated in the introduction, numerous natural occurring substances are currently being considered as possible candidates for a role in metabolic regulation of blood flow. In the present studies the vascular effects of some of the more likely substances have been characterized in vascular beds in which their effects are substantially unknown.

The renal constriction produced by adenosine, AMP and ADP is surprising in view of their well documented vasodilator effects in the forelimb (14) and heart (59). Intravenous administration of the compounds is also associated with a fall in systemic pressure (20). Even ATP produced only minimal dilation in kidney, whereas it is known to be a potent vasodilator in other vascular beds. This finding may be partly related to the fact that the renal vascular bed is normally relatively dilated and further dilation is often hard to produce (16). Since only one concentration (6.5 μg) of the agents was studied it is possible that their vascular effects might be different at other concentrations. Some recent evidence indicates that epinephrine produces vascular dilation at very low blood concentration and constriction at higher concentrations. However, from the present studies it appears that of the agents studied only ATP could be involved in renal autoregulation.

In contrast to the renal bed, all the adenyl compounds produced vasodilation in the intestinal vascular bed over a wide range of

concentrations. Also, the magnitude of dilation produced by each agent was approximately equal. These findings are similar to those reported by Frohlich (14) in the dog forelimb. None of the compounds appeared to have any affect upon intestinal smooth muscle as indicated by the unaltered lumen pressure. Thus, it is conceivable that all the agents may play a role in local regulation in the intestinal vascular bed.

The effects of acetylcholine and serotonin upon ileal blood flow emphasizes the role of intestinal muscle in regulating intestinal blood flow. The dilation produced by acetylcholine at the lower concentrations is not seen at higher concentrations probably because of increased extravascular compression subsequent to increased activity of the gut smooth muscle. Support for this interpretation is the large overshoot in blood flow and decrease in lumen pressure seen immediately upon stopping the agent. This may indicate that the duration of acetylcholine's effect on intestinal smooth muscle is short relative to the duration of its effect on vascular smooth muscle.

The findings that serotonin increases lumen pressure but does not affect blood flow may indicate the agent does produce some vascular dilation which is perfectly antagonized by an increased extravascular pressure. Support for this statement is the low flow and elevated lumen pressure seen immediately upon stopping the drug. However, local administration of serotonin, in the dog forelimb, often fails to alter total resistance to flow because of a concomitant fall in small vessel resistance and rise in venous and arterial resistance (24). It is impossible to determine from the present studies if the above segmental response also occurs in the intestine. In any event, the action of

serotonin on intestinal muscle appears to be long relative to its effect upon vascular muscle.

The effects of the various cations solutions upon ileal blood flow and calculated resistance are similar to their effect in other vascular beds (16, 43, 49, 50) with the exception of the calcium ion.

The slight increase in blood flow as a function of the sodium chloride infusion rate is that expected on a dilutional basis (decreased viscosity). This dilutional effect (16, 43, 49, 50) has been previously described in the heart, kidney and forelimb. Sodium chloride is apparently without affect on intestinal smooth muscle as indicated by the constant lumen pressure and lack of activity throughout the infusion. However, the saline solution did not affect the sodium concentration of the perfusing fluid, because the solution contained the same amount of sodium as blood.

The magnesium ion appears to be a very potent dilator of the intestinal vasculature and apparently has little effect upon intestinal smooth muscle. However, the technique used to measure intestinal tonus is not sensitive enough to ascertain small changes in tonus, thus part of the dilator effect produced by magnesium may have resulted from a passive relaxation of intestinal smooth muscle.

The slight average increase in ileal blood flow and decrease in calculated resistance produced by calcium chloride infusion is surprising in view of its well documented constrictor effects in several other systemic vascular beds (16, 43, 50). The dilation probably represents a dilutional effect rather than a change in vessel radius because the flow increase is of the same order of magnitude as that produced by

sodium chloride. However, the apparent lack of constriction associated with the calcium chloride infusion is difficult to explain. It may be that the intestinal smooth muscle was relaxed by the calcium infusion and thus masked any vascular constriction. This contention, however, is not supported by the unaltered lumen pressure during the calcium chloride infusion.

The biphasic response of the intestinal vascular bed to potassium chloride infusion, i.e., dilation over the lower range of infusion rates and constriction at the higher infusion rates is compatible with its reported effects in other vascular beds (49, 50). In contrast to the limb and kidney, part of the changes in resistance with the potassium chloride infusion may be related to a passive mechanism invoked by the changes in extraluminal pressure. Some evidence for this statement is the finding that the infusion of potassium plus atropine prevented the rise in lumen pressure and the fall in blood flow that occurred at the higher potassium infusion rates. However, it is also possible that atropine blocks the vascular effects of high potassium concentrations as well as its effect upon intestinal smooth muscle.

An incidental observation of interest is the rise in aortic pressure that always accompanies the infusion of isotonic potassium chloride at rates of 1.0 ml or more per minute. Since the pressor response is elicited before the ileal venous blood has been returned to the systemic circulation it cannot be mediated through a general rise in blood potassium levels. Therefore, the response is probably initiated by local stimulation of afferent nerves from the intestine. Preliminary studies have demonstrated the response cannot be elicited after the ileal section

is denervated. A similar reflex pressor response (13, 37) has been recently demonstrated by local infusion of acetylcholine or lowering of blood through the intestinal vascular bed of the cat. The latter two maneuvers failed to elicit the response in the present studies.

Thus, it appears of the agents tested that only magnesium, potassium and acetylcholine could possibly be involved in local regulation of flow through the intestine.

Interplay Between Local and Remote Mechanisms During Hemorrhage

These studies indicate that under conditions that effect the cardiovascular system as a whole (hemorrhage), the blood vessels are regulated by both local and remote mechanisms.

Immediately following hemorrhage, blood flow through the forelimb, renal and intestinal vascular beds falls proportionately more than the pressure gradient. Calculated resistance is therefore increased. The resistance rise is mediated by active constriction via a baroreceptor induced sympathico-adrenal discharge and by passive constriction from fall in transmural pressure (27). Within a few minutes flow and pressure began to rise toward control and the rise in flow is proportionately greater than the rise in pressure; calculated resistance falls. After twenty minutes the resistance to flow through all three beds is considerably decreased from the maximum value produced by hemorrhage. However, upon re-infusion of the shed blood there is a transient rise in resistance.

If the fall in flow is prevented by pump perfusion during hemorrhage a slightly different response is obtained. Resistance again rises rapidly with the onset of bleeding and reaches a peak value within three

minutes after cessation of bleeding. However, in contrast to the natural flow studies the resistance increase is well maintained during the entire hypovolemic period and promptly falls toward the control value upon re-infusion of the shed blood.

These studies demonstrate that constriction of precapillary vessels in the limb, kidney, and intestine following hemorrhage is better maintained when blood flow is held constant. Thus, the greater waning in resistance seen in the natural flow studies must, in part, result from some local mechanism (autoregulation) probably activated by the reduction in blood flow (accumulation of vasodilator metabolites). The transient increase in resistance seen only in the natural flow studies upon re-infusion of the shed blood is also consistent with this hypothesis (washing out of vasodilator metabolites). That some non-local mechanism is also involved is indicated by the slight disappearance of the constriction even at constant flow. This non-local mechanism could be a lessening of the sympathico-adrenal discharge subsequent to a decreased baroreceptor stimulation as blood volume is partially replaced by fluid movement into the vascular bed.

CHAPTER V

SUMMARY AND CONCLUSIONS

Local regulation of blood flow was compared in four systemic vascular beds of the dog under a variety of experimental conditions. The four theories postulated to explain local regulation (tissue pressure, oxygen tension, myogenic, and metabolite) were separately examined in one or more of the vascular beds with new or slightly modified techniques. Interplay between local and remote regulating mechanisms was investigated in an experimental condition which elicits both types of regulation.

The local regulatory responses were elicited by either altering blood flow through the organ (intestine, forelimb, heart and kidney), and measuring the change in perfusion pressure or altering perfusion pressure (intestine, forelimb, and kidney) and measuring the change in blood flow. The role of transmural pressure (myogenic response) in local regulation was investigated in the forelimb and renal vascular beds by producing square wave changes in blood flow through these organs and measuring the resultant change in perfusion pressure. The role of interstitial pressure in local regulation was evaluated in the kidney, intestine, and limb by using renal hilar lymphatic vessel pressure, muscle tissue pressure, and gut lumen pressure as an index of tissue

pressure in the kidney, limb, and intestine, respectively. The function of oxygen tension in the autoregulatory response was examined in the renal vascular bed by comparing the magnitude of the response in the same kidney before and during ventilation with 100% oxygen. The role of metabolites in local regulation was examined by using forelimb vascular bed of the dog as an assay system for vasoactive material in venous blood from various regulating organs in the same animal. This was accomplished by diverting a portion of the venous outflow from an organ undergoing local regulation through the forelimb while monitoring forelimb perfusion pressure.

The interplay between local and remote mechanisms was investigated in hemorrhage. This was accomplished by comparing the effects of hemorrhage upon vascular resistance through four systemic beds when flow was held constant with the effects in the same beds when flow was allowed to vary.

An inter-organ comparison revealed autoregulation to be efficient in the kidney, only slightly less efficient in the intestine, moderately efficient in the heart and very inefficient in the forelimb. Reactive hyperemia, following brief periods of ischemia, was consistently seen in the limb and kidney but was irregularly seen in the intestine. The venous-arteriolar response could be demonstrated in the pump perfused forelimb, intestine and kidney and in the naturally perfused intestine, but not in the naturally perfused kidney.

Square-wave changes in blood flow to the forelimb produced changes in perfusion pressure that are not consistent with the myogenic hypothesis. However, the maneuver in the kidney was often associated

with pressure changes that are compatible with the myogenic theory of local regulation. Lymphatic vessel pressure, ileal lumen pressure, and muscle tissue pressure were not affected during alteration of arterial pressure in the kidney, intestine, and limb, respectively. Neither did alteration of venous pressure affect ileal lumen pressure or muscle tissure pressure, but lymphatic vessel pressure was affected by alteration of renal venous pressure. The magnitude of renal autoregulation was not affected when the fall in oxygen tension during the maneuver was prevented by ventilation with 100% oxygen. In general, venous blood from a regulating organ produced changes in resistance to blood flow through an assay organ that were similar to the resistance changes in the organ undergoing regulation.

Evidence from the present studies is consistent with the hypothesis that local regulation results predominantly from changes in the contractile state of smooth muscle in the walls of the resistance vessels. Further, that the contractile state of smooth muscle is in part regulated by the ratio of blood flow to metabolic rate of the tissue. Other factors remaining constant, an increase of the ratio enhances the contractile state of the smooth muscle, whereas a decrease in the ratio decreases the contractile state of the smooth muscle. The studies substantiate the theory that local regulation is mediated through changes in concentrations of vasoactive metabolites. Equivocal evidence is also provided in support of the myogenic theory, but little support is furnished for either the tissue pressure or oxygen theories of local regulation.

Evidence is also presented which indicates that both local and

remote mechanisms play an important role in determining organ blood flow under conditions that affect the whole cardiovascular system.

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