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

George Edward Lister

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

PAGE

RESULTS & DISCUSSION (Cont.)

LIST OF FIGURES

LIST OF TABLES

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 contribution 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,