SPLANCHNIC CAPACITANCE RESPONSE DURING CHANGES IN BLOOD VOLUME IN CATS

A Thesis Presented to

The University of Manitoba

In Partial Fulfillment of

the Requirements for the Degree of

Master of Science

in

Pharmacology & Therapeutics

George Edward Lister

1974

SPLANCHNIC CAPACITANCE RESPONSE DURING CHANGES IN BLOOD VOLUME IN CATS

by

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A dissertation submitted to the Faculty of Graduate Studies of the University of Manitoba in partial fulfillment of the requirements of the degree of

MASTER OF SCIENCE

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ABSTRACT

These experiments were designed to measure how much blood is mobilized from or pooled in the liver, spleen and gastro-intestinal tract to compensate for a hemorrhage or infusion of blood.

Hepatic volume, splenic weight and intestinal volume were recorded in cats anesthetized with sodium pentobarbitone. Whole blood was removed or infused at rates of 0.5 - 0.6 ml/kg/min until 10 ml/kg (19% blood volume) had been removed or 18 ml/kg (34% blood volume) had been infused. These blood volume changes produced only small changes in arterial and portal pressures except after removal of 8 ml/kg (15% blood volume) when arterial pressure began to decrease rapidly.

With small hemorrhages of up to 4% blood volume, the liver contributed 16%, the gastro-intestinal tract 23% and the spleen a negligible proportion of the blood volume removed. With hemorrhages of 15% blood volume, the liver contributed 21%, the gastro-intestinal tract 22% and the spleen 19% of the volume removed; a total splanchnic contribution of 62%.

During infusions of 5 - 18 ml/kg (10 - 34% blood volume), the liver pooled 20%, the gastro-intestinal tract 40% and the spleen 6% of the volume infused; a total splanchnic contribution of 66%.

It is concluded that the splanchnic bed mobilizes or pools up to 65% of the volume of blood removed from or infused into the cats. The mechanisms responsible for this blood reservoir function are discussed. While several factors may be involved, it seems likely that a reflex regulation involving atrial receptors and the sympathetic innervation of the splanchnic capacitance vessels is of predominant importance.

PREFACE

I would like to express my appreciation to Dr. Clive V. Greenway for his valuable criticism and guidance throughout the course of this investigation and during the preparation of this manuscript. I am most grateful to him.

Because some of the technical procedures could not be carried out by one person, I wish to extend my thanks to Mr. Gary Scott and Miss Linda Hart for their valuable assistance and to Mr. Roy Simpson for photograghy.

I would also like to thank the other members of the academic staff who have never been too busy to show concern and interest in my progress.

I wish to acknowledge the financial support of the University of Manitoba Graduate Fellowship Committee.

Last but certainly far from least, I am deeply indebted to my wife Jean. With her companionship and support this endeavor was greatly facilitated.

DEDICATED TO JEAN

INTRODUCTION

GENERAL INTRODUCTION

"La Constance Due Milieu Interieur Est La Condition
De La Vie Libre." Claude Bernard (1813-1878)

Blood Volume and Capacity

The central position of the blood and the circulation as the transport system which serves to maintain the temperature, composition, and volume of the interstitial fluid ('le milieu interieur' of Claude Bernard) and upon which all organs and tissues depend for continuous supply of nourishment and for removal of waste products, makes it evident that the regulation of volume must be a complex problem (Gregersen & Rawson, 1959). Therefore, to construct an integrated picture of how the blood volume is maintained relatively constant, one would have to systematically analyze the innumerable mechanisms alone and in relation to each other as well as in relation to the direct and indirect effects on blood volume.

The most obvious determinant of blood volume control is the inherent structural size or capacity of the system. Although blood volume and capacity are both subjected to the same control mechanisms, they must be regarded as distinct entities.

In order to maintain the venous return and cardiac output, the system must be adequately distended with blood. Thus, a proper relation must exist between blood volume (what is in the system) and capacity (the size of the system). Since many components of the system can actively dilate or constrict, thus changing the elastic properties of the system, the capacity of the system can vary considerably either to conform to the volume of the blood in the system, or independently thereof.

For the discussion of the control of blood volume and capacity, it might be advantageous to briefly discuss the general organization of the cardiovascular system.

Series - Coupled Sections of Peripheral Vascular Beds

The systemic circulation consists of a great number of parallel - coupled vascular circuits. However, each individual circuit can be divided into a number of series - coupled sections consisting of the heart, the Windkessel vessels, the resistance vessels, the sphincters, the exchange vessels and the capacitance vessels, which are connected to the filling side of the other half of the heart (Folkow and Neil, 1971). The resistance vessels consist of a major precapillary section (small arteries and arterioles) and a minor postcapillary section (venules and small veins). The capacitance vessels consist of a major venous system and also the heart and other vascular sections that have a minor capacitance function. Therefore, the venous system seems to be of great importance in cardiovascular performance as a dominating element in the capacitance function.

Resistance Function of Veins

Let us first consider the resistance function of the veins. The capillaries are situated between two variable resistors, the precapillary and postcapillary resistance vessels, which adjust the mean capillary hydrostatic pressure that controls the filtration exchange across the capillary walls. This function illustrates the importance of the venules acting as the postcapillary resistance.

Capacitance Function of Veins

The dominant role of the venous system is its capacitance function,

because it contains 65 to 75% of the systemic blood volume (Weideman, 1963), and it serves as a cardiac forechamber by being the return route to the heart. It therefore appears to be exactly regulated as even minor adjustments can affect the filling and, therefore, the cardiac output. In their capacitance function, the venules of the different circuits serve the cardiovascular system as a whole rather than serving any local tissue needs.

The present study was undertaken to further investigate the generally accepted hypothesis that an adequate compensation for blood loss in an animal could be achieved in acute situations by a reflex increase in venous tone. This capacitance response in which the overall capacity of the system is reduced causing a redistribution of the blood in the vascular system with little change in the cardiac output would indicate that a certain amount of the blood in the body functions as a reserve. Therefore, the capacitance response may be said to form a 'first line of defense' for maintaining an adequate supply of blood to the tissues.

Blood Reservoirs

Barcroft's theory that most of the reserve blood is closed off from the circulating blood in so - called depots or reservoirs has been refuted (Erslev, 1955). The idea of blood reservoirs has been extended to include vascular areas which can take up or yield large quantities of blood without interfering with the local blood supply to the tissues. In this sense most of the organs and vascular areas within the systemic circulation, especially in the abdomen, have been labelled a blood reservoir (Greenway and Oshiro, 1972). Considerable amounts of blood can be expelled from various organs by the injection of vasoactive substances and direct nerve stimulation

(see later). Therefore, a blood reservoir may be defined as an area from which a significant volume of blood can be rapidly redistributed in a precise and controlled way to maintain cardiovascular homeostasis in response to stimuli such as postural changes or hemorrhage. An area which contains a significant proportion of the blood volume is usually, but not necessarily, a blood reservoir since a mechanism may not exist to mobilize this blood in a controlled way. Thus, the distribution of blood volume and the distribution of blood reservoirs are not synonymous terms. Experimental data on the blood content and the blood reservoir function of various organs are scattered in the literature. Greenway and Oshiro (1972) made a tentative tabulation of this data and later it was modified by Greenway and Lister (1974) (Table 1).

It appears from Table 1 that 28% of the blood volume can be mobilized from the blood reservoirs if the sympathetic nerves supplying these capacitance vessels are stimultaneously and maximally activated. This represents the maximum volume of blood which could theoretically be removed from an animal over a relatively short period of time without causing marked hypotension and disruption of the cardiovascular homeostasis, the 'blood volume reserve' of Groom, Rowland and Thomas (1965). However, simultaneous maximal activation of the sympathetic nerves to these reserves is unlikely to occur after small hemorrhages and in an experimental situation, anaesthesia and surgical preparation of the animal would be expected to further modify the results (Chien, 1967). On this basis one might expect to be able to remove some 15 to 20% of the blood volume before hypotension develops (Groom et al., 1965). From table 1, 6/28 or 21% of the volume removed would be mobilized from the liver, 32% from the spleen and 14% from the intestine, a total splanchnic contribu-

tion of 67% of the volume removed. As will be seen later, the results of this thesis tend to directly confirm these predictions. However, this makes no allowance for a 'second line of defense', reabsorption of extracellular fluid as in skeletal muscle after hemorrhage. This might replace up to one third of the volume of the blood removed (Kerr and Kirklin, 1970; Lundgren, Lundwall and Mellander, 1964) by concomitant adjustments of the precapillary to postcapillary resistance ratio. When this ratio is increased, tissue fluid will be absorped into the vascular compartment. This type of adjustment, where the veins play the role of postcapillary resistance vessels, would not involve a sympathetic venoconstriction as occurs in the mobilization of venous blood. Therefore, reabsorption of tissue fluid and mobilization of venous blood must be two separate events occurring at different times and/or in different areas. In skeletal muscle, reabsorption of tissue fluid seems to be the more important compensatory mechanism for the loss of blood (Lundgren, Lundwall and Mellander, 1964), while in liver, reabsorption of tissue fluid does not seem to occur (Greenway and Lautt, 1970).

Systemic Circulatory Control

In approaching the problem of how the venous system is controlled, one has to take into consideration (a) the functional characteristic of its smooth muscles, (b) the superimposed nervous and hormonal influences, (c) its reflex and central control, and also (d) the co-operation versus competition between neurogenic mechanism and local factors which influence venous tone. Our knowledge of the venous system is very incomplete due to the difficulties involved in studying it. However, enough studies have been made to permit some generalizations concerning the adjustment of venous return,

and the distribution of available blood volume. Generally, control tends to be organized at various levels and based on functional differentiation of the different cardiovascular sections.

Resistance versus Capacitance Vessels. Let us first deal with some principles of the control of the resistance vessels. Their inherent smooth muscle activity is the basis of their maintained flow resistance for it establishes a basal vascular tone. This tone creates a kind of 'blood flow reserve' which is easily mobilized whenever an accumulation of metabolites inhibits the vascular smooth muscle.

The resistance vessels myogenic activity can be reinforced by centrally controlled nerves. Since resistance to flow decreased little after the vessels were denervated as long as the pressure head is kept constant, it is suggested that local control of the resistance vessels predominates in the normal physiological state. This principle seems reasonable, for these vessels subserve the nutritional blood supply of the tissues. However in states of emergency the central nerves can produce very powerful effects on blood flow (Folkow and Neil, 1971).

In contrast to the resistance vessels, the situation on the venous side is markedly different in the control of the flow resistance. In terms of its capacitance functions, venous control appears to be dominated by its extrinsic nervous supply (Folkow and Oberg, 1961). The capacitance system, unlike the resistance system does not show myogenic activity with the exception of the portal vein (Folkow, Heymans and Neil, 1965; Holman, 1969; Mellander and Johansson, 1968; Sutter, 1965). This contrast between the control of flow in the resistance and capacitance vessels appears logical when one compares

the function of the two vessels. The veins subserve the integrated cardiovascular performance as an 'adjustable forechamber' for maintaining the cardiac output while the resistance vessels and the portal veins (which supplies 75% of the liver blood supply) subserve the local needs of the tissues.

Reaction to Pharmacological Agents. Ablad and Mellander (1963) observed that different pharmacological agents seem to produce different response patterns in the resistance and the capacitance vessels of the same tissue. Whereas acetylcholine and isoprenaline dilate both these sections, histamine and hydrazine dilate primarily the resistance vessels and nitrates dilate the capacitance vessels (Ablad and Mellander, 1963; Haddy, 1960). Folkow, Johansson and Mellander (1961) found that angiotensin produced a more pronounced constrictor effect on precapillary than on postcapillary vessels. Greenway and Lautt (1972) and Greenway and Stark (1969) demonstrated that angiotensin and vasopressin produced their constrictor effect primarily on the resistance vessels of the liver and spleen. Infusions of noradrenaline cause an effect on the venous system similar to that of the sympathetic nerves and injections of adrenaline indirectly increase blood pressure through its cardiac action. However, the concentration of these substances in the circulation is very low and therefore, the adrenal medulla play little, if any role in the circulatory adjustments (Hodge et al., 1969; Regoli and Vane, 1966; Celander, 1954).

Circulatory Changes Associated with Venous Pooling or Distension. The veins with their thin, distensible and wide - bore walls with consequent low resistance are well suited to accommodate a volume load. Such a volume load

occurs when man moves from the supine to the erect position. This type of movement is associated with a great hydrostatic load that would be exerted on the capillaries. The counteracting mechanisms, that may be used to decrease the tendency of transcapillary loss of fluid in the above situations are: (a) in the abdomen, the hydrostatic tissue pressure of the internal organs is likely to be similar to that produced if the abdomen were filled with fluid. This would create an extramural pressure that may balance the raised intravascular pressure (Lam, 1939; Rushmer, 1947). (b) On the precapillary side, there will be an increase in the precapillary to postcapillary resistance ratio due to sympathetic nerve activation and myogenic automaticity of the precapillary resistance vessels (Mellander, Oberg and Odetram, 1964; Folkow and Oberg, 1961). This activity may lead to closure of a number of sphincters and therefore the blood flow would be shunted through fewer capillaries than normally and hence the capillary surface area available for flow and filtration exchange would be reduced. Mellander, Oberg and Odetram (1964) showed that the functional capillary surface area in the human foot will decrease from one third to one eighth of normal on shifting the body to an erect postion, and the tendency for filtration loss of fluid correspondingly decreases. Therefore, this seems to be an important mechanism to protect against the formation of edema.

Baroreceptors. It is well established that both aortic and carotid baroreceptors, and also the chemoreceptors, participate in the regulation of the resistance vessels and for many years were also thought to cause a significant constriction of the capacitance vessels (Bartelstone, 1960; Oberg, 1964; Alexander, 1954; Salzman, 1957; Heymans and Neil, 1958; Ross,

Frahn and Braunwald, 1961; Kabler, Goldblatt and Braunwald, 1962). However in recent years serious doubt has been raised as to whether the venous compartment is affected by these reflexes. A venoconstriction would be expected to cause a redistribution of blood and an increase in cardiac output but it has been shown that cardiac output changes very little during baroreceptor reflex responses. (Polosa and Rossi, 1961; Corcondilas et al., 1964; Bond and Green, 1969; Epstein et al., 1969; Resnicoff et al., 1969; Vatner et al., 1970). Direct studies on the capacitance vessels also showed that the involvement of these vessels is minimal in the vascular beds of skeletal muscle, intestine and liver (Browse et al., 1966; Hadjaminas and Oberg, 1968; Mason and Bartter, 1968; Brender and Webb-Peploe, 1969; Epstein et al., 1969; Kizirka et al., 1970; DiSalvo et al., 1971; Greenway and Lautt, 1972).

Low Pressure Receptors. Low pressure regions of the circulation have been demonstrated to elicit reflexes via low pressure receptors located in the central venous, atrial and pulmonary compartments which when stimulated lead to bradycardia, arterial hypotension and vasodilation (Aviado and Schmidt, 1955; Alexander, 1956; Folkow, Johansson, Mellander and Oberg, 1960; Salisbury, Cross and Rieben, 1960; Ross, Frahm and Braunwald, 1961; Paintal, 1973). However, there is still no clear evidence as to the quantitative influence of such reflexes, for selective stimulation of these low pressure receptors often seems to involve serious interference with normal cardiac performance.

There are at least two different types of atrial pressure receptors: type A, whose natural stimulus is increased with atrial tension; and type B, whose natural stimulus is increased with atrial volume (Paintal, 1973).

Stimulation of the left atrial receptors by overdistention caused bradycardia by activation of the vagus nerve and a generalized reflex vasodilation of resistance and capacitance vessels. This reflex vasodilation was due to inhibition of adrenergic vasoconstrictor fibre activity with no evidence of any cholinergic vasodilator fibre activation (Oberg and Thoren, 1973). Following hemorrhage, these same low pressure receptors have been indicated in the release of and production of vasopressin and angiotensin respectively (Weinstein, Berne and Sachs, 1960; Beleslin, Bisset, Halder and Polak, 1967; Henry and Pearce, 1956; Gauer and Henry, 1963; Henry, Gauer and Reeves, 1956; Murdaugh, Sieker and Manfiedi, 1959; Ginsgurg, 1954; Share and Levy, 1962; Share, 1965; Share, 1967; Henry, Gupta, Meehan, Sinclair and Share, 1968; Scornik and Paladine, 1964; Regoli and Vane, 1966; Hodge, Lowe and Vane, 1966; Hodge, Lowe, Ng and Vane, 1969). These vasoactive peptides have been demonstrated to produce their constrictor effects in the splanchnic vascular bed to be primarily on the resistance vessels (Greenway and Lautt, 1972; Greenway and Stark, 1969).

To date, there is no known data on the effect of low pressure receptors on veins. However a mechanism similar to that on the arterial side is teleogically attractive. Right atrial pressure receptors, by affecting venous sympathetic tone, could adjust central venous pressure and hence the load on the heart.

Passive Changes. Another important mechanism which deals with blood volume and capacity changes is that of passive collapse and distension. Passive changes in the capacitance vessels would be due to changes in transmural venous pressure that resulted from changes in central venous pressure or from changes in organ blood flow which itself is a compensatory

response in the regulation of blood volume and distribution. Oberg (1967) noted that blood was mobilized from the hindquarters and from the intestine in cats in response to sympathetic nerve stimulation and that this expulsion of blood from these organs had both an active and passive component. Chien (1967) and Brooksby and Donald (1972) observed that the reduction in splanchnic blood volume consisted also of a passive and active response of the capacitance vessels.

Venous distensibility is shown in figure 1, the pressure - volume curve for veins (Folkow and Neil, 1971). At high pressure, venous distensibility is small because of the stretching of stiff collagen elements. The high wall distensibiltiy at low transmural pressure is not true distensibility but reflects a change in the geometry of the vessel. Below a venous pressure of 6 mmHg., the cross-sectional area of the vein changes from a round to an elliptical shape. Because the cross-sectional area of an ellipse is less than a circle of the same perimeter, then the capacity of the venous segment alters greatly as the pressure rises from zero to six mmHg. Therefore, 'true distensibility' of veins, ie., the increase in perimeter produced by a stretching force, is low in most veins (Oberg, 1967). Since the portal vein has a higher venous pressure than most veins, then according to Oberg, the portal vein should show only minimal passive changes. However, it could be very misleading to extrapolate Oberg's work, which was performed on isolated veins, to include the venules, the site of the capacitance response 'in vivo'. Therefore, it is difficult to draw any sort of conclusion of passive capacitance changes due to transmural pressure changes.

However, the capacitance vessels appear to have some basal sympathetic

tone and therefore this basal tone could resist passive changes causing them to be only minimal. Evidence for this comes from Nickerson (1970) who demonstrated that the administration of an adrenergic alpha-receptor blocking agent caused a redistribution of blood volume from the pulmonary to the systemic bed. Chien (1967) found this tone was increased in animals which were anaesthetized and subjected to surgery.

Summary. Our present knowledge about control of the venous system is still fragmented. Work to date has shown that the veins are not a passive draining system of tubes but a specific vascular section that is at least as reactive and well controlled as any of the other compartments within the circulation. Generally, the venous system and the arterial system are responsive to the same stimuli but, by special organization, the veins may react differently from the arterial system, both quantitatively and qualitatively. This is so because the venous system has two main dynamic functions, the resistance function, ie., of importance in the regulation of intravascular/extravascular volume ratio, and the capacitance function, ie., of importance in the displacement of blood within the cardiovascular system as an integrated unit rather than in meeting any local tissue demands.

The Splanchnic Vascular Bed

In view of the dimensions of the splanchnic vascular bed which suggest its importance in the cardiovascular system, it is surprising how little is known about the mechanisms involved in the response of the splanchnic capacitance vessels to serve as a blood reservoir. Our continuing interest in this vascular bed (Greenway and Stark, 1971) led to a study of its capacitance function after hemorrhage and blood volume expansion. However,

before I describe the experimental results obtained, an up to date functional description of the circulatory system in each of the organs of the splanchnic vascular bed is necessary.

Intestinal Vascular Bed

Johnson and Selkurt (1958) observed a number of changes in the intestine during hemorrhagic shock which indicated a complex intestinal vascular response to hemorrhage. Generally, a sudden drop in weight in the lower intestinal region was observed in hemorrhage which persisted for the duration of hypotension. In the upper intestinal region, an increase in weight was observed which could be abolished with adrenalectomy (Johnson, 1960). Therefore, systemic hypotension seems to induce sympathetic discharge which by way of the intestinal nerves causes a decrease in the intestinal blood volume and via the adrenal medulla secretion of adrenaline causes an increase in the intestinal blood volume. The increase in the intestinal blood volume may be caused by adrenaline causing an arterial vasodilation (Greenway and Lawson, 1966) and therefore an increased blood flow to the upper intestine

The intestine is richly supplied with sympathetic nerves. Stimulation of these nerves produces a reduction in the gastro-intestinal tract volume (Folkow et al., 1964). Haglund (1973) also observed a reduction in the gastro-intestinal tract volume which was maintained at its maximum during the period of the induced hypotension. Folkow et al. (1964) observed that intestinal volume decreased at the onset of intestinal sympathetic nerve stimulation and that this volume change reached a plateau. Maximal responses were obtained at frequencies of about 4 to 6 Hz. when 30 to 40% of the intestinal blood volume was expelled. This represents about 4% of the animal's total blood

volume when the portal pressure was zero. Haglund and Lundgren (1972) observed no significant intestinal blood volume change in a denervated small intestine when the arterial inflow pressure was suddenly lowered to 55 - 50 mmHg. as compared to a significant decrease in blood volume observed in the innervated small intestine. However, upon exposing the whole animal to 40 mmHg. level, the denervated intestine decreased in volume and this decrease is due to passive collapse of the veins (Haglund, 1973). These results suggest that there can be both an active and passive capacitance response to severe hemorrhage and that the active capacitance response is mediated through sympathetic nerves.

The afferent mechanism of this sympathetic reflex is unclear. As described previously under capacitance vessel control, the low pressure receptors may play the major role in such a reflex while the high pressure receptors probably play a minor role. Hadjiminus et al. (1968) observed that the high pressure baroreceptors produce a resistance and capacitance response in the intestine similar to sympathetic nerve stimulation. Since, in his experiments, the venous pressure was zero, it is unclear as to how much of the intestinal capacitance response was due to an active and/or a passive response.

Splenic Vascular Bed

The splenic contribution to control of distribution of blood volume has been studied more intensively than that of any other organ. The spleen's reputation as a reservoir began in the 17th century with Malpighi's description of muscular trabeculae (cited by Franklin, 1937) and was advanced by Roy's studies with an oncograph, relating splenic contraction to factors affecting the blood pressure (Roy, 1881). Barcroft and Barcroft (1923) and Barcroft and

Steven (1927) firmly established the spleen as a reservoir in dogs and cats by showing sequestration of erythrocytes and by direct observation of exteriorized spleens.

The vascular bed of the spleen empties via the portal vein into the liver. The capacitance function of the spleen has been studied by plethysmography (Roy, 1882; Barcroft, Khunna and Nisimara, 1932), chronic exteriorization (Barcroft and Stephens, 1972), visualization through an abdominal window (Barcroft et al., 1972), photographic (Celander, 1954), radiography (Barcroft, Harris, Orahovats and Weins, 1925) and weighing (Stick, MacLean and Vischner, 1959; Greenway and Stark, 1970).

The expulsion of blood from this depot could be accomplished by activity of the capsule and trabeculae or the venules and sinusoids. The spleens of cats and dogs greatly change their blood volume, while in man, the splenic capsule contains only little muscle, the organ is small and its role as a blood reservoir is negligible (Folkow and Neil, 1971). The above observations and the demonstration by Bickerton (1963) on isolated spleen strips support the view that the capsule and trabeculae are responsible for contraction of the spleen.

The micro - circulation of the spleen is extremely confused. However, in spite of the disagreements, it is generally agreed that the spleen constitutes a storage system for high hematocrit blood. Therefore, the blood expelled from the spleen due to splenic contraction as in hemorrhage is concentrated and has a hematocrit value higher than the circulating blood. The observations by Greenway, Lawson and Stark (1968) were that the splenic weight recovered slower than flow when sympathetic splenic nerve stimulation

ceased and that occlusion of the splenic vein for two minutes did not appear to accelerate the recovery process of splenic weight. This suggests that either there is a slow relaxation of the capacitance mechanism or the filling of the spleen with concentrated erythrocytes is a complex process requiring time. Schafer et al., (1896) observed that splenic volume varied when arterial pressure changed. Barcroft et al., (1925 and 1927) observed the spleen to contract when a cat exercised and the response was dependent on an intact nerve supply. In the dog (Grindlay, Herrick and Mann, 1939) and in the cat (Barcroft et al., 1927; Greenway and Stark, 1969), it was observed that the smooth muscle of the splenic capsule and trabeculae did not show either pressure - induced myogenic contraction or passive responses to change in arterial pressure.

Stimulation of the sympathetic nerves to the spleen produced a splenic contraction (Greenway, Lawson and Stark, 1968). The splenic volume decreased at the onset of splenic sympathetic nerve stimulation and the volume change reached a plateau at about 3 Hz. indicating that a maximum capacitance response had been reached. This maximum capacitance response indicated that 74% of the splenic blood volume was expelled and this represents about 9% of the animal's total blood volume. After denervation of the spleen, the spleen still showed a contraction during a hypotensive hemorrhage. This contraction was abolished after adrenalectomy (Greenway, Lawson and Stark, 1968; Greenway and Stark, 1969). These observations suggest that the splenic capacitance vessels are controlled by the sympathetic nerves and secretions from the adrenal medulla.

Extracts of the adrenal medulla caused contraction of the spleen in

dogs (Oliver and Schafer, 1895). Adrenaline was found to produce a greater capacitance response in the spleen than noradrenaline (Ahlquist, Taylor, Rawson and Sydow, 1954; Celander, 1954; Bickerton, 1963; Greenway and Stark, 1970) while noradrenaline was found to be similar to nerve stimulation (Davies, Gamble and Withrington, 1968; Greenway and Stark, 1970). However, Regoli and Vane (1966) have found that a slow non-hypotensive hemorrhage does not produce an adrenal medullary discharge. Hodge et al. (1969) and Celander (1954) have concluded that the quantitative importance of hormones, released from the adrenal medulla after different stimuli, is insignificant when compared to the effects of activation of the regional sympathetic nerves.

Phenoxybenzamine decreased splenic contraction in response to splenic nerves and injection of adrenaline or noradrenaline (Green et al., 1960; Thoenen et al., 1964; Haefely et al., 1965; Bickerton, 1963; Ottis, et al., 1951). Splenic volume was unaltered by beta - adrenergic agonists (Davies et al., 1969; Greenway and Stark, 1970). Thus splenic contraction seems to be mediated by alpha - adrenergic receptors.

Passive collapse of the splenic capacitance vessels during hemorrhage seems unlikely for splenic volume remains constant with a reduction in portal flow or arterial pressure (Greenway, Lawson and Stark, 1968).

Thus, the available evidence favors sympathetic control of the splenic capacitance response. The afferent pathway involved in such a response mechanism is unclear but I believe it to be elicited by low pressure venous and atrial receptors along with minimal involvement of the high pressure baroreceptors that have been previously described under capacitance vessel control. This belief is supported by a small amount of evidence presented

by Pelletier et al. (1971).

Hepatic Vascular Bed

The liver has been regarded as a substantial blood reservoir since 1915 on the basis of pharmacological studies with thermostromhrs. The hepatic vascular bed receives about 33% of the cardiac output (Greenway and Stark, 1971) and of this about one third reaches the liver via the hepatic artery (greenway et al., 1966). The remainder is via the portal vein which drains both the gastro-intestinal tract and the spleen.

A number of studies have been reported on the effects of hemorrhage on the hepatic vascular bed. In the liver of the cat a prompt decrease in volume occurred after a small hemorrhage and this response was abolished after section of the hepatic nerves (Griffith and Emery, 1930). In man the size of the radiograph shadow of the liver decreased after hemorrhage (Glaser, McPherson, Prior and Charles, 1954).

Investigations of the effects of hepatic sympathetic nerve stimulation on hepatic volume in cats were reported by Greenway and Stark (1969) and similar responses have been observed in dogs (Greenway and Oshiro, 1972). Hepatic volume decreased at the onset of stimulation of the hepatic nerves and reached a plateau after 4 minutes. Maximal responses were obtained at frequencies of about 6 Hz. when 50% of the liver blood volume was expelled. The hepatic capacitance response was therefore large and up to 7% of the animal's total blood volume was expelled. This hepatic capacitance response is mediated through alpha - receptors (Greenway and Lautt, 1972).

The effects of hepatic nerve stimulation on fluid exchange in the liver have been looked at by Greenway, Stark and Lautt (1969), who showed that

after the initial decrease the hepatic volume remained steady during the period of hepatic nerve stimulation. This suggested that net fluid movement across the sinusoidal walls did not occur and therefore the sinusoidal hydrostatic pressure and the presinusoidal to postsinusoidal resistance ratio were unchanged. In this aspect the liver resembled intestine (Folkow, Lewis, Lundgren, Mellander and Wallentin, 1964) and spleen (Greenway, Lawson and Stark, 1968) rather than skeletal muscle (Mellander, 1960).

When the hepatic venous pressure was raised, Greenway and Lautt (1970) observed an initial increase in hepatic blood volume which was followed by a slower steady increase in volume which did not indicate that it would reach a maximum. The initial increase in hepatic volume appears to be due to distension of the capacitance vessels and the slower increase due to filtration. It therefore appears that the hepatic tissue hydrostatic pressure changes in the liver do not play a significant role in the balance of fluid exchange across the sinusoids. In this aspect, the liver did not resemble the intestine and the spleen. Upon returning the hepatic venous pressure to zero, the hepatic blood volume returned close to the control level without any evidence of reabsorption of the filtered fluids. Brauer (1959) and Greenway and Lautt (1970) reported no effect on hepatic volume when hepatic venous pressure was reduced to below zero.

Since hepatic volume was unaltered by a dose of vasopressin that reduced intestinal flow by 60%, by altering arterial pressure, and by autoregulatory escape of blood flow seen during hepatic nerve stimulation, it may be concluded that passive capacitance changes in the liver as a result of hemodynamic alterations are minimal (Greenway and Lautt, 1972).

Thus, the available evidence suggests that the hepatic capacitance response is under direct sympathetic control. It has been shown by Lautt and Greenway (1972) that activation of the high pressure baroreceptors did not result in a significant capacitance response. Therefore, as a working hypothesis, the afferent limb of this sympathetic reflex could be low pressure venous and atrial receptors as previously described.

Present Study

In the resting cat, the splanchnic vascular bed accommodates about 36% of the total blood volume (table 1), receives a similar proportion of the cardiac output, and thus is a major determinant of total peripheral vascular resistance and systemic arterial blood pressure (Folkow and Neil, 1971). Experimental data on the blood content and the blood reservoir function of the splanchnic vascular bed are scattered in the literature. Table 1 (Greenway and Lister, 1974) indicates that the splanchnic vascular bed releases 19% out of the possible 28% of the total blood volume which can be mobilized from all the vascular beds upon maximum sympathetic nerve stimulation.

The experiments in this study were designed to further confirm the predictions for the splanchnic vascular bed made in table 1 and to measure the splanchnic bed ability to pool blood during an infusion of whole blood.

Many investigations were devised to explore the response of the splanchnic vascular bed to hemorrhage. These investigations involved a rapid hemorrhage to create a hypotensive state (Alexander, 1955; Friedman, Frank and Fine, 1951; Glaser, McPherson, Prior and Charles, 1954; Johnson, 1960; Reynell, Marks, Chidsey and Bradley, 1955). Such an investigational procedure creates

involved and complex problems for a large rapid hemorrhage would maximize all compensatory mechanisms in attempting to return the animal to its homeostatic state. It is not easy to standardize hemorrhage. Besides using the same species and anesthetic agent, there is need to consider the body weight, blood volume, cardiac output, regional blood flows, arterial pressure and the depth of anesthesia and hence the activity of the compensatory mechanisms. Hemorrhage in different experiments may be compared by reducing cardiac output by a constant proportion, by removal of a similar volume in each cat, or by production of similar degrees of hypotension. Since satisfactory measurements of cardiac output involves considerable surgical intervention, this means of standardization was not employed. In order to avoid the problems created by a large rapid hemorrhage, I used a slow nonhypotensive hemorrhage and therefore bleeding to a given blood pressure was not reasonable. Therefore, blood was removed at a constant rate, 0.5 ml/kg/min., through a cannula inserted into the inferior vena cava.

Anesthesia

All experiments were done in cats anesthetized with sodium pentobarital. A variety of studies in dogs has indicated that anesthesia with pentobarbital has negligible effects on the splanchnic vascular bed; splanchnic blood flow remains essentially unchanged and this has been associated with a slight decrease in splanchnic vascular resistance (Evringham, Brenneman and Howath, 1959; Gilmore, 1958; Katz and Bergman, 1969; MacCannell, 1969; Pratt, Holmes and Sheid, 1952). Most cardiovascular studies are done in animals anesthetized with either pentobarbital or chloralose. Baroreceptor and chemoreceptor reflexes are somewhat depressed under pentobarbital anesthesia but they are

exaggerated and less uniform under chloalose (Geisheimer, 1965; Clifford and Soma, 1969; Brown and Hilton, 1956; Armstrong, Porter and Langston, 1961; Strobel and Wollman, 1969). In the cat, Greenway, Lawson and Mellander (1967) found that the response of the hepatic arterial bed to carotid occlusion and hepatic nerve stimulation was similar under pentobarbital or chloralose and urethane anesthesia. Fisher et al. (1956), Gilmore (1958), Evringham (1959), Galindo (1965), and Katz (1969) showed no significant alteration in hepatic vascular parameters in cats anesthetized with pentobarbital or other barbituate anesthetics.

Pentobarbital has been reported to cause dilation of the dog's spleen (Hahn, Bale and Bonner, 1943) and to relax the capsule of the spleen (Wakim, 1946; Hausner, Essex and Mann, 1938), but this enlargement or relaxation was seen only when the spleen had been contracted within the preceding 5 or 10 minutes by some other mechanism. With small doses given to cause a fall in blood pressure the spleen always contracted (Guntheroth and Mullins, 1963).

A great deal of the previous work on the effects of hemorrhage on the splanchnic vascular bed has been done using pentobarbital (Greenway and Stark, 1971). Since much more is known about the pharmacological actions of pentobarbital than about chloralose and since pentobarbital tends to minimize rather than exaggerate the responses, pentobarbital was chosen as the anesthetic agent. The present results may be applied only to cats anesthetized with sodium pentobarbital. Further investiagation is required to confirm these results in different species and in conscious animals.

Technique

The techniques available for studying the capacitance vessels are few.

Many studies have been performed using isolated veins. However, this technique really does not measure in vivo capacitance responses which take place in the small venules. Therefore, an extrapolation of results from isolated veins to venules in vivo could be very misleading. Another method that has been used to measure the capacitance responses in a vascular bed is to take the difference between the summed change in arterial inflow into the bed and the summed changes in venous outflow from the bed. The validity of measuring a change in blood volume from the difference between inflow and outflow depends on the accuracy with which blood flow can be measured and on the completeness with which the region under study can be vascularly isolated.

The method chosen for these experiments was Folkow's plethymsographic technique which was modified by Greenway, Stark and Lautt (1969) to measure directly the hepatic volume. The plethysmograph technique allows direct volume measurements of the intestine and liver. Althrough the plethymsograph is a valid technique to measure the splenic volume, the gravimetric technique for direct volume measurement was used so that this work could be compared with the work of Greenway and Stark. The major disadvantage of the plethysmograph and gravimetric technique is their inability to separate active from passive effects.

METHODS

METHODS

General

Thirty six cats of either sex and weighing between 1.9 - 2.9 kg. body weight, mean 2.4 kg., were fasted for 24 hours. Anesthesia was induced by intraperitoneal injection of sodium pentobarbital (Abbott, 30 mg/kg). When reflex ear, limb and swallowing movements returned, supplementary doses of pentobarbital (2 mg/kg) were given through a cannula in a forelimb cutaneous vein. A heating element, positioned under the operating table, maintained the rectal temperature of the cats at 38°C. The cats respired spontaneously, but to ensure a free airway the trachea was cannulated. Mean systemic arterial pressure was recorded from a cannula placed in the left femoral artery and connected to a P23AC Stathum pressure transducer. The abdomen was opened by a mid-line incision and the free edges of the peritoneum muscle and skin were sewn together. Mean portal pressure was recorded (P23BC Statham transducer) from a cannula inserted into the portal vein through a small branch from the appendix. All recordings were made on a Beckman Type R dynograph recorder. A cannula was inserted through a femoral vein so that its tip lay in the lower abdominal inferior vena cava; this cannula was used for infusion or withdrawal of blood.

After completion of the surgery, all animals were given 5 ml. of 5% dextran in 0.9% w/v NaCl and the recorded variables were allowed to stabilize for 30 - 45 minutes. In the cats subjected to hemorrhage, blood was removed at a constant rate, 0.50 ml./kg./min., through a cannula inserted into the inferior vena cava into a glass syringe containing heparin (10 mg.) and a magnetic stirring bar. In the volume expansion studies, fresh whole blood

was obtained from a large doner cat which was anesthetized with ether and the jugular vein cannulated. Blood was withdrawn using 20 ml. syringes and the collected blood was placed into a glass container with 10 mg. heparin. This blood was infused through a similarly placed cannula at approximately the same rate, 0.56 ml/kg/min., as in the hemorrhage experiments. The blood was mixed by a magnetic stirring bar.

Blood Volume Determinations

The blood volume of the intestine and liver was determined at the end of the experiments by the method of Mellander (1960) for the intestine and by the same method modified by Greenway, Stark and Lautt (1969) for the liver. A sample of intestinal or hepatic blood was taken and a cord was tied around the outlet from the plethysmograph thereby simultaneously clamping all vessels. The vessels were cut below the cord and the weight of the portion of the intestine or liver in the plethysmograph was determined as was the total weight of the gastro-intestinal tract and liver. The intestine and liver were flushed out with 0.9% saline and the washout was collected and measured.

An ammonia solution was prepared by diluting 1.4 ml of stock solution (28% ammonia) to 100 ml with deionized water. Forty ml. of this solution was placed in each of four plastic containers and 1 ml of washout sample was added to one, duplicate samples of 0.1 ml. blood were added to two other containers and the fourth served as a blank. Light absorbance was determined with a spectrophotometer at wave length 540 .. Intestinal and hepatic blood volumes were calculated (table 1) by the equation:

$$\frac{\text{Abs. Read. Washout Samp.}}{\text{Abs. Read. Mix Ven. Samp.}} \times \frac{\text{Vol. Mix Ven. Samp.}}{\text{Vol. Washout Samp.}} \times \frac{\text{Washout Vol.}}{\text{Organ Wt.}} \times 100$$

This expression gives the volume in ml/100g of tissue.

The splenic blood volume and the cat's mean total blood volume was not determined but taken from the literature (see results and table 1).

Intestine

Experiments were performed on twelve cats (six subjected to hemorrhage, six to infusion). A section of ileum, usually weighing 32 ± 1.5 g, was chosen for the experiment. This section of the ileum was separated from the remainder of the intestine by division between ligatures at each end. The mesentery was divided between ligatures down to the origin of the superior mesenteric artery and vein, thus providing a vascular pedicle to the separated loop. The loop was placed in a triangular plexiglass plethysmograph which was sealed with plastibase (Squibb). The method was similar to that previously described (Folkow, Lundgren and Wallentin, 1963) except that the intestinal vein was left intact. The vascular pedicle containing the superior mesenteric artery and vein came out of the plethysmograph through a closely fitting opening at the proximal angle. In these experiments, the tip of the portal pressure cannula lay in the mesenteric vein within the plethysmograph and the pressure was recorded before and after the plethysmograph was sealed. Great care was taken to avoid obstruction to the vessels and nerves. With this arrangement, the intestine was enclosed in the plethysmograph in a perfectly air and water tight way without interference with either the arterial inflow, the venous outflow or nerve conduction, and the mobility and color of the intestine could be directly inspected. The plethysmograph was filled with Ringer-Locke solution at 37°C and connected to a float recorder which operated an isotonic transducer (Harvard Apparatus Co. Model 356) (fig. 2). The pressure within the plethysmograph was adjusted to zero with respect to the level of the heart. The temperature inside the plethysmo-

graph was maintained at 36°C with the aid of a lamp. The abdominal cavity was closed by pulling the skin and muscle (which have been sewn together) in around the sides of the plethysmograph to minimize exposure of the mesentery. The mesentery that led into the plethysmograph was kept moist by being wrapped in gauze soaked with saline.

In each experiment, the recorded volume change was multiplied by the total weight of the stomach, intestine and colon and divided by the weight of the intestine in the plethysmograph and the body weight to convert the data into ml. change in gastro-intestinal volume/kg. body weight. Using this unit, ml/kg, the mean volume change is expressed as:

(a) a percentage of the mean blood volume removed or infused

$$\frac{\text{G.I.Tract Vol. Change (ml/kg)}}{\text{Mean Vol. Removed or Infused (ml/kg)}} \times 100$$

(b) a percentage of the mean total blood volume of the animal (Groom et al., 1965)

$$\frac{\text{G.I.Tract Vol. Change (ml/kg)}}{52.0 \text{ ml/kg}} \times 100$$

(c) a percentage of the mean gastro-intestinal blood volume (table 1)

$$\frac{\text{G.I.Tract Vol. Change (ml/kg)}}{5.2 \text{ ml/kg}} \times 100$$

Spleen

In another twelve cats (six subjected to hemorrhage, six to infusion), splenic weight was recorded by the method previously described and evaluated (Greenway, Lawson and Stark, 1968). When the spleen was exposed by a mid-line abdominal incision, the vessels in the gastro-splenic ligament and the inferior part of the lieno-renal ligaments were tied and the ligaments divided to allow mobilization of the spleen. The vessels to the body and tail of the pancreas were tied.

The spleen was lifted through the abdominal incision, wrapped in gauze moistened with warmed saline solution, 37°C, and surrounded by thin polythene sheet. It was then placed on a weighing cradle made from polythene covered wire which was bent to the shape of the spleen and indented to accommodate, and prevent undue tension on the vascular pedicle. The cradle was suspended freely just above the abdominal wall from a force displacement transducer (Grass FT03C) calibrated by weights to record the splenic weight (fig. 3). The signal from the transducer was fed into a Beckman dynograph recorder (Type R). The temperature of the spleen was checked periodically and it did not vary by more than 2°C from the rectal temperature. In the infusion experiments, the portal pressure cannula was placed in such a way that the cannula tip lay in the portal vein close to the entry of the splenic vein. At the end of each experiment the pedicle was tied and cut. Any difference in recorded weight caused by the procedure was due to tension on the pedicle and this weight was substracted from the values obtained during the experiment. It was assumed that the pedicle tension remained constant during the experiment. This assumption was shown to be valid since if the splenic pedicle is tied but not cut there is no change in weight over several hours (Greenway, Lawson and Stark, 1968). In each experiment, the recorded weight changes were divided by the body weight to convert the data to gram change in splenic weight/kg. of body weight. This unit, gm/kg, was directly expressed as ml/kg inorder that the splenic change could be in volumetric terms. This calculation assumes that the specific gravity of blood expelled from the spleen is 1.0. This assumption is incorrect for splenic blood with its high hematocrit would have a specific gravity of about 1.07. However,

since the splenic blood hematocrit was not determined and therefore the above calculation would overestimate the splenic response by some 7%. Using the unit, ml/kg, the mean volume change is expressed as:

(a) a percentage of the mean blood volume removed or infused

$$\frac{\text{Splenic Vol. Change (ml/kg)}}{\text{Mean Vol. Removed or Infused (ml/kg)}} \times 100$$

(b) a percentage of the mean total blood volume of the animal

$$\frac{\text{Splenic Vol. Change (ml/kg)}}{52.0 \text{ ml/kg}} \times 100$$

(c) a percentage of the mean splenic blood volume (table 1)

$$\frac{\text{Splenic Vol. Change (ml/kg)}}{6.2 \text{ ml/kg}} \times 100$$

Liver

In another twelve cats (six subjected to hemorrhage, six to infusion), hepatic volume was recorded by the plethysmograph method previously described and evaluated (Greenway, Stark and Lautt, 1969; Greenway and Lautt, 1970). Inorder to fit the hepatic plethysmograph within the abdominal cavity, it was necessary to make an incision along the right subcostal margin (4 - 5 cm) beside the mid-line abdominal incision (6 - 8 cm). In cats weighing less than 2.3 kg or in cats with a narrow chest, a left subcostal margin incision (2 cm) was also made. The anterior ligaments connecting the left medial and quatrate lobes to the diaphragm and the dorsal ligaments connecting the left lateral lobe of the liver to the diaphragm were ligated and cut.

Portal pressure was recorded from a cannula inserted (to within about 1 cm. of the hilum of the liver) through a small vein from the appendix.

A carrier, lubricated with paraffin oil, was then slid under the entire

liver except for the right lateral and caudate lobes, and, when the liver was securely in place on the carrier, it was lifted and the lower or base plate of the plethysmograph was slid under the carrier which was then removed. The second section of the plethysmograph, the side or center piece, and the lid or top section were inserted into place (fig. 4). In this way the liver was not exposed to hard or sharp edges or to undue manipulation.

Plastibase was injected around the aperture and by this method, the liver was sealed within the plethysmograph and the hepatic artery, portal vein and hepatic vein passed, intact, through a 2 cm. aperture. The plethysmograph was filled with warm (37°C) Ringer-Locke solution and connected to a float recorder which is attached to an isotonic transducer similar to the way the intestinal plethysmograph was set up (fig. 5). The pressure in the plethysmograph was set at zero relative to the hilum of the liver. Because of the transparent nature of the plethysmograph, any bleeding or discoloration of the liver which would indicate gross macroscopic damage could be observed.

The gallbladder was not a factor in the volume response measured. The gallbladder was visible through the transparent wall of the plethysmograph and its volume of 2 - 3 ml. did not appear to change during the experiments.

In each experiment, the recorded volume changes were multiplied by the total liver weight, divided by the weight of the part of the liver within the plethysmograph and divided by the body weight, to convert the data into ml. change in hepatic volume/kg. body weight. Using this unit, ml/kg, the mean volume change is expressed as:

(a) a percentage of the mean blood volume removed or infused

$$\frac{\text{Hepatic Vol. Change (ml/kg)}}{\text{Mean Vol. Removed or Infused (ml/kg)}} \times 100$$

(b) a percentage of the mean total blood volume of the animal

$$\frac{\text{Hepatic Vol. Change (ml/kg)}}{52.0 \text{ ml/kg}} \times 100$$

(c) a percentage of the mean hepatic blood volume (table 1)

$$\frac{\text{Hepatic Vol. Change (ml/kg)}}{7.3 \text{ ml/kg}} \times 100$$

Calibrations

The femoral arterial and portal venous pressure transducers were calibrated with a mercury and water manometer respectively once every month. The transducer and recorder were found to be stable. The hepatic and intestinal volume recording along with splenic weight recording were checked for linearity and calibrated before every experiment. The full range of operation was checked by stepwise injections of 1 ml. to a total of 10 ml. into the hepatic plethysmograph, of 1 ml. to a total of 5 ml. into the intestinal plethysmograph and by the addition of 1 mg. weights to the splenic weighing cradle.

General Observations

The control values presented here are means $\pm$ standard errors of the data from every cat which was used. Control values for each series of experiments are presented in the appropriate 'Results' sections.

All control pressures, liver and intestinal volumes and splenic weight were measured after the surgery was completed, immediately before the first experimental maneuver, and was monitored continuously throughout the experiment. The arterial and portal pressures were well maintained and the volume of the liver and the intestine and the weight of the spleen remained stable in the control period.

The general state of the animals was good. Corneal, ear flick and swallowing reflexes returned repeatedly as the effects of each supplementary dose of pentobarbital wore off. Blood loss during surgery was always very small.

RESULTS & DISCUSSION

GENERAL

The results of the experiments in this thesis are presented in sequence to answer the following questions: (1) how much blood is mobilized from or pooled in each of the splanchnic organs, gastro-intestinal tract, spleen and liver to compensate for the hemorrhage or infusion and what percentage does this represent, (2) what percentage of the animal's total blood volume does this represent and (3) what percentage of each organ's blood volume does this represent?

Eighteen cats were used in each of the hemorrhage and infusion experiments. The eighteen cats were equally divided into three groups: group 1, where the gastro-intestinal volume was measured; group 2, where the splenic volume was measured and group 3, where the hepatic volume was measured.

Tests of significance between means of the three groups were evaluated by a completely random analysis of variance test (Steel and Torrie, 1960). In all analyses a probability of 0.05 was selected as the criterion of statistical significance.

SECTION 1

Blood Pressure and Portal Pressure Response to a Slow Nonhypotensive Hemorrhage

RESULTS (SECTION 1)

Blood Pressure Response to Hemorrhage

Arterial blood pressure was measured in all eighteen cats subjected to hemorrhage. The effect of these hemorrhages on arterial pressure was not significantly different between the three groups of cats involved: group 1, where the gastro-intestinal volume was measured; group 2, where the splenic volume was measured and group 3, where the hepatic volume was measured (table 2).

The mean control arterial pressure of the eighteen cats was 121 ± 6.0 mmHg. This pressure decreased 13 mmHg. during the first 16 minutes when 8 ml/kg. of blood had been removed. After this point, the arterial blood pressure decreased rapidly (fig. 6). Therefore, the point where 8 ml/kg. of blood had been removed was taken as the start of hypotension and the organ volume changes up to this point were analyzed. Removal of 8 ml/kg. of blood represents the removal of 15% of the total blood volume of the cats (mean blood volume 52 ml/kg; Farnsworth, Paulino-Gonzalez and Gergersen, 1960; Groom et al., 1965; Scott, 1972; C.V. Greenway, unpublished observations).

Portal Pressure Response to Hemorrhage

Portal pressure response to hemorrhage was measured in six cats that were involved in the hepatic volume experiments and in five of the six cats involved in the intestinal volume experiments. The effect of these hemorrhages on portal pressure was not significanty different between the two groups of cats in which the measurements were taken (table 2).

Portal pressure was not monitored in the cats involved in the splenic volume experiments because the experiments with the liver and intestine showed no significant changes in portal pressure. The mean portal pressure

during the control period was 8.6 ± 0.8 mmHg. and this decreased to 7.3 ± 0.9 mmHg. when 8 ml/kg. of blood had been removed from the animal (table 2).

SECTION 2

Gastro-Intestinal Blood Volume Response to a Slow Nonhypotensive Hemorrhage

RESULTS (SECTION 2)

Gastro-Intestinal Volume Changes in Response to Hemorrhage

Figure 7 shows the experimental record of one cat subjected to hemorrhage. The initial arterial pressure was 110 mmHg., portal pressure was 7 mmHg. and the cat's weight was 2.4 kg. The ileum responded immediately to hemorrhage while the blood pressure and portal pressure remained relatively stable up until the point where 5 ml/kg. of blood had been withdrawn. Then the arterial pressure started to drop along with the portal pressure.

The resultant volume changes that were recorded in the piece of ileum were extrapolated on a weight basis to the whole gastro-intestinal tract. This extrapolation may not be entirely valid. There is not any direct data to support this extrapolation for the stomach but Hulten (1969) showed that the blood content of the large intestine and colon was very similar to that of the ileum in cats. The extrapolation was used to estimate the total splanchnic blood reservoir function and to allow comparison of this work with that of Brooksby and Donald (1971 and 1972). Their work, which was published during the course of this investigation, involved equally important but different limitations and the similarity of the data on the total splanchnic bed (which will be presented later) suggests that both methods give reasonable estimates of the true values. Therefore, from now on, all results will refer to volume changes in ml/kg. of body weight in the gastro-intestinal tract, which includes the stomach, small intestine and large intestine plus colon.

The mean weight of the ileum in the plethysmogragh of all six experiments was 35.5 ± 3.9 gm. The mean weight of the stomach, small intestine and large intestine plus colon was 26.8 ± 2.3 gm., 76.6 ± 0.9 gm. and 22.8 ± 1.7

gm. respectively. Therefore, the total average weight of the gastro-intestinal tract was 126.3 ± 1.9 gm., or 55.4 ± 2.3 gm/kg. of the animal's weight which averaged 2.3 ± 0.1 kg.

The mean gastro-intestinal volume showed a steady decrease from the start of the hemorrhage. The gastro-intestinal volume decreased 0.5 ml/kg. when 2 ml/kg. of blood was removed and 1.7 ml/kg. when 8 ml/kg. was removed (fig.8). To allow assessment of the role of the gastro-intestinal tract as a blood reservoir, the mean volume change is expressed as (a) a percentage of the mean blood volume removed from the six animals, (b) a percentage of the mean blood volume of the animal and (c) a percentage of the mean gastro-intestinal volume (table 3).

It can be seen from figure 8 that the gastro-intestinal tract mobilized 23% of the volume removed when the hemorrhage was 2 ml/kg. When 8 ml/kg. was removed, the gastro-intestinal tract mobilized 22% of the volume removed. This volume change which is believed to be due to whole blood expulsion from the gastro-intestinal tract represents 0.9% and 3.3% of the cat's blood volume of 52 ml/kg. when the hemorrhage was 2 ml/kg. and 8 ml/kg. respectively. Since the gastro-intestinal tract contains 10% of the blood volume of 52 ml/kg. (table 1), it contains 5.2 ml/kg. of blood. After a hemorrhage of 2 ml/kg. (3.9% of the total cat's blood volume) and 8 ml/kg. (15% blood volume), 0.5 ml/kg. and 1.7 ml/kg. had come from the gastro-intestinal tract respectively. Thus, the gastro-intestinal tract content was reduced 8.9% and 33.0% respectively.

SECTION 3

Splenic Blood Volume Response to a Slow Nonhypotensive Hemorrhage

RESULTS (SECTION 3)

Splenic Weight Changes in Response to Hemorrhage

Figure 9 shows the experimental record of one cat subjected to hemorrhage. The initial arterial pressure was 125 mmHg. and the cat's weight was 2.7 kg. The spleen did not respond immediately to hemorrhage and very little change was observed until 2.5 ml/kg. of blood had been removed. However, as the hemorrhage became greater, the spleen decreased rapidly in size. The blood pressure remained relatively constant in this experiment.

The mean weight of the spleen was 30.15 ± 0.99 gm. or 10.82 ± 0.43 gm/kg. and the mean weight of the cats was 2.8 ± 0.12 kg.

The mean splenic weight showed a linear decrease with hemorrhage beyond 2.5 ml/kg. (fig. 8). The splenic weight remained constant, without change when 2 ml/kg. of blood was removed and then decreased 1.5 gm/kg. when 8 ml/kg. of whole blood had been withdrawn. In order to assess the role of the spleen as a blood reservoir, the same calculations were performed as were done on the gastro-intestinal tract. The blood mobilized from the spleen was expressed as (a) a percentage of the mean blood volume removed, (b) a percentage of the mean total blood volume of the animal and (c) a percentage of the mean splenic volume (table 3).

It can be seen from figure 8 that the spleen was observed to mobilize 0.0% of the volume removed when the hemorrhage was 2 ml/kg. and 19% when the hemorrhage was 8 ml/kg. This volume change which is believed to be due to whole blood expulsion from the spleen represents 0.0% and 3.0% of the cat's mean blood volume of 52.0 ml/kg. when the hemorrhage consisted of 2 ml/kg. and 8 ml/kg. respectively. The spleen contains 12% of the blood volume of the cat (table 1) which represents 6.2 ml/kg. of blood. After a hemorrhage

of 2 ml/kg. and 8 ml/kg. of blood, the spleen mobilized 0.0 ml/kg. and 1.5 ml/kg. respectively. Thus, the splenic content was reduced 0.0% and 25% respectively.

SECTION 4

Hepatic Blood Volume Response to a Slow Nonhypotensive Hemorrhage

RESULTS: (SECTION 4)

Hepatic Volume Changes in Response to Hemorrhage

Figure 10 shows the experiment record of one cat subjected to hemorrhage. The initial arterial pressure was 124 mmHg., portal pressure was 9.5 mmHg. and the cat's weight was 2.6 kg. The liver responded immediately to hemorrhage while the blood pressure and portal pressure remained relatively constant up until the point where 8 ml/kg. of whole blood had been removed from the animal.

The mean weight of the liver that was within the plethysmograph was 67.0 ± 2.4 gm and the total mean weight of the liver was 84.0 ± 2.6 gm or 35.12 ± 1.56 gm/kg. where the mean weight of the cats was 2.4 ± 0.05 kg.

The mean hepatic volume showed a linear decrease during the hemorrhage (fig. 8). The liver volume decreased 0.3 ml/kg. when 2 ml/kg. of blood was removed and 1.7 ml/kg. when 8 ml/kg. was removed. To allow assessment of the role of the liver as a blood reservoir, the same calculations were performed as were done with the gastro-intestinal tract and spleen. The blood mobilized from the liver was expressed as (a) a percentage of the mean blood volume removed, (b) a percentage of the mean total blood volume of the animal and (c) a percentage of the mean hepatic volume (table 3).

It can be seen from figure 8 that the liver mobilized 16% of the volume removed when the hemorrhage was 2 ml/kg. When 8 ml/kg. was removed, the liver mobilized 21% of the volume removed. This amount of the blood expelled from the liver represents 0.6% and 3.2% of the cat's blood volume of 52 ml/kg. when the hemorrhage was 2 ml/kg. and 8 ml/kg. respectively. Since the liver contains 14% of the blood volume of 52 ml/kg. (table 1), it contains 7.3 ml/kg. of blood. After a hemorrhage of 2 ml/kg. and 8 ml/kg.,

the liver expelled 0.3 ml/kg. and 1.7 ml/kg. of blood respectively. Thus, the hepatic blood content was reduced 4.4% and 23% respectively.

SECTION 5

DISCUSSION OF THE SPLANCHNIC VASCULAR BED VOLUME CHANGES DURING A SLOW NONHYPOTENSIVE HEMORRHAGE

DISCUSSION (SECTION 2, 3 & 4)

General

Two questions now arise: (1) is the decrease in the splanchnic vascular bed volume due solely to a blood **loss** or could there be also some tissue fluid reabsorption and (2) what is the mechanism of expulsion of this blood from the splanchnic vascular bed?

Whole Blood v.s. Tissue Fluid Reabsorption

In the splanchnic vascular bed, reabsorption of tissue fluid would be expected to be small, because the mean portal pressure did not decrease more than 1.3 mmHg. (8.6 - 7.3 mmHg.) (table 2). Such a small change would result in insignificant net fluid movements.

This assumption tends to be confirmed in the gastro-intestinal tract by the works of Johnson and Hanson (1966) and Wallentin (1966). Therefore, with these facts and with the work of Folkow et al. (1964) who showed that there was no evidence of tissue fluid reabsorption under the conditions of a well maintained constriction of the capacitance vessels, it is suggested that the volume change in the gastro-intestinal tract observed in these experiments are due entirely to mobilization of whole blood.

Similarly, the volume mobilized from the spleen and liver during hemorrhage is probably whole blood and since the spleen is a storage site for red blood cells, the blood mobilized from the spleen would have a higher hematocrit than the blood expelled from the liver and gastro-intestinal tract. This assumption is confirmed in the spleen by Greenway, Lawson and Stark (1968), who showed that during stimulation of the sympathetic nerves there was no reabsorption of tissue fluid. In the liver, no evidence

of reabsorption of extracellular fluid was obtained previously during stimulation of the sympathetic nerves (Greenway et al., 1969), during reduction in hepatic venous pressure (Greenway and Lautt, 1970) or during infusions of a variety of vaso-active drugs (Greenway and Lautt, 1972).

Mechansim of Mobilization

The mechanism of mobilization of blood from the splanchnic vascular bed could be due to active constriction of the capacitance vessels and/or to passive collapse due to decreased transmural pressure. In the case of the spleen, the mobilization of splenic blood could be due to active constriction and/or passive collapse of the splenic capsule and trabeculae instead of its capacitance vessels (see introduction).

Passive Collapse. The changes in arterial pressure, 13 mmHg. (121 - 108 mmHg.) and portal pressure, 1.3 mmHg. (8.6 - 7.3 mmHg.) recorded in these experiments (table 2 and fig. 6) were minimal and therefore the passive consequences of these changes would appear to be at the most a small part of the observed responses. It has been previously shown that during vasopressin infusion, marked splenic and intestinal vasoconstriction with a consequent reduction in portal flow did not alter hepatic or splenic volume (greenway and Lautt, 1972; Greenway, Lawson and Stark, 1968, respectively) and changes in splenic flow due to partial occlusion of the splenic artery also did not alter splenic weight (Greenway, Lawson and Stark, 1968). Haglund and Lundgren (1972) observed no significant intestinal blood volume changes in the denervated small intestine when the arterial inflow pressure was lowered to 50 - 55 mmHg. Therefore, it appears that the major factor controlling mobilization of blood from the splanchnic vascular bed during slow, non-

hypotensive hemorrhages is an active constriction of the capacitance vessels or capsule and trabeculae through some efferent pathway.

Humoral Factors. Although the low pressure receptors in the atrium have been shown to release vasopressin and cause the production of angiotensin (see introduction), endogenous rates of vasopressin secretion and angiotensin production seem unlikely to produce significant capacitance responses in the splanchnic vascular bed. Experiments by Greenway and Stark (1969) showed, that after denervation and adrenalectomy, the splenic volume did not change in response to hemorrhage. Thus, it seems reasonable to conclude that the vaso-active peptides, vasopressin and angiotensin, did not affect splenic weight to any significant degree. This was confirmed by Greenway and Stark (1970) by intravenous infusion of angiotensin and vasopressin. Similarly, Greenway and Lautt (1972), showed that endogenous rates of secretions of vasopressin and the production of angiotensin appear unlikely to produce significant hepatic blood volume response for only very large doses produce minor capacitance responses.

Slow, nonhypotensive hemorrhage of this type were shown by Regoli and Vane (1966) not to release catecholamines from the adrenal medulla. Therefore, secretions from the adrenal medulla appear unlikely to cause the capacitance response observed in the splanchnic vascular bed.

From this data, it seems reasonable to conclude that humoral factors do not cause any significant capacitance response in the splanchnic vascular bed when cats were subjected to a slow, nonhypotensive hemorrhage. Therefore, the efferent pathway for such an observed response appears to be mediated through sympathetic nerve stimulation which is well known to produce a large

decrease in the blood content of the splanchnic organs (table 1).

Sympathetic Nerves. The absolute gastro-intestinal tract volume curve, the absolute splenic weight curve and the absolute hepatic volume curve (fig. 8) obtained during hemorrhage compare with a sympathetic nerve frequency response curve for the intestine (Folkow et al., 1964), spleen (Greenway, Lawson and Stark, 1968) and liver (Greenway, Stark and Lautt, 1969). The afferent pathway involved in the stimulation of the sympathetic nerves to produce the observed splanchnic capacitance response could be due to activation of high pressure baroreceptors and/or to low pressure receptors located in the central venous, atrial and pulmonary compartments. Due to minimal changes in arterial pressure (table 2, fig. 6), it is unlikely that arterial high pressure baroreceptors are the afferent pathway involved.

However, it is possible that these low pressure receptors were affected by hemorrhage. These receptors have been shown to normally alter their firing rate during hemorrhage (Gupta, Henry, Sinclair and von Baumgarten, 1966) and they are known to cause other responses to hemorrhage such as tachycardia and arteriolar vasoconstriction (Pelletier, et al., 1971; Paintal, 1973; Gilmore and Zucker, 1974). Therefore, inhibition of these receptors could be responsible for increased activation of the sympathetic nerves to the capacitance vessels of the splanchnic vascular bed.

Summary. Thus, the available evidence suggests, as a working hypothesis, that mobilization of splanchnic blood during hemorrhage is by a sympathetic reflex from low pressure receptors, such as those located in the atrium of the heart.

SECTION 6

Blood Pressure and Portal Pressure Response to a Slow infusion of Fresh Whole Blood

RESULTS (SECTION 6)

Blood Pressure Response to Whole Blood Infusion

Arterial blood pressure was measured in all eighteen cats subjected to an infusion of whole blood. The effects of these infusions on arterial pressure was not significantly different between the three groups of cats involved: group 1, where the gastro-intestinal volume was measured; group 2, where the splenic weight was measured and group 3, where the hepatic volume was measured (table 4).

The mean control arterial pressure was 115.8 ± 7.5 mmHg. and this pressure increased steadily to 114.2 ± 8.7 mmHg. after 18 ml/kg. of blood had been infused (fig.11). This volume represents an increase of 35% in the cat's total blood volume (mean blood volume 52 ml/kg., see section 1).

Portal Pressure Response to Whole Blood Infusion

Portal pressure response to infusion was measured in seventeen out of the eighteen cats involved in these experiments. The effects of these infusions on portal pressure were not significantly different between the three groups of cats in which the measurements were taken (table 4).

The mean portal pressure during the control period was 7.9 ± 0.6 mmHg. This increased to 8.9 ± 0.7 mmHg. when 9.0 ml/kg. of whole blood had been infused and to 10.6 ± 0.8 mmHg. when 18 ml/kg. had been infused.

SECTION 7

Gastro-Intestinal Blood Volume Response to a Slow Infusion of Fresh Whole Blood

RESULTS & DISCUSSION (SECTION 7)

Gastro-Intestinal Volume Changes in Response to Infusion

Figure 12 shows the experimental record of one cat subjected to whole blood infusion. The initial arterial pressure was 110 mmHg., portal pressure was 11.5 mmHg. and the cat's weight was 2.5 kg. The ileum responded immediately to the infusion of whole blood. The arterial and portal pressures also increased from the beginning of the infusion.

The resultant volume changes that were recorded in a small piece of the ileum were extrapolated on a weight basis to the whole gastro-intestinal tract similar to that which was done in the hemorrhage experiments. Therefore, from now on, all results will be in terms of the gastro-intestinal tract as described under the results of the intestinal hemorrhage experiments.

The mean weight of the ileum in the plethysmograph was 30.8 ± 1.5 gm. The mean weight of the stomach, small intestine and large intestine plus colon were 23.79 ± 2.51, 74.66 ± 3.56 and 20.92 ± 1.63 gm. respectively. Therefore, the total average weight of the gastro-intestinal tract was 119.36 ± 6.08 gm. or 58.82 ± 3.23 gm/kg. of the animal's weight which average 2.10 ± 0.12 kg.

The mean gastro-intestinal tract showed a steady increase in volume from the start of the infusion of whole blood (fig.13). The gastro-intestinal volume increased by 0.79 ml/kg., 1.7 ml/kg., 3.2 ml/kg., 4.7 ml/kg. and 6.2 ml/kg. when the amount of fresh whole blood infused was 2.3 ml/kg., 4.5 ml/kg., 7.9 ml/kg., 12 ml/kg. and 18 ml/kg. respectively. As with the hemorrhage experiments, the results are expressed as (a) a percentage of the mean blood volume infused into the six cats, (b) as a percentage of the mean total blood volume of the six animals and (c) as a percentage of

the mean gastro-intestinal volume, so that the ability of the gastro-intestinal tract to function as a blood collecting reservoir could be assessed (table 5).

It can be seen from figure 13 that the gastro-intestinal tract can pool 35.0%, 39.0%, 39.0%, 39.0% and 34.0% when the volume of whole blood infused was 2.3 ml/kg., 4.5 ml/kg., 7.9 ml/kg., 12 ml/kg. and 18 ml/kg. respectively. This volume change which is believed to be due to whole blood expansion of the gastro-intestinal tract represents 1.5 3.4 %, 6.1 %, 9.1 % and 12.0 % of the cat's normal blood volume of 52 ml/kg. when the infusion was 2.3 ml/kg., 4.5 ml/kg., 7.9 ml/kg., 12 ml/kg. and 18 ml/kg. respectively. Since the gastro-intestinal tract contains 10% of the blood volume of 52 ml/kg. (table 1), it contains 5.2 ml/kg. of blood. After an infusion of 2.3 ml/kg., 4.5 ml/kg., 7.9 ml/kg., 12 ml/kg. and 18 ml/kg. the gastro-intestinal tract increased in volume by 0.79 ml/kg., 1.7 ml/kg., 3.2 ml/kg., 4.7 ml/kg. and 6.2 ml/kg. respectively. Thus, the gastro-intestinal tract content was increased by 15.0 %, 33.0 %, 61.0 %, 91.0 % and 119.0 % respectively.

Discussion of the Gastro-Intestinal Tract Volume Changes

The gastro-intestinal tract volume expansion curve expressed as a percentage of blood infused (fig.13) shows that a maximum percentage increase in capacitance response occurs when the volume of blood infused was between zero and 2.3 ml/kg. The maximum capacitance response was then maintained at a steady percentage with a tendency to drop after 12 ml/kg. had been infused. This drop would seem to indicate that the gastro-intestinal tract had reached its limit to function as an organ capable of pooling excess blood and that limit is about 40% of the infused blood.

SECTION 8

Splenic Blood Volume Response to a Slow Infusion of Fresh Whole Blood

RESULTS & DISCUSSION (SECTION 8)

Splenic Weight Changes in Response to Infusion

Figure 14 shows the experimental record of one cat subjected to whole blood infusion. The initial arterial pressure was 110 mmHg., portal pressure was 8.5 mmHg. and the cat's weight was 2.4 kg. The arterial and portal pressures responded immediately to the infusion and very little change was observed in splenic weight until 4.5 ml/kg. of blood had been infused.

The mean weight of the spleens of the six cats in these experiments was 24.01 $\pm$ 2.24 gm. or 10.44 $\pm$ 0.66 gm/kg. where the mean weight of the cats was 2.3 $\pm$ 0.15 kg.

The splenic weight showed a steady increase in weight when the infusion of whole blood was between 4.5 ml/kg. and 12 ml/kg. After 12 ml/kg. of blood was infused, the splenic weight curve expressed as gm/kg. becomes flattened showing a maximum capacitance response (fig. 13).

The mean splenic weight increased zero gm/kg., 0.05 gm/kg., 0.37 gm/kg., 0.85 gm/kg. and 0.95 gm/kg. when the volume of blood infused was 2.3 ml/kg., 4.5 ml/kg., 7.9 ml/kg., 12 ml/kg. and 18 ml/kg. respectively. Inorder to assess the role of the spleen as a reservoir for extra blood infused, the same calculations were performed as were done with the gastro-intestinal tract infusion experiments. The blood pooled in the spleen was expressed as (a) a percentage of the mean blood volume removed, (b) as a percentage of the mean total blood volume and (c) as a percentage of the mean splenic volume (table 5).

It can be seen from figure 13 that the spleen can pool 0.00%, 1.1%, 4.6%, 7.0% and 5.3% of the volume infused when the infusion was 2.3 ml/kg., 4.5 ml/kg., 7.9 ml/kg., 12 ml/kg. and 18 ml/kg. respectively. This volume which is believed to be due to whole blood expansion of the spleen

represents zero %, 0.10%, 0.71%, 1.6% and 1.8% of the cat's normal blood volume of 52.0 ml/kg. when the infusions were 2.3 ml/kg., 4.5 ml/kg., 7.9 ml/kg., 12 ml/kg. and 18 ml/kg. respectively. Since the spleen contains 12% of the blood volume of the cat (table 1) which represents 6.2 ml/kg. of blood. After an infusion of 2.3 ml/kg., 4.5 ml/kg 7.9 ml/kg., 12 ml/kg. and 18 ml/kg. the spleen increased by zero gm/kg., 0.05 gm/kg., 0.37 gm/kg., 0.85 gm/kg. and 0.95 gm/kg. respectively. Thus, the spleen content was increased by zero %, 0.81%, 6.0%, 14.0% and 15.0% respectively.

Discussion of the Splenic Volume Changes

The splenic weight expansion curve expressed as a percentage of blood infused (fig. 13) shows that the spleen did not react immediately to the volume load. On the average, the spleen increased in volume in a linear relationship between the infused volumes of 4.5 ml/kg. and 12.0 ml/kg. after which a maximum was reached and at that point the curve flattens and becomes stable indicating that a maximum capacitance response has been reached. Such a maximum capacitance response to a volume load indicates that the spleen is now increasing its volume at a constant proportion with the amount infused. This value, when expressed as the percentage of the infused blood stored by the spleen is 6%. When this value, 6%, is compared to the percentage that the spleen can mobilize during hemorrhage, 19%, it can be seen that the spleen was much less able to pool blood than to mobilize it.

SECTION 9

Hepatic Blood Volume Response to a Slow Infusion of Fresh Whole Blood

RESULTS & DISCUSSION (SECTION 9)

Hepatic Volume Changes in Response to Infusion

Figure 15 shows the experimental record of one cat subjected to whole blood infusion. The initial arterial pressure was 80 mmHg., portal pressure was 9.5 mmHg. and the cat's weight was 2.4 kg. The hepatic volume responded immediately to the infusion of whole blood. The arterial and portal pressure also increased from the beginning of the infusion.

The mean weight of the liver in the plethysmograph was 70.93 ± 4.38 gm. The mean weight of the total liver was 86.04 ± 5.28 gm or 35.69 ± 2.33 gm/kg. of the animal's weight which averaged 2.4 ± 0.07 kg.

The mean hepatic volume showed a steady increase from the start of the infusion (fig. 13). The hepatic volume increased 0.36 ml/kg., 0.75 ml/kg., 1.5 ml/kg., 2.6 ml/kg. and 4.0 ml/kg. when the volume of fresh whole blood infused was 2.3 ml/kg., 4.5 ml/kg., 7.9 ml/kg., 12 ml/kg. and 18 ml/kg. respectively. Again, the results are expressed as (a) a percentage of the mean blood volume infused, (b) as a percentage of the mean total blood volume and (c) as a percentage of the mean hepatic volume, in order that the reserve pooling capacity of the liver may be assessed. (table 5).

From figure 13 , it can be shown that the liver can pool 16.0 %, 17.0 %, 19.0 %, 21.0 % and 22.0 % of the volume infused when the infusion was 2.3 ml/kg., 4.5 ml/kg., 7.9 ml/kg., 12 ml/kg. and 18 ml/kg. respectively. The volume change which is believed to be due to whole blood expansion of the liver represents 0.69%, 1.4 %, 2.9 %, 5.0% and 7.7 % of the cat's normal blood volume of 52 ml/kg. when the infusion was 2.3 ml/kg., 4.5 ml/kg., 7.9 ml/kg., 12 ml.kg. and 18 ml/kg. respectively. Since the liver contains 14% of the blood volume of 52 ml/kg. (table 1), it contains 7.3

ml/kg. of blood. After an infusion of 2.3 ml/kg., 4.5 ml/kg., 7.9 ml/kg., 12 ml/kg. and 18 ml/kg. the hepatic volume increased by 0.36 ml/kg., 0.75 ml/kg., 1.5 ml/kg., 2.6 ml/kg. and 4.0 ml/kg. respectively. Thus, the hepatic volume content was increased 4.9%, 10.0%, 21.0%, 36.0% and 55.0% respectively.

Discussion of the Hepatic Volume Changes

The hepatic volume expansion curve expressed as a percentage of the blood infused (fig. 13) shows that the maximum rate of pooling blood occurs when the volume of blood infused was between zero and 2.3 ml/kg. This same response was also seen in the gastro-intestinal tract. However, from this point onwards, the response in the liver was different from that observed in the gastro-intestinal tract. The hepatic response did not level out and become stable but continued to increase in a linear manner at a slower rate than that which occurred between zero and 2.3 ml/kg. of the infusion.

SECTION 10

DISCUSSION OF THE SPLANCHNIC VASCULAR BED VOLUME CHANGES DURING A SLOW INFUSION OF FRESH WHOLE BLOOD

DISCUSSION (SECTION 7, 8 & 9)

General

The changes in the volume of the gastro-intestinal tract, spleen and liver were measured and they represent the total fluid pooled in each organ. As with the hemorrhage experiments, the same two questions arise: (1) is the volume increase in these organs of the splanchnic vascular bed due solely to an increase in blood pooling in the capacitance vessels or could there also be some transcapillary fluid movement to cause an increase in the organ's interstitial fluid volume and/or infiltration of this interstitial fluid into the plethysmograph and (2) what is the mechanism of pooling of this blood into the splanchnic vascular bed?

Whole Blood v.s. Tissue Fluid Filtration

Gastro-Intestinal Tract. In the gastro-intestinal tract, net transcapillary fluid movements would be expected to occur during infusions where the portal pressure is increased Witte et al. (1969). However, the mean portal pressure changes did not increase more than 2.1 mmHg. (8.7 to 10.8 mmHg.) (table 4), such minor changes would only minimally increase capillary pressure resulting in insignificant net fluid movements. (Johnson and Hanson, 1966; Wallentin, 1966; Witte et al., 1969). This then suggests that the increase in volume of the gastro-intestinal tract is due mainly to whole blood pooling into the organ's capacitance vessels.

Spleen. Greenway, Lawson and Stark (1968) showed that elevations of the venous pressure produce an increase in splenic volume with no evidence of net transcapillary fluid movements. Therefore, from this result and from the data obtained from the experiments described in this thesis where the

portal pressure did not increase more than 1.3 mmHg. (6.7 to 8.0 mmHg.) (table 4) and where the splenic weight curve (fig. 13) showed a maximum response, it can be concluded that the splenic volume increase observed is due to pooling of blood into the organ's capacitance vessels.

It is generally agreed that the spleen constitutes a storage system for high hematocrit blood. Therefore, the increase in splenic weight that occurs is probably due to an increase in blood cells more than whole blood. This ability of the spleen to concentrate blood cells may be the reason why the spleen did not react immediately to the infusion. Another reason why the spleen did not react immediately may be because the mechanism of splenic constriction and relaxation is through the smooth muscles of the capsule and trabeculae and not the splenic capacitance vessels (see introduction) and therefore the smooth muscle of the capsule and trabeculae may react slower than that found in capacitance vessels. However, what ever the cause, the result obtained is in agreement with the observations of Greenway, Lawson and Stark (1968) who observed that splenic weight recovered slower than flow when sympathetic nerve stimulation ceased.

Liver. In the liver, net transcapillary fluid movements would be expected to occur during the infusion. Greenway and Lautt (1970), by elevating the venous pressure by 7 mmHg., found that this caused the hepatic volume to increase rapidly at first and by 5 - 20 minutes the hepatic volume increase continued at a constant but lower rate. By the use of ^{51}Cr - tagged red blood cells, it was possible to conclude that the slower steady rate of volume increase represented filtration of interstitial fluid into the hepatic plethysmograph. In this set of experiments, central venous pressure was not measured but

since it is known that the portal pressure increased 3.1 mmHg., from 8.4 to 11.5 mmHg. (table 4), then this increase in portal pressure must reflect an increase in central venous pressure similar to that observed by Greenway and Lautt (1970). Therefore, from the above information, it seems reasonable to assume that the maximum capacitance response, where the liver is increasing its volume at a constant proportion with the amount infused, is reached in the hepatic bed and is due to the pooling of blood in the hepatic capacitance vessels. The further increase in volume which is observed (fig. 13) may be due to a net transcapillary fluid movement into the hepatic interstitial fluid and filtration into the plethysmograph. Thus, when 18 ml/kg. of whole blood was infused, the liver appeared to have pooled 22.0% of the infused blood. However, since filtration is occurring at a rate of 0.06 ml/min/mmHg./100 gm liver (Greenway and Lautt, 1970), this value of 22.0% could be an overestimate of about 25%. Therefore, the actual percentage of blood that is pooled in the hepatic capacitance vessels would be between 16 to 17% of the blood infused.

Mechanism of Pooling

The mechanism of pooling of whole blood into the splanchnic vascular bed could be due to active dilation of the capacitance vessels and/or to passive dilation due to an increased transmural pressure. In the case of the spleen, the pooling of splenic blood would be due to active dilation and/or passive distension of the splenic capsule and trabeculae instead of its capacitance vessels (see introduction).

Passive Dilation. In the normal, normovolaemic resting animal, there appears to be some basal sympathetic tone on the capacitance vessels as

shown by the redistribution of blood volume from the pulmonary to the systemic vascular bed after administration of an adrenergic alpha-receptor blocking agent (Nickerson, 1970). This is increased in animals anaesthetized and subjected to surgery (Chien, 1967). Thus, a part of the pooling during infusions could involve inhibition of tonic sympathetic activity to the capacitance vessels. The change in arterial pressure was large, 28.4 mmHg. (115.8 to 144.2 mmHg.), while the portal pressure change was small, 2.7 mmHg. (7.9 to 10.6 mmHg.) (table 4) and the pressure in the inferior vena cava was not measured. Thus, the role of passive distension is difficult to assess from this investigation and further experiments are required.

Active Dilation. The mechanism of active dilation of the splanchnic capacitance vessels or capsule and trabeculae is probably due to the inhibition of the basal sympathetic tone that is postulated to be present rather than to a stimulation of any cholinergic vasodilator fibre activity in which there is no evidence of or to a decrease in vasopressin, angiotensin or adrenal medulla catecholamines levels which have previously been shown to cause no significant splanchnic capacitance response.

The change in arterial pressure was large, a mean difference of 28.4 mmHg. This increase in arterial pressure could stimulate the high pressure baroreceptors to cause a reflex decrease in sympathetic nerve traffic to the splanchnic capacitance vessels causing them to relax and therefore dilate as the transmural pressure increases with infusion. However, the high pressure baroreceptors seem to have minimal effects on the splanchnic capacitance bed (see introduction). Also, the increase in arterial pressure (fig. 11) was not linear as was the increase in the absolute volume of the splanchnic

organs (fig. 13). This suggests that the high pressure baroreceptors probably played only a minor role in this reflex.

Another mechanism by which the above reflex could be initiated is through low pressure receptors located in the central venous, atrial and pulmonary compartments. Since central venous pressure was not measured, it can only be postulated that infusion of fresh whole blood into the inferior vena cava would increase the central venous pressure. This increased venous pressure could stimulate these low pressure receptors which can cause vasodilation of the capacitance vessels (Oberg and Thoren, 1973) via inhibition of adrenergic vasoconstrictor fibre activity. If the central venous pressure had been monitored, it may have shown a linear increase similar to the splanchnic organ volume increase. Such a linear increase would favor the low pressure receptors as the major afferent pathway involved.

Summary. Therefore, the available evidence suggests, as a working hypothesis, that pooling of whole blood into the splanchnic vascular bed during infusion is probably due to an inhibition of basal sympathetic tone to the capacitance vessels causing then to relax and therefore distend as a result of increased transmural pressure due to the infusion.

SECTION 11

Total Splanchnic Volume Changes

DISCUSSION (SECTION 11)

The sum of the volume changes in the three organs represents essentially the total splanchnic volume changes. These changes during both hemorrhage and infusions are shown in figure 16. It can be seen that the splanchnic bed is able to mobilize or pool 50 - 70 % of the volume of blood removed or infused respectively. With small hemorrhages up to 2 ml/kg. (4% blood volume), the gastro-intestinal tract contributes 23%, the spleen a negligible proportion of the volume removed, and the liver 16%. When these small volumes are removed, the small but readily mobilizable reservoirs are presumably most important, for example, the large veins (Kerr and Kirklin, 1970). With hemorrhages of 8 ml/kg. (15% blood volume), the splanchnic bed is clearly an important blood reservoir mobilizing 62% of the removed volume in which 22%, 19% and 21% comes from the gastro-intestinal tract, spleen and liver respectively. Another 15% of the removed blood comes from the lungs (Magiligan, Oleksyn, Schwartz and Yu, 1972). The remaining 23% of the blood is mobilized from other reservoirs (table 1) and of these, skeletal muscle appears to be of major importance (Lundgren, Lundwall and Mellander, 1964).

This data is in reasonable agreement with the data of Brooksby and Donald (1971), whose work was published during the course of this investigation. Their data were obtained in dogs anaesthetized with chloralose and by summation of the excess of outflow over inflow to the splanchnic area. After a hemorrhage of 7.2 ml/kg. over 2 minutes, their average decrease in arterial pressure was 10 mmHg. as opposed to 13 mmHg. in these experiments, and 54% of the volume removed was mobilized from the splanchnic bed as opposed to 62% in my experiments. This difference may be due to the slower rate of hemorrhage used in the experiments of this thesis.

The major factor causing a decrease in splanchnic blood content during hemorrhage has been concluded to be a vasoconstriction of the capacitance vessels (see results, section 2, 3 & 4). Brooksby and Donald (1972) favored a more important role for passive collapse in their experiments but the design of their experiments favored passive responses. In their experiments, the 18 second periods of nerve stimulation which they used will markedly overestimate the passive component since the flow response, and hence the passive component, is essentially complete within this time while the active capacitance response takes several minutes to become maximal (Mellander, 1960 and Greenway, Stark and Lautt, 1969). The obvious approach of repeating the hemorrhage after section of the splanchnic nerves is also full of pit falls. As Brooksby and Donald (1972) showed and experiments by Greenway and Lister (unpublished observations) confirmed, after splanchnic nerve section a given hemorrhage causes a much more marked arterial and portal hypotension and the passive component of the response to hemorrhage is increased and overestimated. This increased hypotension is itself strong evidence that the splanchnic nerves normally cause important active capacitance responses after hemorrhage since their removal does not markedly affect flow responses after hemorrhage in cats (McNeil et al., 1970; Greenway and Stark, 1971). In skeletal muscle, the situation may be rather different and passive collapse secondary to flow reduction may be more important (Lesh and Rothe, 1969).

As previously described, humoral factors causing contraction of the splanchnic capacitance vessels are also unlikely to be of major importance. Thus it seems reasonable to conclude that the predominant pathway causing constriction of the splanchnic capacitance vessels is that of the sympathetic

nerves. The afferent pathways which cause activation of these nerves in response to hemorrhage are unlikely to be from arterial baroreceptors. Arterial pressure did not change markedly and although there may have been changes in pulse pressure, these baroreceptors, which have been previously discussed, do not cause marked response in capacitance vessels (Hainsworth, Karim and Stoker, 1973; Lautt and Greenway, 1972; Pelletier, Edis and Shepherd, 1971). Atrial low pressure receptors may be of greater importance. These receptors, which have been previously discussed, have been shown to markedly alter their firing rate during hemorrhage (Gupta, Henry, Sinclair and von Baumgarten, 1966) and they are known to cause other responses to hemorrhage such as renin release (Hodge, Lowe, Ng and Vane, 1971), tachycardia and arteriolar vasoconstriction (Pelletier et al., 1971; Paintal, 1973). Direct evidence of their role in the splenic contraction after small hemorrhages was presented by Pelletier et al. (1971).

Thus the available evidence suggests, as a working hypothesis, that mobilization of blood from the splanchnic region during hemorrhage involves active constriction of the capacitance vessels mediated through a sympathetic reflex from atrial low pressure receptors.

The mechanism of the pooling of blood during infusions is not entirely clear. As previously described (under the appropriate result sections), vasoactive peptides such as vasopressin and angiotensin can be omitted as possible explanations as well as adrenal medullae secretions.

Infusion of fresh whole blood produced large changes in arterial pressure, 28.4 mmHg. (115.8 to 144.2 mmHg.). This pressure change would certainly stimulate the arterial high pressure receptors to cause a generalized

vasodilation and bradycardia. However, as discussed earlier, the high pressure baroreceptors probably play only a minor role in the pooling of blood in the splanchnic vascular bed.

Since central venous pressure was not monitored, it can only be postulated, that infusion of fresh whole blood into the inferior vena cava would increase the central venous pressure. Indirect evidence for this comes from the observation that the portal pressure increased 2.7 mmHg. (from 7.9 to 10.6 mmHg.). This increase in venous pressure could stimulate the low pressure receptors to cause a reflex venodilation (as discussed earlier). However, there is no clear evidence as to the quantitative influence of such reflexes but logically it would seem reasonable that such low pressure receptors would be able to adjust central venous pressure and also prevent overloading of the heart by relaxing the venous side of the vascular bed.

Therefore, the available evidence suggests, as a working hypothesis, that pooling of whole blood into the splanchnic vascular bed during infusion is probably due to an inhibition of basal sympathetic tone to the capacitance vessels causing them to relax and therefore distend as a result of increased transmural pressure due to the infusion. Just how much of a role passive distension plays is difficult to assess from our data and further experiments are required.

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APPENDIX

FIGURES

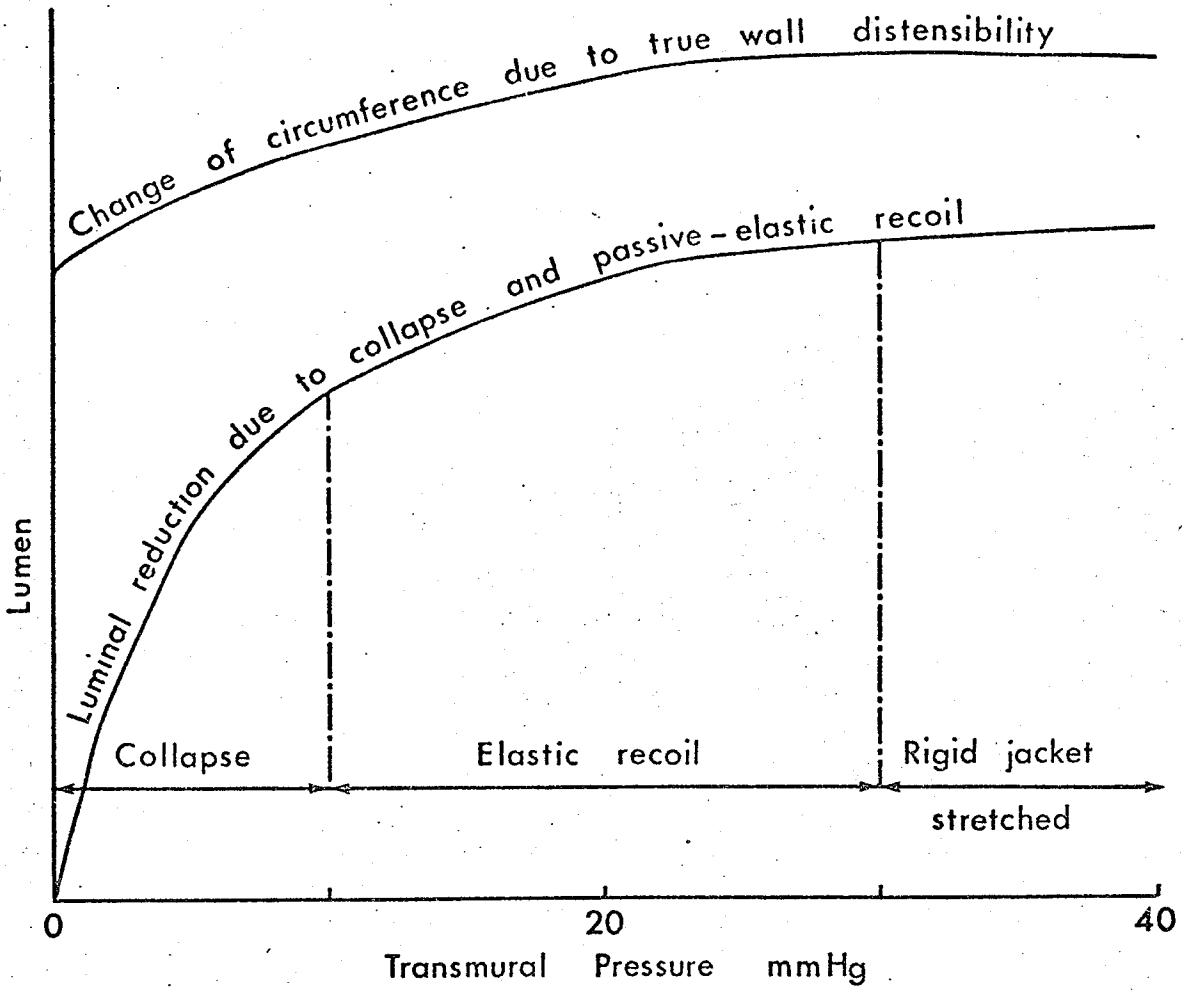


Figure 1

Pressure - volume curve for veins

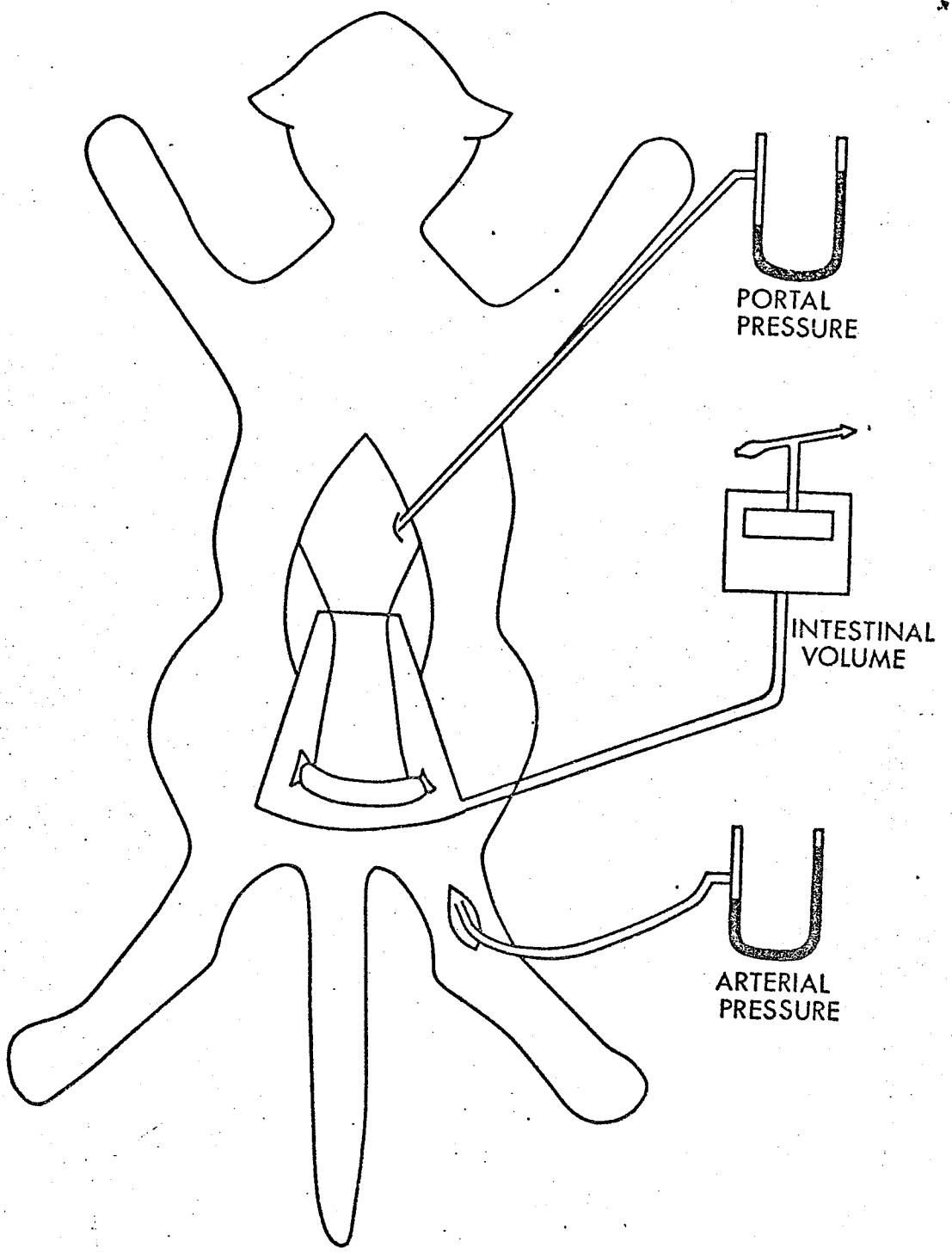


Figure 2

Diagram of the method used to record intestinal volume changes in hemorrhage and infusion

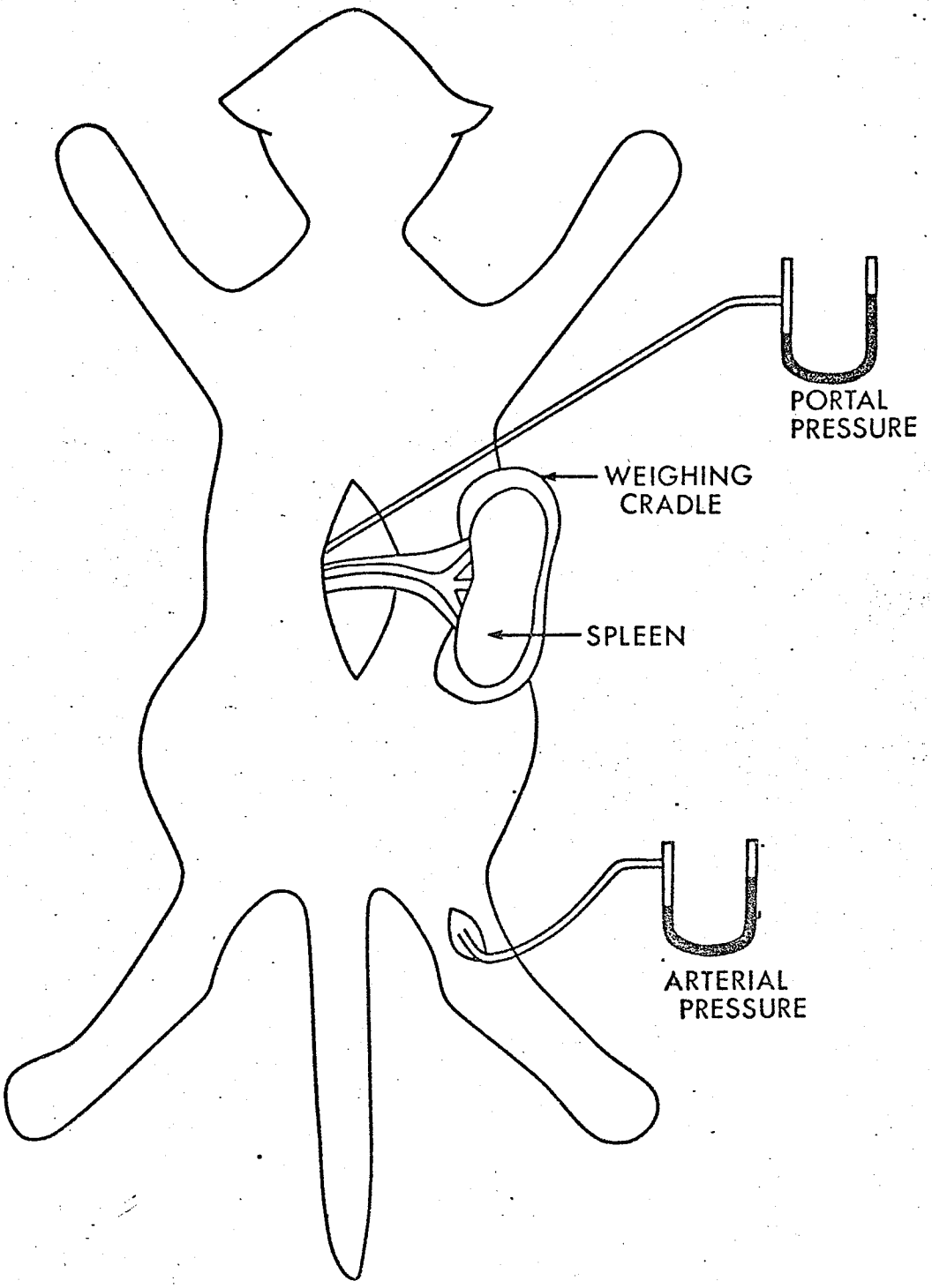
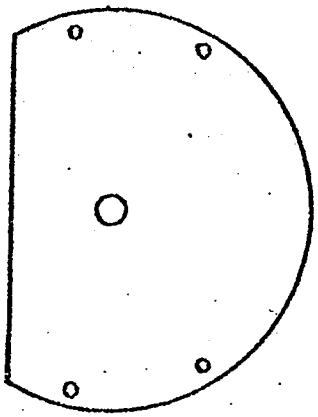


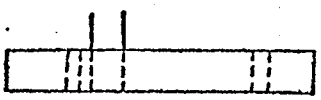
Figure 3

Diagram of the method used to record splenic volume changes in hemorrhage and infusion

TOP VIEW



SIDE VIEW



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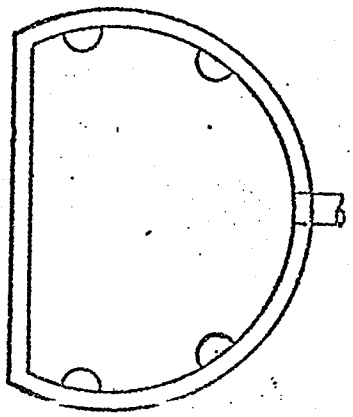
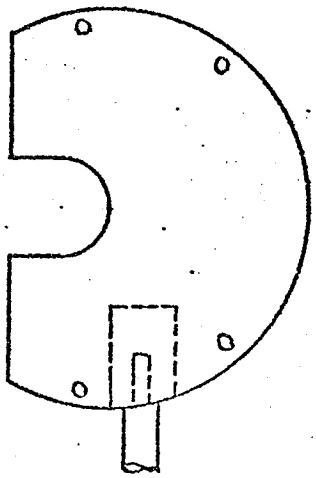
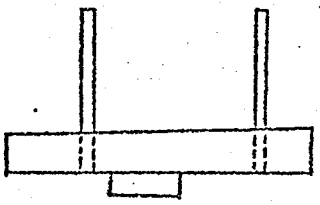


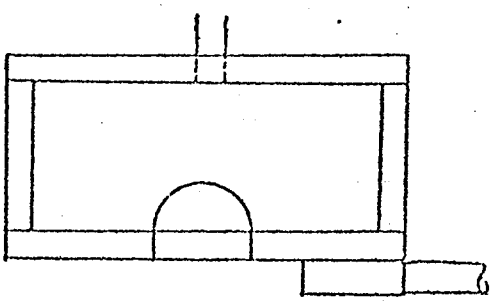
OUTLET TO FLOAT RECORDER

CENTER PIECE





BASE PLATE



FRONT VIEW OF ASSEMBLED MODEL

Figure 4

Diagram of sections of plethysmograph

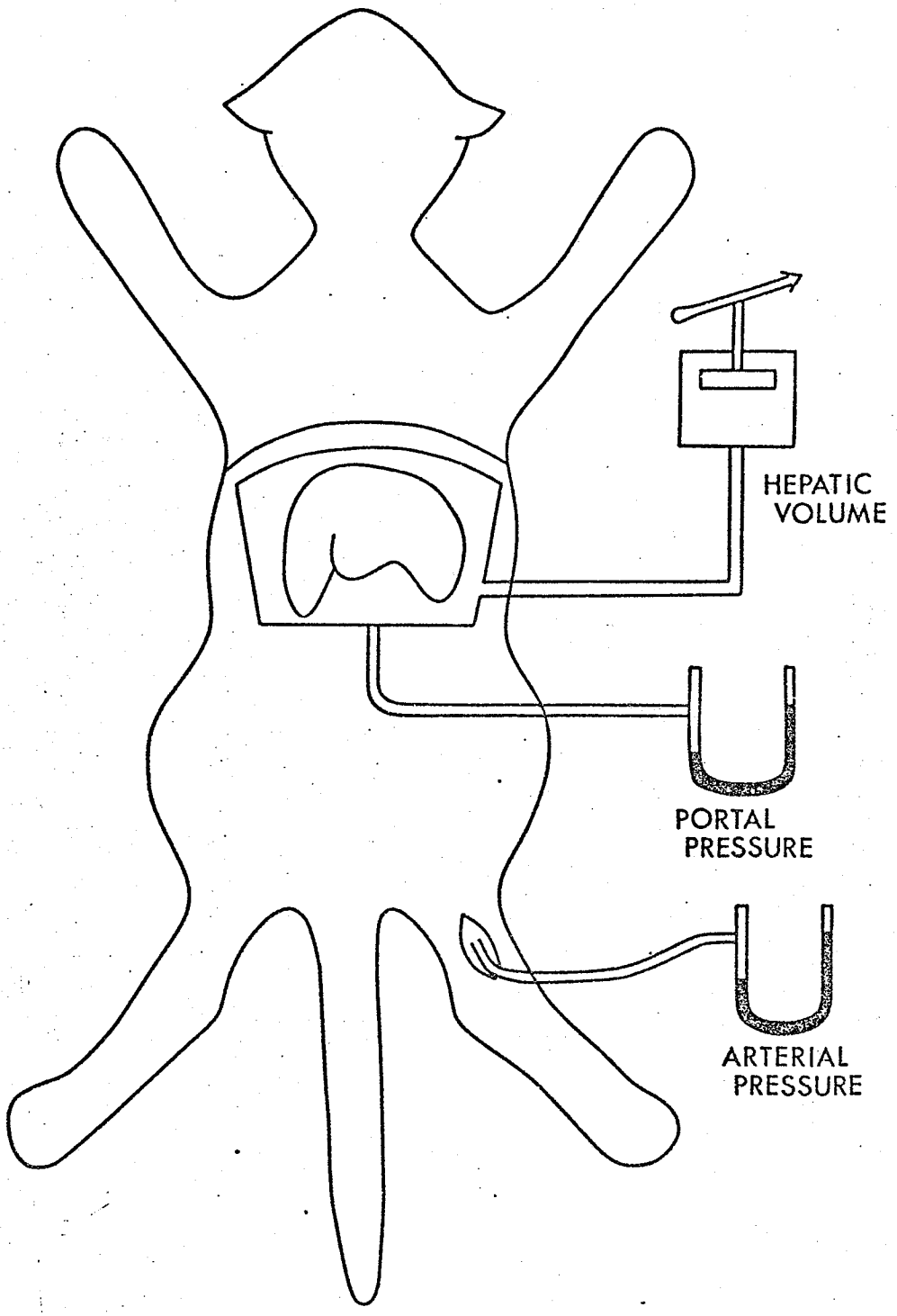


Figure 5

Diagram of the method used to record hepatic volume changes in hemorrhage and infusion

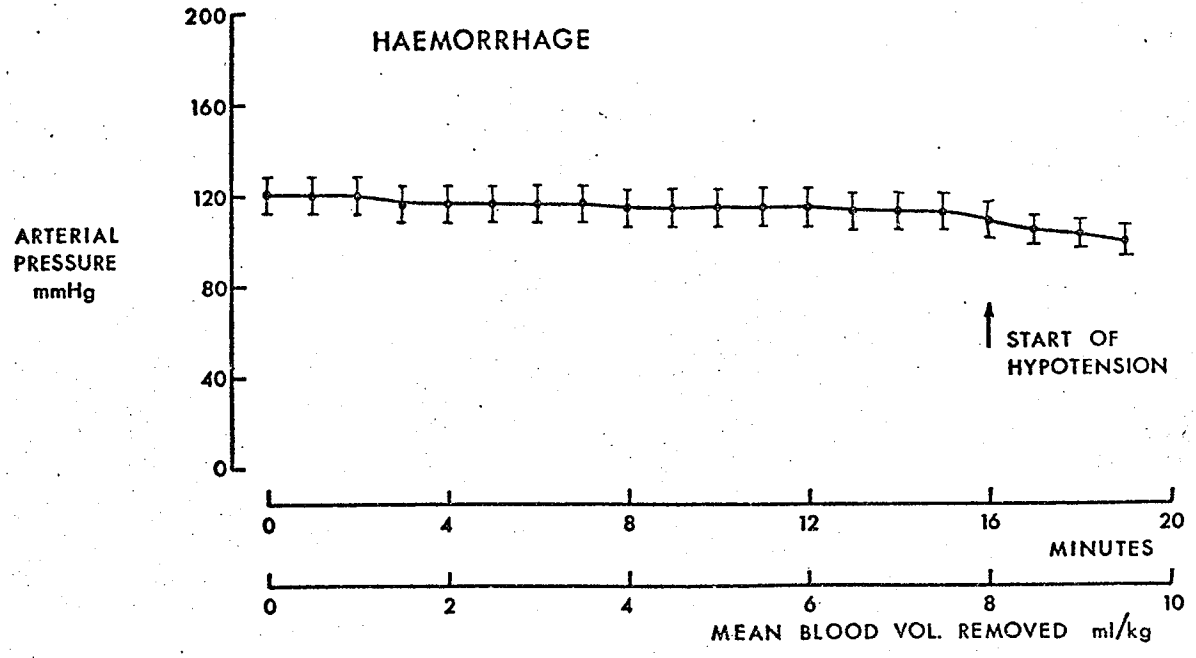


Figure 6

The means (± S.E.) of the arterial pressure in the eighteen cats subjected to hemorrhage

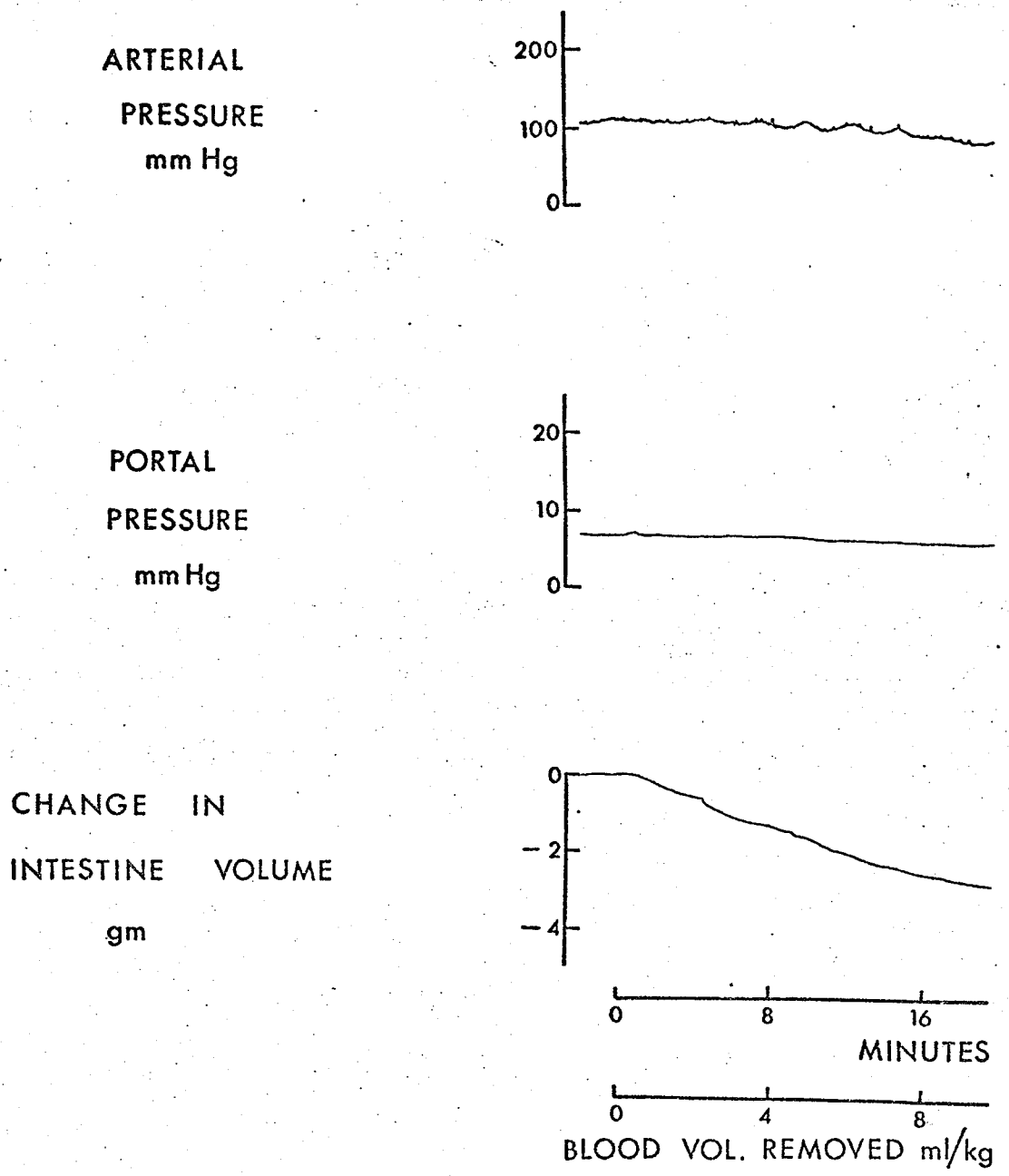


Figure 7

Cat 2.4 kg., Intestinal weight within the plethysmograph 38.5 g. Effects of hemorrhage on arterial pressure, portal pressure and intestinal volume

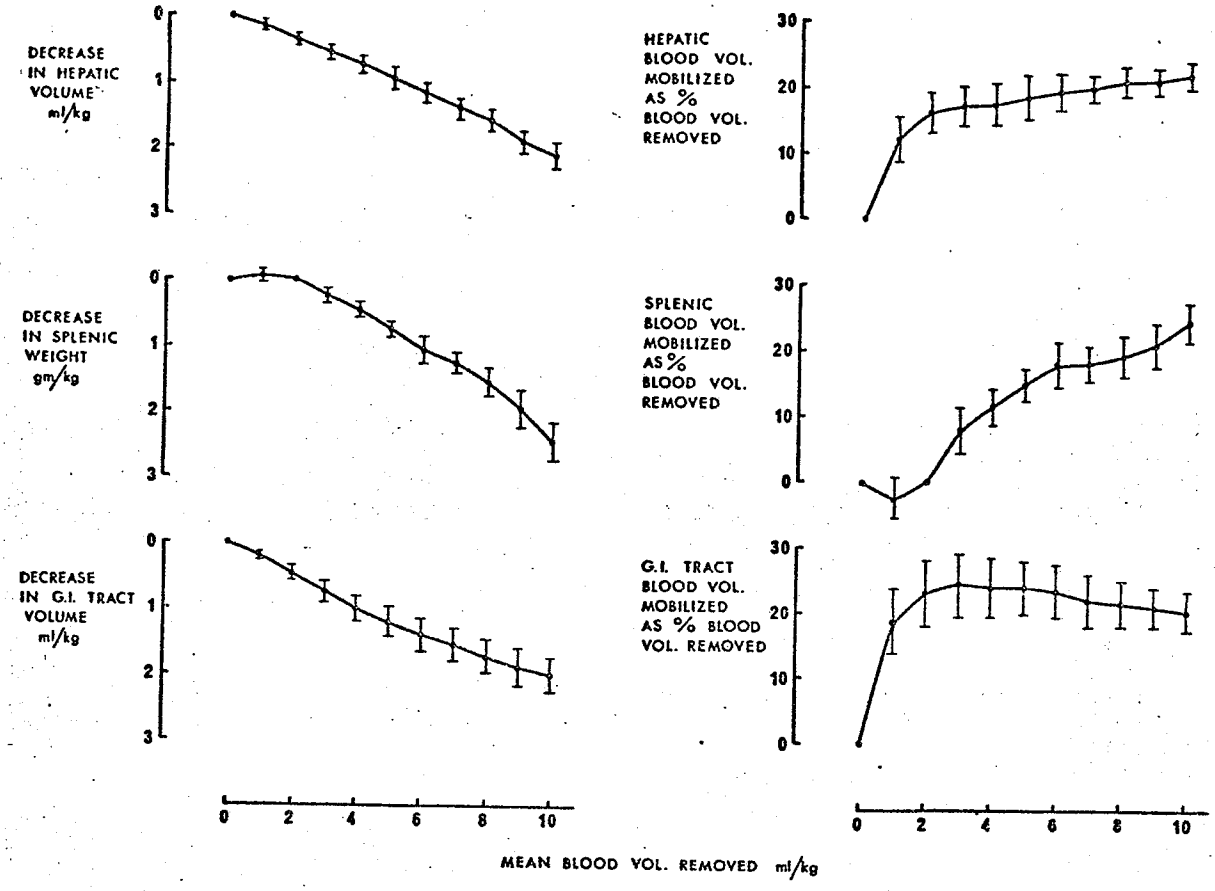


Figure 8

The means (± S.E.) of the decreases in hepatic volume (six cats), Splenic weight (six cats) and gastro-intestinal volume (six cats) during hemorrhage and the means (± S.E.) of these values expressed as proportions of the volume of blood removed

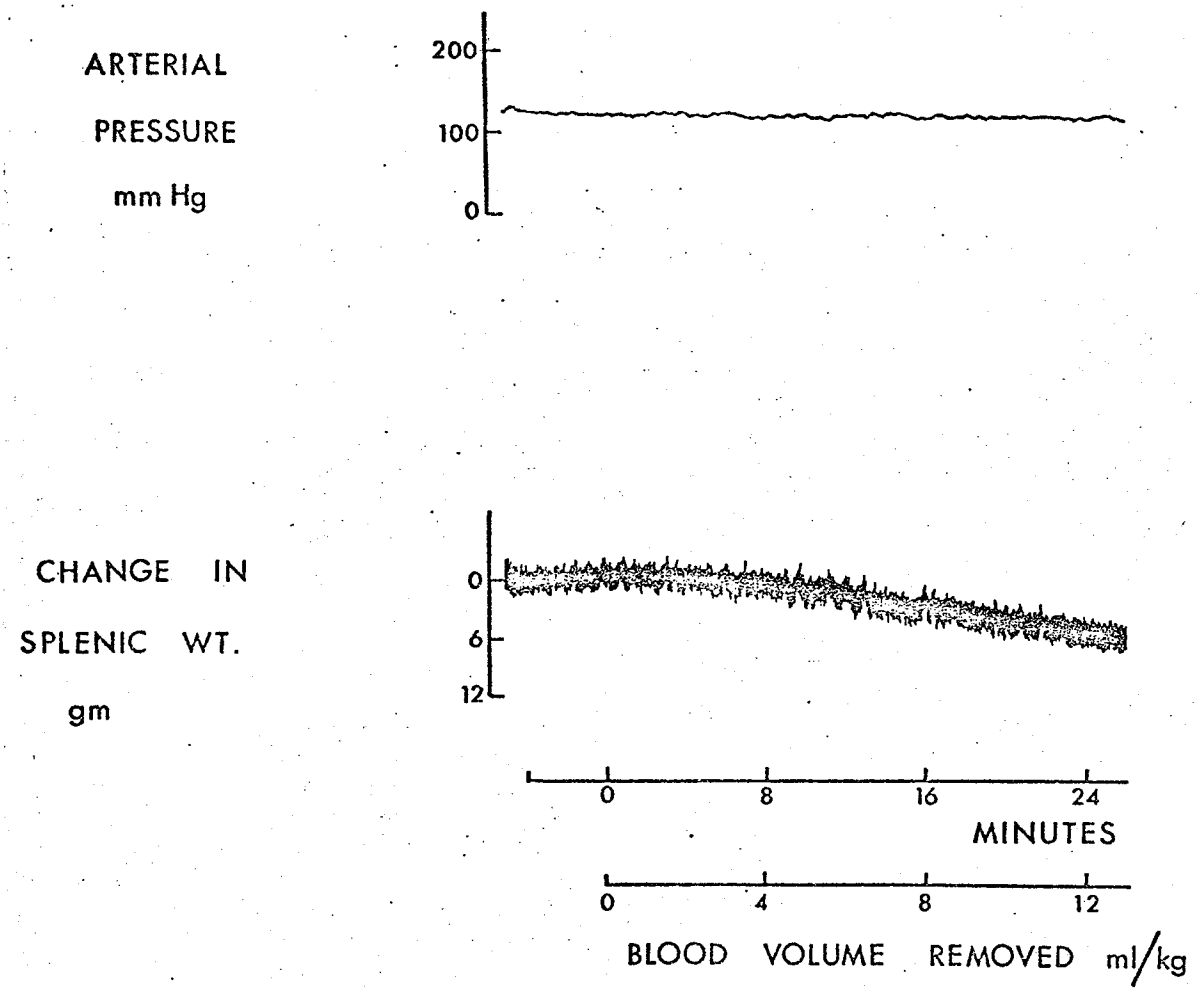


Figure 9

Cat 2.7 kg., Splenic weight 29.8 g. Effects of hemorrhage on arterial pressure and splenic volume

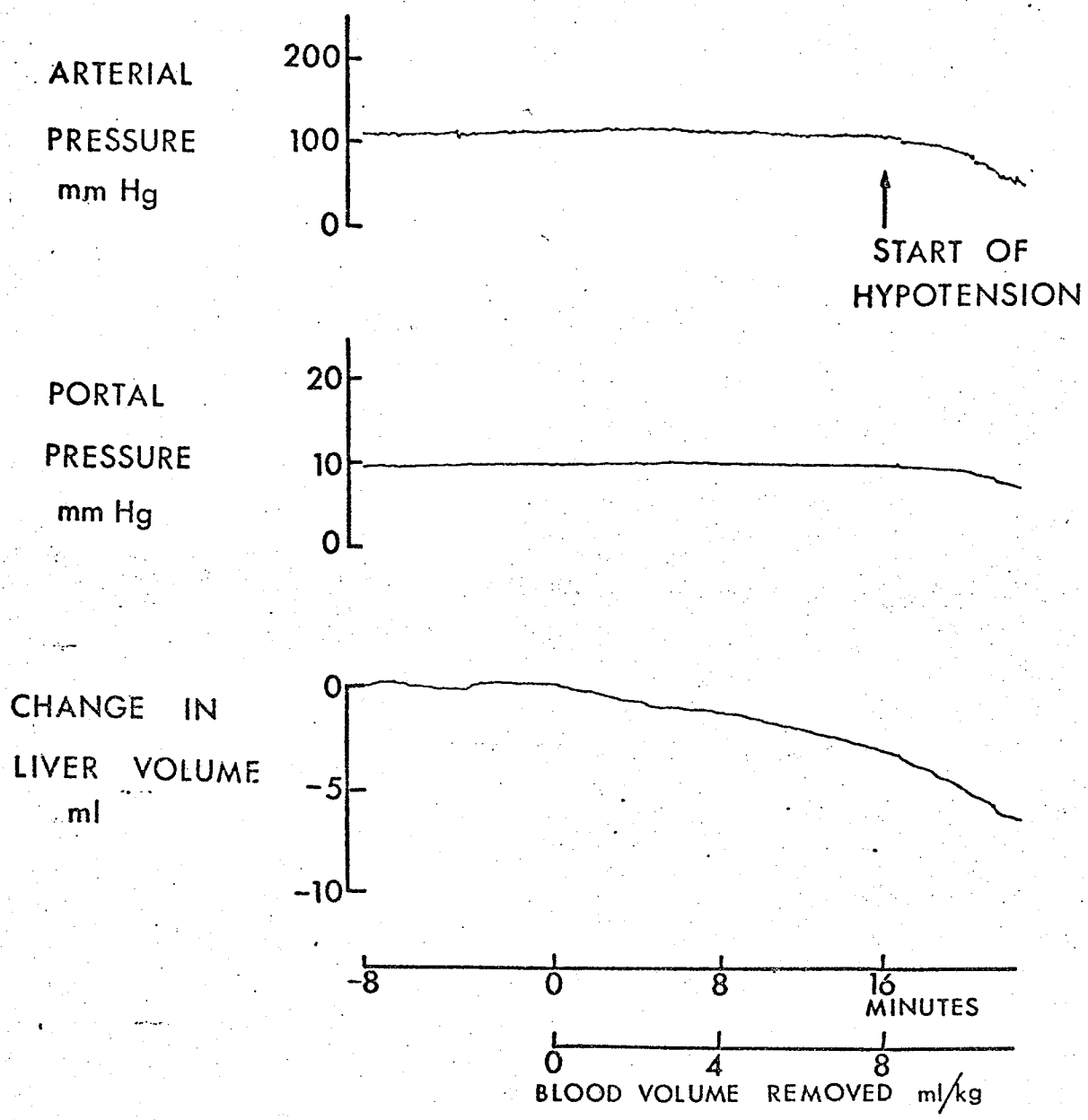


Figure 10

Cat 2.6 kg., Liver weight within the plethysmograph 66 g. Effects of hemorrhage on arterial pressure, portal pressure and hepatic volume

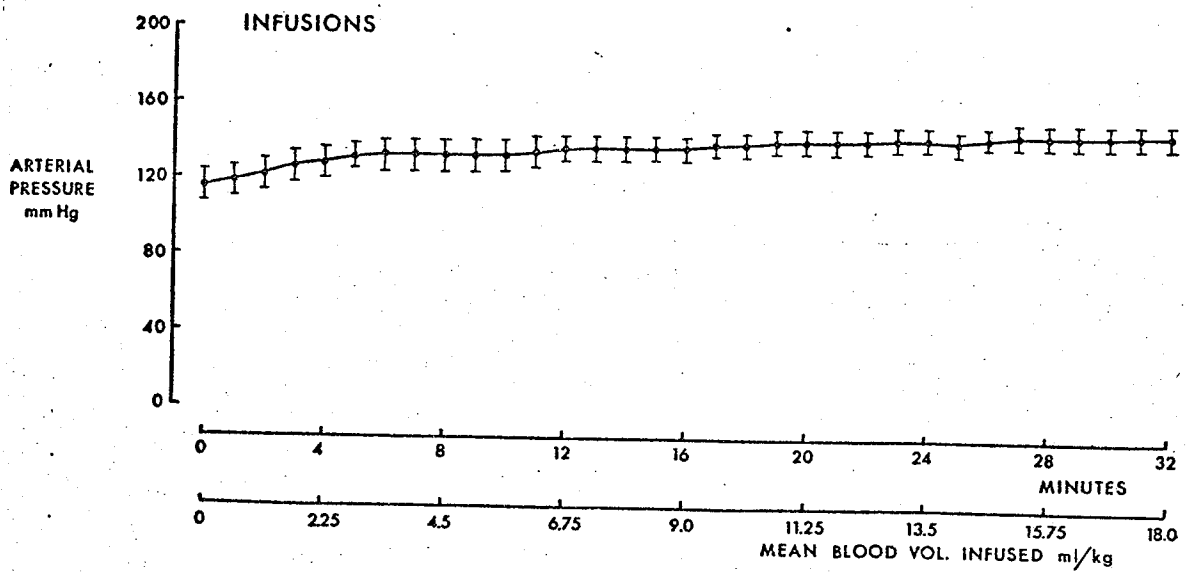


Figure 11

The mean (± S.E.) of the arterial pressure in the eighteen cats given infusions of whole blood

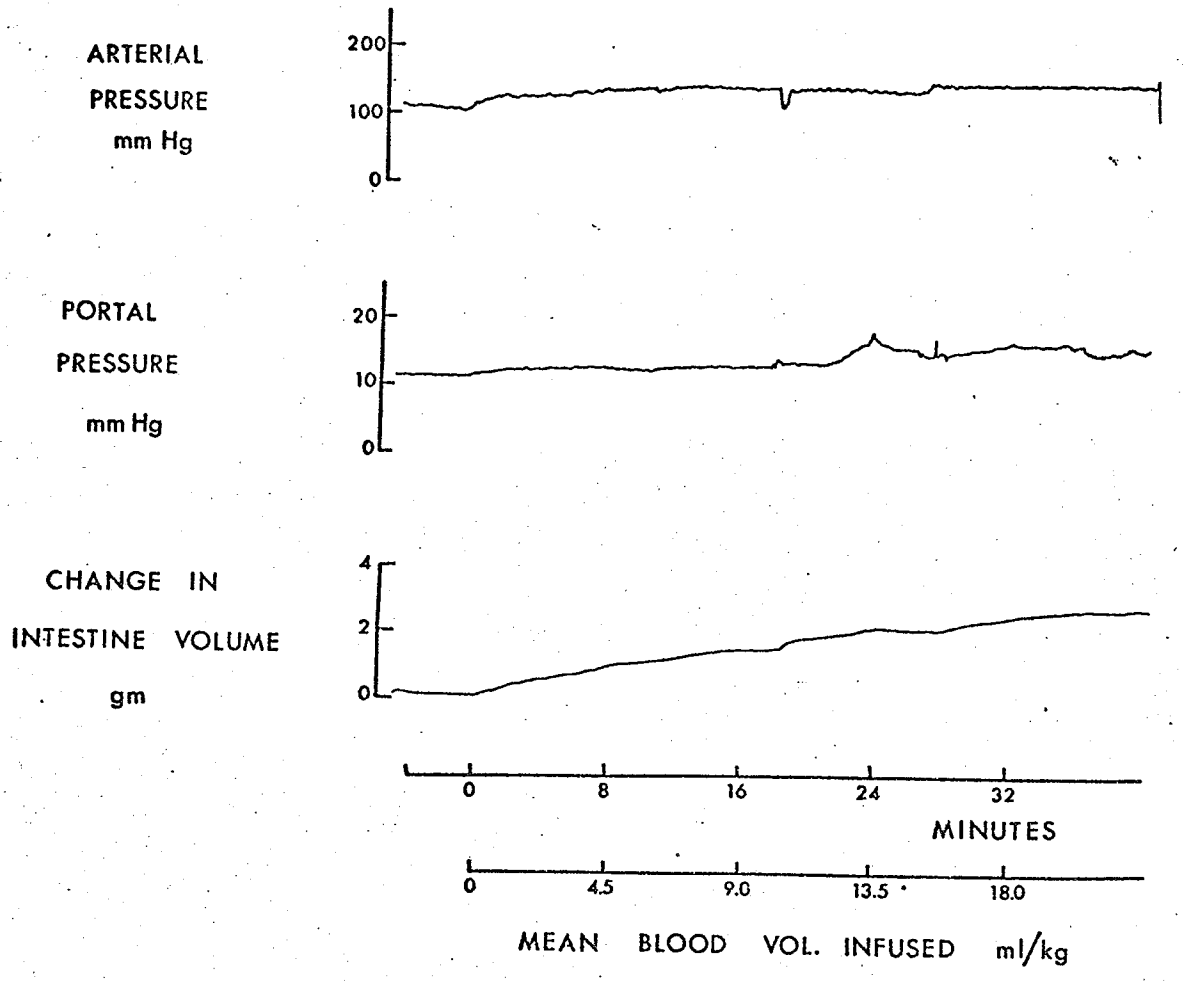


Figure 12

Cat 2.5 kg., intestinal weight within the plethysmograph 31.4 g. Effects of infusion of fresh, whole blood on arterial pressure, portal pressure and intestinal volume

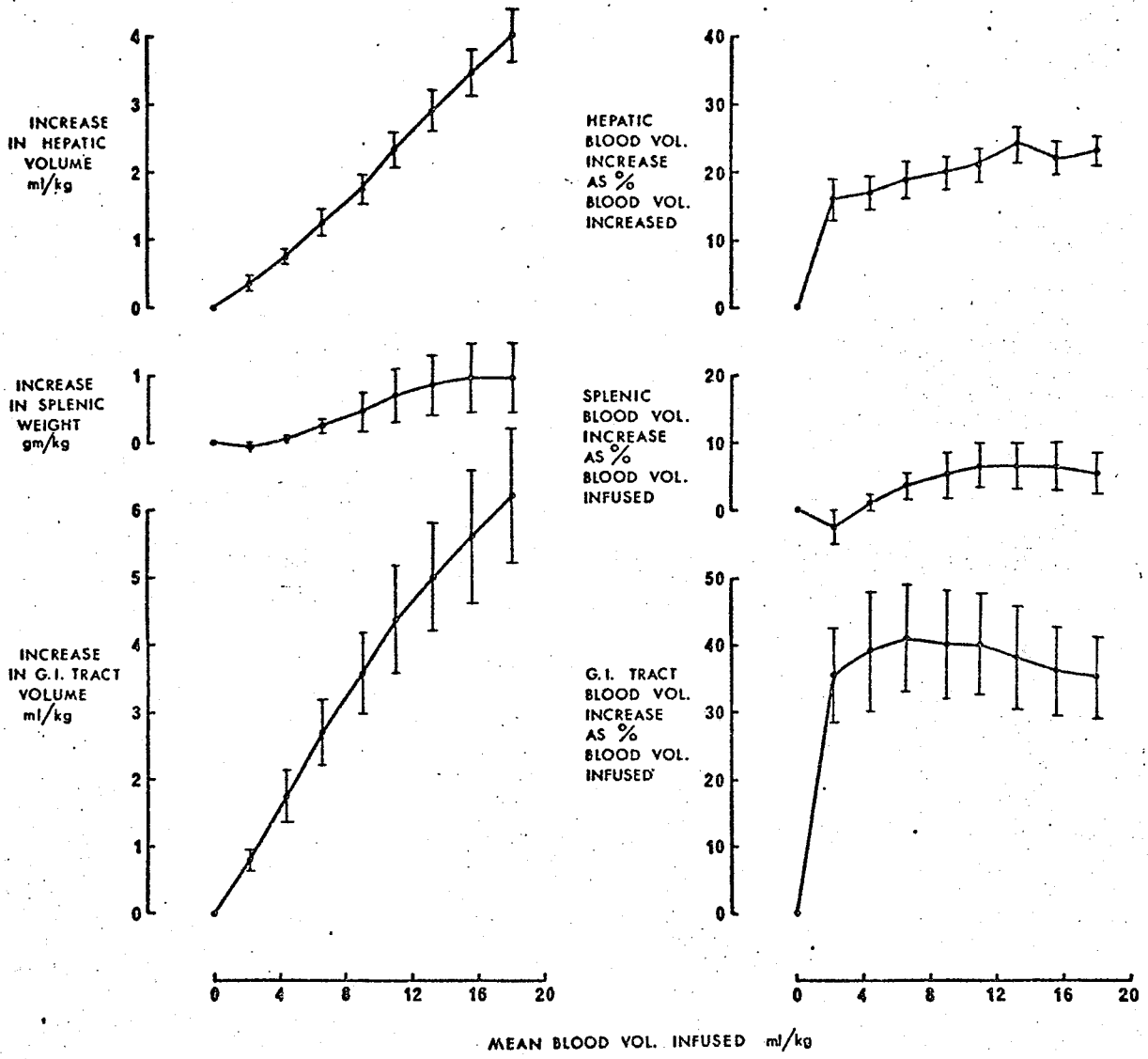


Figure 13

The means (± S.E.) of the increases in hepatic volume (six cats), splenic weight (six cats) and gastro-intestinal volume (six cats) during infusions of whole blood and the means (± S.E.) of these values expressed as proportions of the volume of blood infused

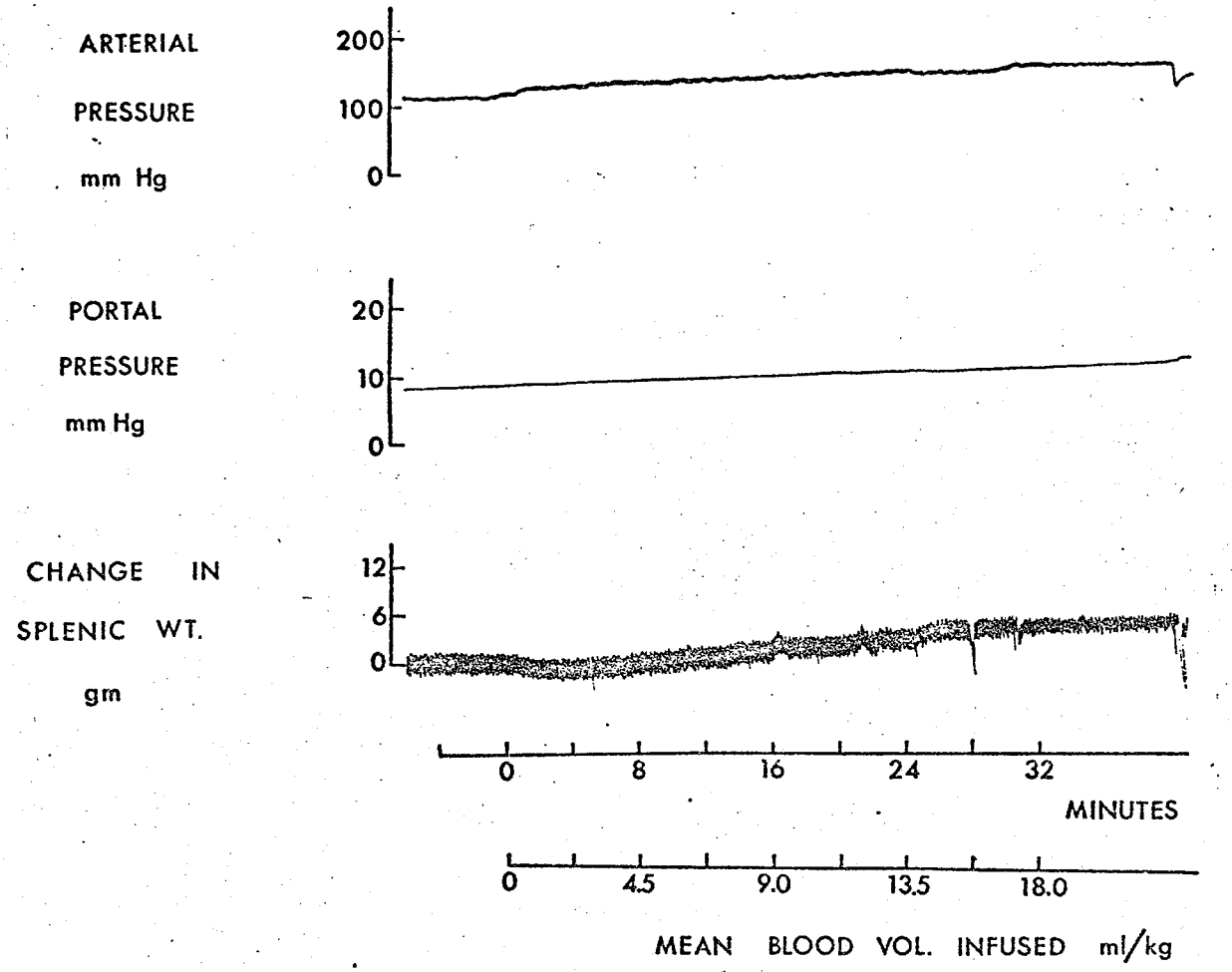


Figure 14

Cat 2.4 kg., Splenic weight 24.9 g. Effects of infusion of fresh, whole blood on arterial pressure, portal pressure and splenic volume

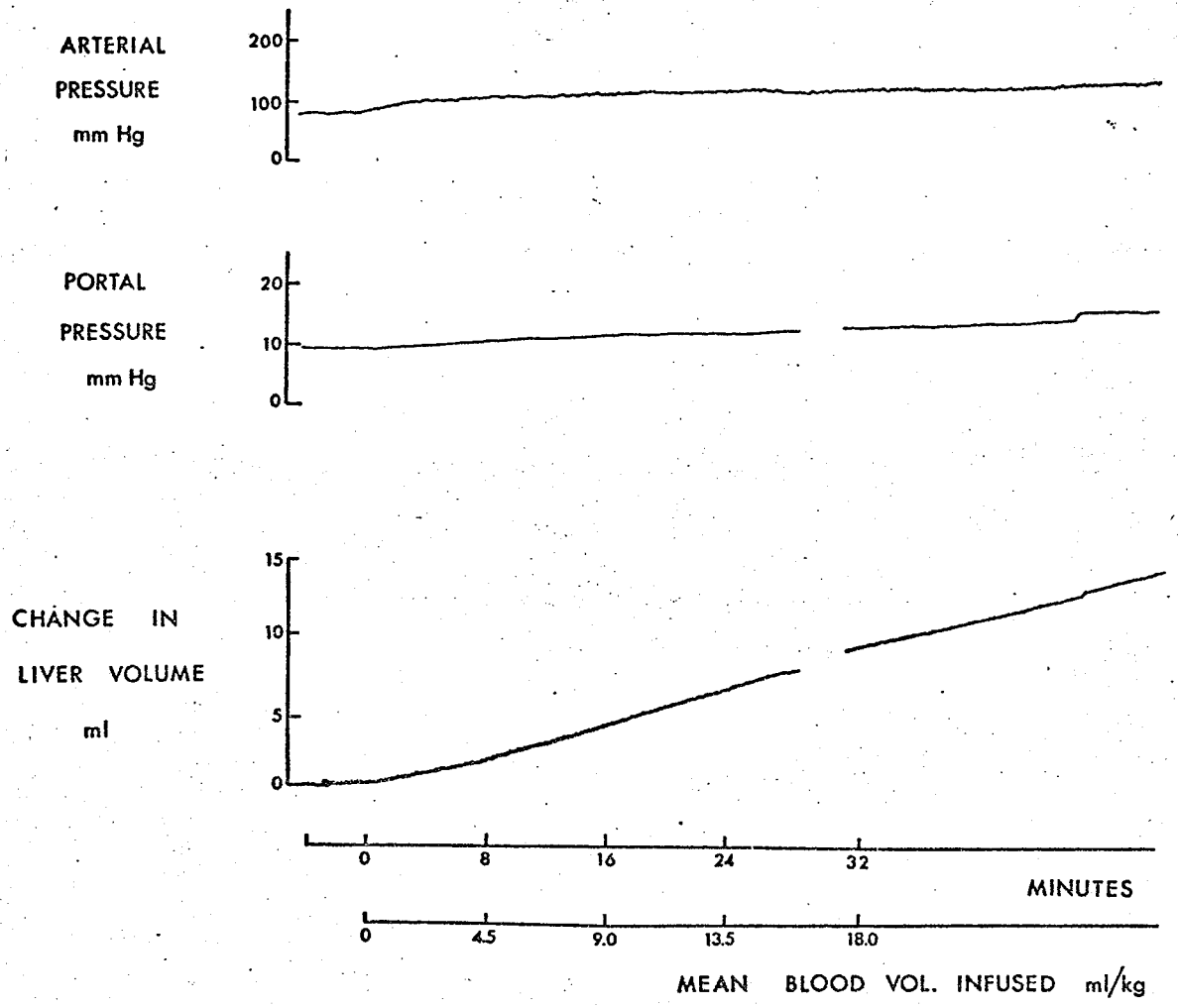


Figure 15

Cat 2.4 kg., Liver weight within the plethysmograph 69.2 g. Effects of infusion of fresh, whole blood on arterial pressure, portal pressure and hepatic volume

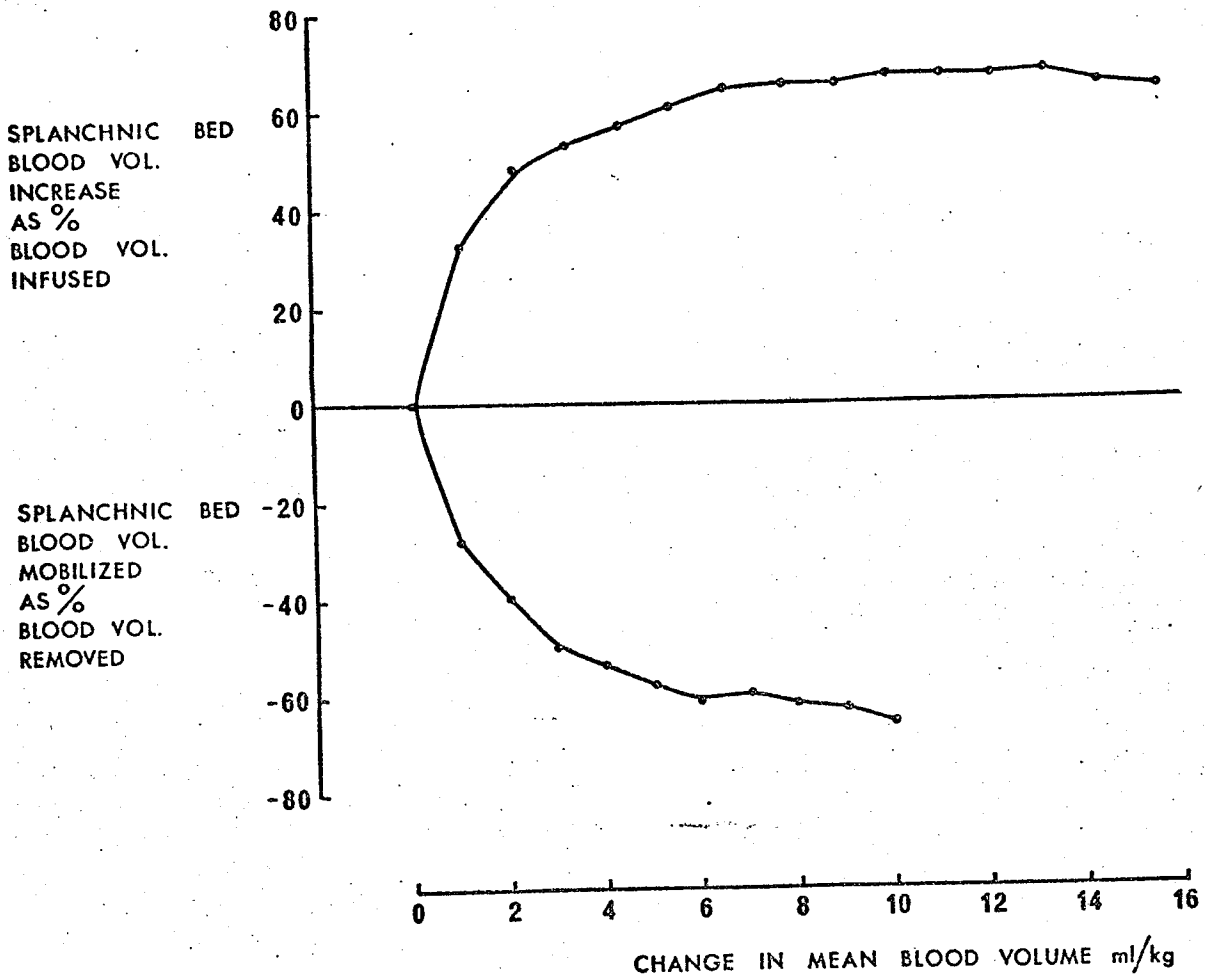


Figure 16

The mean proportions which are contributed by the splanchnic vascular bed to the volume of blood infused into or removed from cats. These values were obtained by summing the contributions of the liver, spleen and gastro-intestinal tracts in figures 8 and 13

TABLES

REGIONAL DISTRIBUTION OF BLOOD VOLUME

	% BODY WT	% BLOOD VOLUME	% BLOOD VOLUME MOBILISED BY NERVES
SPLANCHNIC BED			
LIVER	3	14	6
SPLEEN	1	12	9
INTESTINE & STOMACH	6	10	4
MUSCLE	45	14	4
ADIPOSE TISSUE	14	11	4
LUNGS	1·5	10	?
SKIN	3	2	1
HEART - CHAMBERS		5	–
MUSCLE	0·5	1	–
KIDNEYS	0·5	1	–
REMAINDER	25·5	20	?
	100	100	28

Table 1

Regional distribution of blood volume: a tentative tabulation for the cat and dog (Greenway & Lister, 1974)

COURSE OF BLOOD PRESSURE (BP) & PORTAL PRESSURE (PP) CHANGES DURING HEMORRHAGE mm Hg

BLOOD REMOVED ml/kg	GROUP 1 (G.I. TRACT) BP (AVG ± $S_{\bar{x}}$)	GROUP 1 (G.I. TRACT) PP (AVG ± $S_{\bar{x}}$)	GROUP 2 (SPLEEN) BP (AVG ± $S_{\bar{x}}$)	GROUP 2 (SPLEEN) PP (AVG ± $S_{\bar{x}}$)	GROUP 3 (LIVER) BP (AVG ± $S_{\bar{x}}$)	GROUP 3 (LIVER) PP (AVG ± $S_{\bar{x}}$)	GROUP 1,2 & 3 COMBINED BP (AVG ± $S_{\bar{x}}$)	GROUP 1,2 & 3 COMBINED PP (AVG ± $S_{\bar{x}}$)
0.0	103 ± 6.0	6.5 ± .6	132 ± 9.0		128 ± 11.0	10.4 ± .8	121 ± 6.0	8.6 ± .8
0.5	102 ± 6.0	6.3 ± .6	132 ± 9.0		127 ± 11.0	10.4 ± .7	120 ± 6.0	8.4 ± .9
1.0	99 ± 7.0	6.2 ± .6	132 ± 9.0		126 ± 11.0	10.2 ± .7	119 ± 7.0	8.4 ± .8
1.5	96 ± 7.0	6.0 ± .7	129 ± 9.0		123 ± 12.0	9.8 ± .6	116 ± 7.0	8.1 ± .7
2.0	92 ± 7.0	5.9 ± .7	131 ± 9.0		125 ± 12.0	9.3 ± .8	116 ± 7.0	7.7 ± .7
2.5	92 ± 7.0	5.5 ± .5	131 ± 9.0		125 ± 12.0	9.3 ± .8	116 ± 7.0	7.6 ± .8
3.0	89 ± 7.0	5.4 ± .5	131 ± 9.0		124 ± 11.0	9.7 ± .6	115 ± 7.0	7.7 ± .8
3.5	90 ± 7.0	5.2 ± .4	131 ± 9.0		124 ± 11.0	9.8 ± .6	115 ± 7.0	7.7 ± .8
4.0	90 ± 7.0	5.3 ± .5	130 ± 9.0		123 ± 11.0	9.6 ± .7	114 ± 7.0	7.6 ± .8
4.5	88 ± 7.0	5.4 ± .5	130 ± 8.0		123 ± 11.0	9.4 ± .7	113 ± 7.0	7.6 ± .8
5.0	88 ± 7.0	5.1 ± .4	131 ± 8.0		121 ± 10.0	9.1 ± .8	113 ± 7.0	7.3 ± .8
5.5	86 ± 7.0	4.9 ± .4	130 ± 9.0		121 ± 10.0	9.0 ± .8	112 ± 7.0	7.1 ± .8
6.0	86 ± 7.0	4.8 ± .5	130 ± 9.0		121 ± 9.0	9.1 ± .8	112 ± 7.0	7.1 ± .8
6.5	86 ± 7.0	4.7 ± .5	128 ± 8.0		115 ± 10.0	9.4 ± .7	110 ± 7.0	7.3 ± .9
7.0	85 ± 7.0	4.7 ± .5	128 ± 7.0		117 ± 10.0	9.5 ± .7	110 ± 7.0	7.3 ± .9
7.5	83 ± 7.0	4.7 ± .5	128 ± 8.0		115 ± 9.0	9.6 ± .7	109 ± 7.0	7.4 ± .9
8.0	82 ± 7.0	4.7 ± .5	128 ± 9.0		115 ± 9.0	9.5 ± .7	108 ± 7.0	7.3 ± .9

Table 2

Course of blood pressure and portal pressure changes during hemorrhage

SPLANCHNIC BED RESPONSE TO HEMORRHAGE

AMT. OF BLOOD REMOVED ml/kg	ABSOLUTE DECREASE IN VOLUME			% OF MEAN BLOOD VOL REMOVED			% OF MEAN TOTAL BLOOD VOL. (52 ml/kg)			% OF MEAN ORGAN VOLUME		
	G.I. TRACT ml/kg	SPLEEN gm/kg	LIVER ml/kg	G.I. TRACT ml/kg	SPLEEN gm/kg	LIVER ml/kg	G.I. TRACT ml/kg	SPLEEN gm/kg	LIVER ml/kg	G.I. TRACT ml/kg	SPLEEN gm/kg	LIVER ml/kg
2	0.5	0.0	0.3	23	0.0	16	0.9	0.0	0.6	8.9	0.0	4.4
8	1.7	1.5	1.7	22	19	21	3.3	3.0	3.2	33.0	25.0	23.0

Table 3

Splanchnic bed response to hemorrhage

COURSE OF BLOOD PRESSURE (BP) & PORTAL PRESSURE (PP) CHANGES DURING INFUSION (mm Hg)

BLOOD REMOVED ml/kg	GROUP 1 (G.I. TRACT) BP (AVG ± Sx̄)	GROUP 1 (G.I. TRACT) PP (AVG ± Sx̄)	GROUP 2 (SPLEEN) BP (AVG ± Sx̄)	GROUP 2 (SPLEEN) PP (AVG ± Sx̄)	GROUP 3 (LIVER) BP (AVG ± Sx̄)	GROUP 3 (LIVER) PP (AVG ± Sx̄)	GROUP 1,2 & 3 COMBINED BP (AVG ± Sx̄)	GROUP 1,2 & 3 COMBINED PP (AVG ± Sx̄)
0.0	116.7 ± 12.8	8.7 ± 1.0	112.5 ± 8.7	6.7 ± 0.6	118.3 ± 19.0	8.4 ± 1.2	115.8 ± 7.5	7.9 ± 0.6
1.1	120.0 ± 11.0	9.0 ± 1.2	121.7 ± 4.9	6.8 ± 0.6	123.3 ± 18.0	8.7 ± 1.1	121.7 ± 6.8	8.1 ± 0.6
2.3	128.3 ± 10.7	9.0 ± 1.3	126.3 ± 4.9	7.0 ± 0.6	128.3 ± 18.0	9.0 ± 1.2	128.3 ± 6.7	8.3 ± 0.6
3.4	131.7 ± 10.8	9.5 ± 1.5	130.0 ± 5.3	7.1 ± 0.7	134.2 ± 19.7	9.3 ± 1.1	131.9 ± 7.2	8.6 ± 0.6
4.5	133.3 ± 10.8	9.5 ± 1.5	132.5 ± 5.3	7.2 ± 0.7	134.2 ± 20.4	9.3 ± 1.1	133.3 ± 7.4	8.6 ± 0.7
5.6	135.0 ± 12.0	9.5 ± 1.4	134.2 ± 5.7	7.3 ± 0.7	131.7 ± 20.4	9.3 ± 1.1	133.6 ± 7.7	8.7 ± 0.6
6.8	137.5 ± 12.2	9.7 ± 1.5	135.8 ± 6.1	7.3 ± 0.8	132.5 ± 21.1	9.3 ± 1.1	135.3 ± 7.9	8.7 ± 0.7
7.9	139.2 ± 11.7	10.1 ± 1.6	135.8 ± 5.1	7.5 ± 0.8	134.2 ± 19.7	9.3 ± 1.1	136.4 ± 7.4	8.9 ± 0.7
9.0	137.5 ± 12.2	9.6 ± 1.5	136.7 ± 5.7	7.6 ± 0.8	135.8 ± 19.6	9.5 ± 1.2	136.7 ± 7.5	8.9 ± 0.7
9.1	139.2 ± 12.7	9.6 ± 1.6	136.7 ± 5.1	7.6 ± 0.8	138.3 ± 21.0	9.8 ± 1.2	138.1 ± 7.9	8.9 ± 0.7
11.0	138.3 ± 13.1	9.4 ± 1.6	139.2 ± 7.7	7.8 ± 0.8	140.0 ± 20.5	9.9 ± 1.1	139.2 ± 8.0	9.0 ± 0.7
12.0	138.3 ± 13.1	9.4 ± 1.8	140.0 ± 8.4	7.8 ± 0.8	142.5 ± 21.4	10.1 ± 1.1	140.3 ± 8.3	9.1 ± 0.7
14.0	140.8 ± 13.5	9.3 ± 2.0	140.0 ± 8.9	7.8 ± 0.8	142.5 ± 21.2	10.3 ± 1.1	141.1 ± 8.4	9.1 ± 0.7
15.0	141.7 ± 13.1	9.6 ± 2.0	139.2 ± 9.3	7.8 ± 0.8	145.8 ± 20.9	10.3 ± 1.1	142.2 ± 8.3	9.2 ± 0.8
16.0	142.5 ± 12.8	10.1 ± 2.3	139.2 ± 9.6	7.9 ± 0.7	147.5 ± 20.9	10.9 ± 0.8	143.1 ± 8.3	9.6 ± 0.8
17.0	144.2 ± 13.0	10.9 ± 2.2	139.2 ± 8.5	8.1 ± 0.8	145.0 ± 21.4	11.4 ± 0.8	142.8 ± 8.3	10.1 ± 0.8
18.0	144.2 ± 13.8	10.8 ± 2.1	140.8 ± 9.6	8.0 ± 0.8	147.5 ± 20.9	11.5 ± 0.6	144.2 ± 8.4	10.6 ± 0.8

Table 4

Course of blood pressure and portal pressure changes during infusion

SPLANCHNIC BED RESPONSE TO INFUSION

AMT. OF BLOOD REMOVED ml/kg	ABSOLUTE INCREASE IN VOLUME			% OF MEAN BLOOD VOL. REMOVED			% OF MEAN TOTAL BLOOD VOL. (52 ml/kg)			% OF MEAN ORGAN VOLUME		
	G. I. TRACT ml/kg	SPLEEN gm/kg	LIVER ml/kg	G. I. TRACT ml/kg	SPLEEN gm/kg	LIVER ml/kg	G. I. TRACT ml/kg	SPLEEN gm/kg	LIVER ml/kg	G. I. TRACT ml/kg	SPLEEN gm/kg	LIVER ml/kg
2.3	0.79	0.00	0.36	35.0	0.00	16.0	1.5	0.00	0.69	15.0	0.00	4.9
4.5	1.7	0.05	0.75	39.0	1.1	17.0	3.4	0.10	1.4	34.0	0.81	10.0
7.9	3.2	0.37	1.5	39.0	4.6	19.0	6.1	0.71	2.9	61.0	6.0	21.0
12.0	4.7	0.85	2.6	39.0	7.0	21.0	9.1	1.6	5.0	91.0	14.0	36.0
18.0	6.2	0.95	4.0	34.0	5.3	22.0	12.0	1.8	7.7	119.0	15.0	55.0

Table 5

Splanchnic bed response to infusion