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VASCULAR RESPONSES TO REDUCED CIRCULATION IN DOGS

by

© Eric Charles Elliot

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

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OF DOCTOR OF PHILOSOPHY

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FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled, Vascular Responses to Reduced Circulation in Dogs, submitted by Eric Charles Elliot, in partial fulfilment of the requirements for the degree of Doctor of Philosophy

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Date October 12, 1968

TO MY WIFE

ABSTRACT

In 61 anesthetized mongrel dogs, ventilated with pure oxygen, the venous return to the heart was quickly lowered and held at a constant level for two hours, at values selected between 13 and 45 ml/kg/min. This was achieved by diverting the venous return to the heart into a reservoir from which the blood was pumped back into the right atrium at a fixed rate.

When the constant cardiac inflow was held between 13 and 17.5 ml/kg /min (called the 'low flow' experiments) the systemic arterial pressure immediately fell to 25 to 30 mmHg, and subsequently, never rose above 50 mmHg. It was concluded that at these low levels of cardiac output the basic abnormality was probably inadequate filling of the arterial tree. However, metabolic acidosis, which developed in these dogs, may also have been a contributing factor by reducing the reactivity of the precapillary resistance vessels.

In contrast, if the venous return was held constant at higher values, e.g., above 27 ml/kg/min (called the 'high flow' experiments) the arterial pressure again dropped, but then in the course of the next two hours steadily rose. There was a biphasic characteristic to this pressure rise. The gradual rise in arterial pressure, to approximately 70 to 100 mmHg, must have been due to a progressive constriction of the precapillary resistance vessels. If phenoxybenzamine (5mg/kg) was given before the two-hour hypotensive period, the arterial pressures remained at levels indistinguishable from the low flow experiments, indicating that there was a strong alpha receptor component in the vasoconstrictor response. In these same adrenergic blockade experiments, the amount of blood that collected in the reservoir during the experimental period (approximately 40 ml/kg) was not different from the amount that collected in the low flow experiments. It would be expected that following alpha receptor blockade there would be pooling of blood in the venous capacitance vessels, but this did not occur. Therefore,

passive-elastic collapse of the veins may have been a factor in the movement of blood into the reservoir.

In the low flow group of experiments, adrenaline and noradrenaline concentrations rose to 100 and 10 ug/liter, respectively. In the high flow group of experiments, in which adrenergic blockade was carried out, adrenaline and noradrenaline concentrations were also elevated, but significantly less than in the low flow experiments (e.g., 27 and 4 ug/liter, respectively). Reflex sympathetic activity may have been less in the latter group because of better perfusion of the chemoreceptors.

A 'best-fit' family of curves was derived from the experimental data to show the over-all trends of the arterial pressure and reservoir blood volume changes at seven different levels of venous return. These showed that at low levels of constant venous return, reservoir blood volume continued to increase beyond the point where the arterial pressure curves levelled off.

This study provides information on vascular adjustments to varying levels of controlled circulation, by utilizing the dog's own heart and lungs rather than by artificial means. This particular approach of examining various levels of reduced circulation has received very little attention in the literature.

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ABBREVIATIONS

A	-	adrenaline
cm	-	centimeter
F	-	French catheter size
g	-	gram
i. a.	-	intra-arterial
I. D.	-	internal diameter
kg	-	kilogram
LBM	-	lean body mass
M	-	molar
M^2	-	meter squared
mg	-	milligram
mEq	-	milliequivalent
min	-	minute
ml	-	milliliter
mmHg	-	millimeters of mercury
mu	-	millimicron
N	-	number of observations
NA	-	noradrenaline
P	-	probability
P_{CO_2}	-	partial pressure of carbon dioxide
Pa_{CO_2}	-	arterial partial pressure of carbon dioxide
Pv_{CO_2}	-	venous partial pressure of carbon dioxide
Pa_{O_2}	-	arterial partial pressure of oxygen
Pv_{O_2}	-	venous partial pressure of oxygen
'r'	-	coefficient of correlation
s^2	-	variance
S. D.	-	standard deviation
S. E.	-	standard error
S. E. of b	-	standard error of regression coefficient
sec	-	second
T-1824	-	Evans' blue dye
THAM	-	Tris-Hydroxymethyl Amino Methane
x	-	individual observations
$\bar{x}$	-	average value of x's
ug	-	microgram
y	-	individual observations
$\bar{y}$	-	average value of y's
'z'	-	'z' transformation (see Statistical Methods)

VASCULAR RESPONSES TO REDUCED CIRCULATION IN DOGS

CHAPTER I

"Si l'on voit un blessé devenir jaune, de couleur verte ou plombée peu de temps après le coup reçû, c'est sans doute que le saisissement ou la commotion a suspendu la filtration de la bile & peut-être même celle de quelqu'autre liqueur."

Le Dran, 1737

Introduction

An English translation of Le Dran's 'Traité ou Reflexions' was published in 1743. In the original publication Le Dran had used three words, la secousse, le saisissement and la commotion to describe the condition arising from a severe blow or injury, but as Simeone (1963) pointed out, the English translator used the single word 'shock' for these. In this unobtrusive way began the indelible association of this term with English medical literature.

Although Le Dran used the above words to refer to the condition arising from the impact of the injury, he was well aware of the dire consequences that could develop in the wounded patient. Nevertheless, the extension of the original meaning of shock, to include the entire sequence of circulatory events following bodily injury of sufficient degree to produce shock was a gradual one and, as Wiggers (1950) explains, the transition probably came about "insidiously in hospital parlance." Guthrie (1827), from his long experience as an English Army surgeon, especially in regard to amputation of lower extremities, gave a modern connotation to 'shock' by stating that, "if there be considerable shock and alarm to the system at large . . . a certain delay and the exhibition of cordials is to be resorted to." Morris (1867) was apparently the first to use the word in a title of a monograph.

In 1913 Short observed,

> "The most probable cause of shock, in the writer's opinion, is oligaemia, induced by loss of fluid partly into the injured area, and partly through the capillaries all over the body in consequence of reflex vasoconstriction due to stimulation of the pressor afferent nerves. Sudden collapse may then be precipitated by stimulation of the depressor afferents."

Although prior to that time it was well known that shock could result from wounds, severe dehydration, hemorrhage or any condition which resulted in an underfilling of the vascular space, experimental approaches leading to the elucidation of its basic mechanisms were sporadic. World War I accelerated interest in the problems associated with the wounded soldier. Keith (1919), using the newly introduced dye method (Keith, Rowntree & Geraghty, 1915), showed that there was a relationship between the severity of shock in the wounded soldier and the degree of blood loss. Other authors also concurred in this finding (Cowell, 1918; Robertson & Bock, 1919).

Acceptance of the oligemic theory of shock was according to Harkins (1961), however, delayed for a time by the report in 1919 of a Joint Commission headed by two of the leading physiologists of the day, Cannon from the United States and Bayliss, from Great Britain, reporting on the evidence as it then presented itself. There was at this time confusion, which exists to this day, between the immediate effects of trauma, hemorrhage or other initiating factors in the final pathway. Crile (1899) was a strong proponent of the 'neurogenic view', that the essence of shock was a massive peripheral nerve stimulation by the injury producing central vasomotor exhaustion. Also prevalent at this time was the theory that shock might be due to a toxic factor. Dale, Laidlaw & Richards (1919) implicated histamine or something like histamine and made a convincing story attempting to supplant the earlier 'neurogenic view'. This received strong support from the work of Cannon & Bayliss who claimed to have prevented shock by placing limb tourniquets in experimental animals before exposing them to trauma, and to various wartime reports of injured soldiers treated with tourniquets. Unfortunately

attempts to repeat this work largely met with failure. Phemister (1928), Parsons & Phemister (1930) and Blalock (1930), were amongst those whose work discredited the earlier findings. They also seemed to show that the necessary oligemia could be accounted for by the blood and tissue fluid lost into the traumatized extremities.

Although oligemic or hypovolemic shock can be produced experimentally by trauma, the most common way has been to bleed the animal. The methods used by different investigators can generally be divided into two groups. 1. A specific amount of blood is withdrawn from the animal based on either a percentage of the total blood volume or body weight. Walcott (1945) worked extensively with this preparation. 2. The arterial pressure is lowered and held at a low level, usually between 30 and 50 mmHg, by means of a shunt between a femoral artery and a bleed bottle. This method was popularized by Wiggers, Ingraham & Dille (1945) and Frank, Seligman & Fine (1945), and has since been extensively used. When these techniques are used to study vascular responses several difficulties arise. With either method the cardiac output can fluctuate, making it difficult to calculate peripheral resistance and in the case of the fixed bleed technique, the blood pressure can vary as well as the cardiac output. Furthermore, as Crowell & Guyton (1964) have pointed out, there is great variation in the oxygen used by the animal when the arterial blood pressure is held at low levels (e.g., 30 mmHg) - the inference being that possibly more consistent results might be obtained were it the cardiac output that was the variable held constant.

In most studies in hemorrhagic shock the objective has been to produce in the experimental animal, levels of hypotension severe enough to lead to irreversible shock. These severe levels of hypotension necessary to produce irreversible shock have largely resulted in a neglect of studies of intermediate levels of reduced circulation, apart from a few minor studies relating to autoregulation in liver, kidney and brain (Grayson & Mendel, 1965). With the advent of modern techniques for blood flow measurements, for instance, electromagnetic flow transducers, this area no doubt will receive greater scrutiny (Gregg,

1962). In this regard, Chien in 1958 stated,

> "Although the literature on hemorrhagic shock is extensive, very few studies have been made on the effect of hemorrhages of a degree less than that required to induce shock."

To study intermediate levels of reduced circulation and shock it appeared probably that a more useful approach might be achieved by controlling the venous return to the heart. Wégria, Rojas & Wiggers (1943) tried this type of experiment but, for reasons the authors were unable to explain, fulminant shock conditions developed even in the presence of relatively high levels of venous return. Although these authors discontinued that approach other investigators used the controlled venous return preparation for different kinds of studies. Rashkind, Lewis, Henderson, Heiman & Dietrick (1953) controlled the venous return to the heart at approximately one litre per minute for an investigation into the effects of drugs on arterial resistance and venous capacitance vessels; but, it can be seen from their Tables I and II that the control levels of mean arterial pressure in many of their experiments were approaching shock levels indicating the integrity of the preparation had likely been compromised. Coleridge & Hemingway (1958) reported their experience with a venous return preparation. Their objective was to "bring the inflow to the heart and the venous return into such a relationship that there was no shift of blood from the animal to the reservoir and vice versa, rather than by setting it to give a pre-determined value of cardiac output or of arterial blood pressure." Greenway & Howarth (1963) were the first to demonstrate that the integrity of the venous return preparation could consistently be maintained for periods as long as five hours. They used a 'caval long-circuit' technique in which the venous return to the heart could be controlled. Evidence of the stability of their preparation was the fact that there was little fluctuation in the systemic arterial pressure - the values remaining above 100 mmHg. The level of venous return in their experiments varied between 590 and 1360 ml of blood flow per minute.

The impetus for experimental investigation into reduced circulatory states by means of controlling arterial systemic circulation actually came from another field and the experiment which started this new approach was reported in 1952 by Andreasen & Watson. These authors showed that dogs could survive 45 minutes of superior and inferior venae cavae occlusion if the azygos vein were left patent. During the intervals when the venae cavae were occluded the systemic arterial blood pressure fell to 25 to 30 mmHg, but rose again to control levels after resumption of caval blood flow. Cohen & Lillehei (1954) repeated and confirmed these experiments and reported that direct measurements of the azygos blood flow under these conditions gave values between 8 and 14 ml/kg/min. These experiments were of considerable importance because they led to a new concept, the 'low flow principle', which Lillehei, Cohen, Warden, Ziegler & Varco (1955) successfully applied in their first open-heart surgery.

Initial experience was gained in the use of the heart-lung machine during extracorporeal circulation experiments in the Department of Surgery under the direction of Professor J. C. Callaghan (Elliot & Callaghan, 1958a, 1959a). Extracorporeal circulation offered the advantage that the blood flow to the arterial side of the circulation could be controlled, thereby offering opportunities to study the vascular responses (Read, Johnson & Kuida, 1957); but, it suffered from the disadvantage that the effects of the pump and oxygenator could not be predicted. A preparation was therefore devised, similar to the venous return preparation used by Weil, MacLean, Visscher & Spink (1956) in their studies on endotoxin shock, in which the artificial oxygenator unit was eliminated and the dog's lungs used for oxygenation (Elliot & Callaghan, 1959b). This resulted eventually in a preparation in which the venous return to the heart could be controlled in closed-chest dogs for periods up to two hours (Elliot, 1961b). In these experiments the venous return to the heart was held at a lower level in each successive experiment. Although there were trends suggesting marked changes in the peripheral resistance during the two-hour period the number of experiments was too small to draw any

definite conclusions.

Statement of the Problem

While working with Professor J. C. Callaghan in the early years of open-heart surgery at the University of Alberta it became apparent that the effects of controlled systemic blood flow attendant on this operation were imperfectly understood and the physiological responses to the hypotension that frequently occurred were not clear. It was therefore decided to investigate the physiological responses at various levels of venous return to the heart (all levels being reduced from those normally existing in the dog). The study was undertaken not only to determine the changes in resistance and capacitance vessels but also to examine the interrelationship between the changes arising in these vascular areas and the underlying mechanisms of these changes.

CHAPTER II

Literature Review of More Fundamental Aspects of Reduced Circulation

Some of the early research establishing the importance of reduced blood volume in shock has been presented. The relevant literature and course of events leading up to the present investigation have been outlined in Chapter I. However, for a fuller understanding of reduced circulatory states, it is expedient to consider several aspects, such as past and current knowledge relating to capillary fluid transfer, the tone of resistance and capacitance blood vessels and the behaviour and interrelationships of the nervous and endocrine systems.

Capillary Fluid Transfer

Of basic importance in capillary fluid transfer is the Starling-Landis hypothesis. Starling proposed his theory in 1896; it was included in a monograph on the fluids of the body published in 1909. Briefly, Starling contended that the transfer of capillary and interstitial fluids depends on three factors: one, the hydrostatic pressure on either side of the capillary wall; two, the osmotic pressure of the capillary and interstitial fluids; and, three, the permeability properties of the capillary membrane. By an interplay of these factors, the pressures at the capillary level were kept in balance.

It was not until a number of years later, however, that exact measurements in individual capillaries in the frog's mesentery were made by Landis (1925-26, 1927a, 1927b). In these experiments, which Landis evidently initiated when he was a medical student, he related capillary filtration to capillary pressure and showed over a range of 5 to 26 cm of water, that it was a linear relationship. Capillary filtration increased markedly after a three-minute occlusion (1927-28).

Pappenheimer and Soto-Rivera (1948), again a number of years later, gave conclusive evidence by means of the isolated dog and cat hindlimb preparation, for the dependency of the rate of filtration or absorption on arterial and venous

pressure when other known factors were held constant. This was achieved, for different pressures, by adjusting the blood flow to the limb until no fluid exchange occurred (constant limb weight); when the venous pressure was then plotted against the flow rate a linear relationship was observed over a wide range; if the line was extrapolated to zero flow it crossed the ordinate at a point representing the mean capillary pressure at which balance was obtained. From experiments in which the concentration of plasma protein was varied, the authors also showed that the mean hydrostatic capillary pressure was opposed by an equal force, which was found to be equivalent to the effective osmotic pressure of the plasma proteins.

Obviously, in conditions such as extensive cutaneous burns where copious amounts of tissue fluids are lost from the intravascular space, there will be incurred an imbalance between the hydrostatic and osmotic capillary pressures, in favour of the former, and hemoconcentration will ensue (Minot & Blalock, 1940). On the other hand, in hemorrhage resulting in severe hypotension the decrease in hydrostatic pressure might be expected to be greater than in osmotic pressure thereby resulting in hemodilution. However, it is not so straightforward and at one time there were two opposing schools of thought. Moon (1938) and Price, Hanlon, Longmire & Metcalf (1941) claimed that hemodilution invariably occurred, whereas others (Blalock, 1934) claimed that hemoconcentration could be dominant. Weston, Janota, Levinson & Necheles (1942-43) found that it depended on the condition of the dog before hemorrhage. They observed that hemoconcentration tended to occur if the dogs were dehydrated before bleeding, but if the dogs had been well hydrated hemorrhage produced hemodilution.

In this regard, Reeve, Gregersen, Allen & Sear (1953) did decisive experiments in which they showed that the F_{cells} ratio (over-all cell percentage/ venous cell percentage) remained remarkably constant (average = 0.899, S.D. = 0.023) in splenectomized dogs, whereas, in non-splenectomized dogs, anesthe-

tized or not, there was a wide scatter of this ratio. Chien (1958), utilizing this information, performed graded hemorrhages in splenectomized dogs, ranging from 5 to 49% of the control blood volume. It was observed: "Almost immediately after hemorrhage, hematocrit and plasma protein began to decrease. In hemorrhages of less than 15% of the control blood volume, the decrease was not marked and there were no subsequent changes after this initial drop. When the amount of hemorrhage was increased from 20 to 30%, the hemodilution was greater, but took 20 - 60 minutes to reach the final level. In hemorrhages greater than 30%, the rate of hemodilution was accelerated. Hemodilution, as judged from the changes in hematocrit and plasma protein concentration, was completed in about 15 minutes after a hemorrhage of more than 40% of the initial blood volume. The changes in hematocrit and plasma protein concentration were parallel."

Capillary fluid transfer has again been studied recently in isolated hind limb preparations. Mellander& Lewis (1963) and Lundgren, Lundwall & Mellander (1964) have studied in cats the changes in pre- and postcapillary resistance vessels and also capillary fluid transfer. They have shown that the effects of hemorrhage increase sympathetic activity and that this elicits a reflex constriction of the resistance and capacitance vessels resulting in an increase in the pre-/postcapillary resistance ratio leading to decreased capillary pressure and absorption of extravascular fluids. They have also shown that in the later stages of hemorrhage, the pre-/postcapillary resistance ratio may decrease to such an extent that fluid escapes from the circulation by filtration; this latter observation could explain the hemoconcentration which has been described in hemorrhagic shock preparations.

These changes in the dog direct attention to two things: (1) the hemodilution process in this species can be a relatively rapid process; (2) owing to the difficulty of using T - 1824 dye in multiple determinations and the fluctuating red cell mass in non-splenectomized dogs, it would seem the best way to approach this is to simultaneously determine the plasma and red cell volumes by means of

radioactive tracers (Gregersen & Rawson, 1959; Grable, Israel, Williams & Fine, 1963).

Another facet has gained attention in respect to the compensatory fluid mechanism. This is the significant amount of protein which apparently returns quite rapidly from extra-cellular spaces via the lymphatics in hemorrhagic and endotoxin shock (Alican & Hardy, 1961; Cope & Litwin, 1962; Kutner, Schwartz & Adams, 1967). The return of protein to the intravascular space was strongly suspected by Elman, Lischer & Davey (1944) in their experiments in which they repeatedly bled conscious dogs. Cope & Litwin (1962) felt so strongly about the importance of this mechanism that they regard the Starling phenomenon as having only a restricted role.

Autonomic Nervous System

The autonomic nervous system plays an important role in the control of the tone of the vascular system. The book by Heymans & Neil (1958) on 'Reflexogenic Areas of the Cardiovascular System' gives a comprehensive review of many aspects of this system and it is worthwhile at this point to recapitulate the important discoveries which have led to an understanding of the functional control of the nervous system over the vascular system.

From this point of view appreciation of the functional aspects of the autonomic nervous system evolved over approximately 15 to 20 years, commencing respectively in 1851, 1852 and 1853 with the experiments of Claude Bernard, Brown-Séquard and Waller, all of whom focussed attention on the vasodilator and vasoconstrictor properties of the cervical sympathetic trunk. The climax of these investigations came with the discovery by Cyon & Ludwig of the depressor nerve in the rabbit in 1866. They observed for the first time the phenomenon of reflexogenic activity - stimulation of the central end of the nerve caused bradycardia and hypotension. Dittmar (1870) localized the vasomotor center and in 1873 observed a rise in systemic pressure by stimulating the central end of the sciatic nerve. He concluded, after ablation of the grey matter and posterior columns of the spinal cord, that the vasomotor center discharged over nerve pathways

which coursed in the antero-lateral columns of the spinal cord.

The next major discovery was made by Hering in 1923 when he showed that the 'Sinusnerv' - named by Knoll (1885) - caused bradycardia and hypotension after stimulation of its central end. The carotid sinus (Hering, 1923) and the cardio-aortic area (Heymans & Ladon, 1924, 1925) are the loci for the receptors of what have become known as the 'buffer nerves' (so-named by Samson Wright, 1932). Koch (1929, 1931) worked out the thresholds for the sinus reflexes in the dog, cat, rabbit and monkey. In dogs, the maximal sensitivity of the reflex is in the region of 120 mmHg. Below 55 to 50 mmHg and above 210 mmHg there is no response to a fall or rise of pressure, respectively. These findings were confirmed by Langren (1952) in an extensive report on the excitation mechanism of the carotid baroreceptor fibers. Thus, in a dog with an arterial pressure below 50 mmHg there can be expected to be no inhibitory influence exerted upon the vasomotor center. This can therefore be one mechanism in hypotensive states of stimulation from the brain stem of the visceral efferent neurons located in the lateral grey columns, which in turn will lead to an increase in sympathetic impulses in the postganglionic fibers. The baroreceptors, particularly in the carotid sinus, have been shown to respond to pulsatile variations in the blood pressure (Bronk & Stella, 1932).

J. F. & C. Heymans (1927) discovered the first of the peripheral chemoreceptors. These receptors are believed to be stimulated during hemorrhage, and Mayer waves, common in hemorrhage, are probably chemoreceptor in origin (Andersson, Kenney & Neil, 1950). The mechanism of stimulation is thought to be glomeric ischemia caused by reduction in carotid body flow resulting from the hypotension.

Accordingly, the net effect of the carotid-aortic baroreceptor and carotid chemoreceptor mechanisms in hypotensive states is an increase in the sympathetic outflow activity.

However, there appears to be surprisingly few studies that show how long sympathetic impulses continue in the presence of protracted hemorrhage or hypotension. Such information would be of great value. Beck & Dontas (1955) report briefly on such a study in dogs bled to an arterial pressure level of 45 mmHg. Recordings from the preganglionic efferents of the splanchnic sympathetic system showed marked increase in activity during the initial bleed. There was also an increase in activity as secondary bleeding took place which decreased during automatic re-infusion and declined further when the blood was returned to the animal. As the blood pressure underwent a secondary decline there was a marked reduction in splanchnic activity.

Rothe, Schwendenmann & Selkurt (1963) have also studied neurogenic control in hemorrhagic shock in dogs. The gracilis muscle, isolated except for its nerve, was perfused at a constant pressure of 160 mmHg from a donor dog, while the recipient dog with the isolated gracilis muscle was bled to hypotensive levels utilizing Wiggers' method (1950). Vasoconstriction was evidenced by the reduction in flow monitored by a bubble flow meter incorporated in the venous outflow circuit of the gracilis muscle; the degree of vasoconstriction was also tested by comparing the blood flow when the nerve was cold blocked and when the nerve was re-warmed. The method of perfusion eliminated the chemical influences from the hypotensive dog. In spite of the high perfusion pressure, the degree of reduction in blood flow through the gracilis muscle was severe and the flow amounted to only 0.6 ml/min/100 g of tissue during the 30 mmHg interval. During the hypotensive period, the severe vasoconstriction persisted, indicating no failure of the sympathetic nervous system in the recipient dog. During nerve block, blood flow in the muscle returned only to disappear again when the conduction in the nerve returned upon re-warming. However, in some dogs, the vasoconstriction decreased suggesting partial failure of the vasoconstrictor centers in the central nervous system; but, the authors do not discount the possible influence of surgical trauma or damage to the nerve from the cold block procedure; in one of these experiments, the authors felt that they had unmistakable evidence of central failure which was relieved by transfusion, the mechanism of action being

presumably the increased cerebral blood flow in the recipient dog. It is interesting that during transfusion of as little blood as 5 ml/kg, the arterial pressure of the hypotensive recipient dog was raised by as much as 20 to 30 mmHg.

Lundgren, Lundwall & Mellander (1964) confirmed the above findings in cats. An isolated calf muscle preparation was created in each hind limb in the recipient cat leaving the innervation intact. One limb was then cross-transfused at normal pressures from a donor cat, while the other limb was auto-perfused from the recipient cat, which was made hypotensive by bleeding. They showed that the increase in the sympathetic vasoconstrictor fiber discharge to the skeletal muscle varied with the extent of the bleed and ranged from 1 impulse/sec up to 7 impulses/sec; the control sympathetic discharge rate before bleeding was 0.5 impulses/sec. They showed in the limb maintained by cross circulation that reflex increase in sympathetic activity was as a rule fairly well maintained during prolonged hemorrhage. They did, however, remark that at times when large amounts of blood were withdrawn and the arterial pressure in the recipient cat fell to levels below levels of 30 to 40 mmHg, that a pronounced fall in the resistance response of the cross-circulated limb was sometimes observed. They, too, like Rothe, Schwendenmann & Selkurt (1963), could reverse this drop in resistance by administering small transfusions to the recipient cat. They interpreted this as being suggestive that temporary insufficiency of the central sympathetic structures had occurred.

Peterson & Haugen (1963, 1965) have presented some of their preliminary findings on the effect of hemorrhage on the central nervous system response. They point out that the nervous system has been neglected in the analysis of homeostatic disintegration resulting from blood loss and sustained hypotension and claim that "a direct evaluation of central nervous system activity in response to hemorrhage has not been done". In regard to the carotid sinus mechanism they state only in their 1963 article that "it is a shock resistant, high-gain servo-mechanism, an important compensatory system sustaining the circulation. As a matter of fact, we could not demonstrate abrogation of this negative control system at mean arterial pressures of well below 50 mmHg". They used the Western Reserve shock

model of Wiggers (1950) - the mean arterial pressure is reduced to 50 mmHg for 90 minutes then at 30 mmHg for an additional 45 minutes after which the bleed volume is re-infused. Spinal cord and brain stem reticular reflexes were investigated in cats and dogs in 150 experiments. In brief, they found that, "A transient state of hyper-excitability reflects an active alerting-type response to the early challenge of blood loss before there is a critical reduction in blood flow. It is during these early phases of blood loss that adaptive compensatory mechanisms of the organism are maximally engaged. If the reduction in blood flow is sustained, a progressive and inexorable deterioration in all parameters of nervous function ensues." Evidence was presented to show that the polysynaptic elements of the ventral root response to dorsal root stimulation were more susceptible to blood loss than the monosynaptic elements. Both these reflexes disappeared at mean arterial pressures of 30 mmHg. In general, there was approximately a linear relationship between the change in amplitude of reflex responses and the extent of reduction in circulating blood volume. Electrodes were stereotaxically placed in the brain stem and the effects were observed of facilitatory and inhibitory responses on motorneurone changes at the spinal cord level, which were simultaneously activated by orthodromic dorsal root stimulation. The brain stem reticular inhibitory system was determined to be powerful and to be more resistant to the effects of hemorrhage, compared with the brain stem reticular facilitatory system which was depressed early and profoundly during the hemorrhagic hypotension. Extensive surgery must have been required in this type of preparation, and it is difficult to assess the degree of influence this might have had on the responses; nevertheless, these investigations give some insight into the central nervous system aspect of protracted hypotension. The authors feel that the progressive decrements in neural function must be related to the increasing oxygen debt which they assume occurs in the central nervous system (authors cite Guyton & Crowell, 1961).

In summary, it would seem that evidence is scarce to illustrate the degree of persistence of compensatory neural activity during severe hypotension,

nevertheless, there are a few reports which suggest that sympathetic activity can persist throughout an interval of severe hypotension. However, there is also some evidence to show that in some instances following severe hypotension (30 to 40 mmHg) failure of the central nervous system may occur.

Resistance and Capacitance Vessels

The terms resistance and capacitance vessels are used in the sense that the Scandinavian group of physiologists give to these terms (Folkow & Mellander, 1964). To quote these authors: "The resistance vessels comprise a major precapillary section (small arteries, arterioles, etc.) and a minor postcapillary section (venules and small veins). The capacitance vessels do largely correspond to the venous sections of the systemic and pulmonary circuits, but not entirely, because the heart itself and also the other vascular sections subserve a capacitance function to some extent."

Before examining the influence of extraneous factors upon the resistance and capacitance vessels, it is prerequisite to ask the question, what residual reactivity of these vessels remains when extrinsic influences are removed, and, if basal vascular tone is present, under these circumstances, what is the mechanism? Bayliss (1902) proposed that a simple distension by the pressure in the vessels could evoke contraction of the vascular smooth muscle. Folkow (1962) presented supportive evidence for this hypothesis and has elaborated the following view: Basal vascular tone varies from one vascular unit to another and appears to be a consequence of truly myogenic activity confined mainly to the precapillary vessels; smooth muscle cells can therefore be likened to the 'visceral' type of muscle. Such a mechanism of vascular tone would be well adapted for blood vessel control in metabolically active tissues (e.g., myocardium and skeletal muscle) or high flow tissues (e.g., myocardium and brain), in which a reserve of blood can be mobilized by the inhibitory action of locally accumulated metabolites on vascular tone. Vascular structures, however, which subserve

the organism as a whole as opposed to locally, as for example, A-V cutaneous shunts and the venous capacitance vessels, appear to be dominated by 'multi-unit' type of smooth muscle, and are accordingly much more under neural vaso-constrictor control. In general, a roughly inverse relationship exists between the extent of basal tone and the superimposed constrictor fiber control. Since tone appears to be a feature of precapillary resistance vessels the Bayliss mechanism if operative could be an important modulator of vascular tone. Folkow reviews experimental evidence to show that this mechanism does in fact exist.

Folkow compares vascular tone to the situation existing in the myogenically active ureter (Bozler, 1948), in which a continuous distension was found to cause a lasting increase in the 'spontaneous' discharge of smooth muscle elements. He views the myogenically active vascular smooth muscle of the precapillary vessel "as a sort of spontaneously active mechano-receptor unit ....". Although, increased wall tension secondary to increased transmural pressure is a positive feed-back mechanism, it can be expected to be self-limiting, because when summation of contractions occurs the distension stimulus will automatically eliminate itself. Finally, Folkow points out that this "locally controlled, primitive mechanism" can be easily overshadowed by neurogenically mediated reflexes if the necessity to do so arises.

Folkow (1964) in a later communication on the same subject remained just as enthusiastic in the support of the Bayliss concept, for it seems by this date, there was further evidence that the precapillary resistance vessel is myogenic in nature. Folkow refers the reader to the findings of Funaki (1961) of intracellular recordings from these muscle cells, which establish that their electrophysiological properties do in fact exhibit the unstable membrane potential characteristics of visceral smooth muscle.

Extrinsic effects on resistance and capacitance vessels, as mentioned, have been studied by perfused limb and organ preparations; either the perfusion

pressure or the blood flow during an experiment is held constant, thus providing a means to evaluate the resistance changes. By techniques worked out by Mellander (1960) and later applied by Mellander & Lewis (1963) to the cat hind limb preparation, the effects of protracted hemorrhagic hypotension at a constant level of between 40 and 50 mmHg were observed. Blood flow was monitored on the venous side of the isolated limb. It is important to realize that in their preparation the innervation to the limb was sectioned and therefore the vascular tonus mechanism was in competition with the accumulated products of metabolism. Periodically throughout the period of hypotension the peripheral ends of the lumbar sympathetic nerves were stimulated supramaximally. Simultaneous measurements of limb volume were taken to indicate the changes in vascular capacitance.

The interesting feature of their experiments during the periodic sympathetic stimulations was the demonstration of a progressive and greater loss in reactivity of the precapillary resistance vessels as compared with the postcapillary resistance vessels. Abolition of reactivity evidently occurred in both areas when the hypotension was continued long enough. The authors suggest that these changes could be caused by the accumulation of metabolic products.

Haddy, Scott & Molnar (1965) studied the effect of hemorrhage during constant rates of perfusion of the innervated forelimb of dogs; the inflow rate was adjusted so that the arterial pressure within the limb was in the same range as the aortic pressure; the inflow rate was then held constant at this value. In this way, it is likely that the metabolites did not build up because the level of hypotension created by the bleed out (approximately 20%) was not severe enough nor the period of hypotension prolonged enough (20 minutes). Abrupt bleed out was accompanied by a drop in aortic pressure from the 130 mmHg control range to approximately 100 mmHg. The brachial artery pressure rose from the 110 mmHg to over 160 mmHg and gradually fell by 20 mmHg during the next 15 minutes. Small artery pressure was also measured; there was a greater rise in it just after

bleed out than in the brachial artery, but only during the first minute, indicating that the small arteries respond first. The pressure gradient from small vein to cephalic vein did not change significantly at any time, which the authors feel implies an absence of a change in resistance to flow through the large veins.

Thulesius & Johnsan (1966) utilized the zero flow-isogravimetric technique in a similar way to Pappenheimer & Soto-Rivera (1948) on the hind limb in 25 dog experiments. In their preparation the hind limb was skinned to avoid the possible dilatory masking effects of cutaneous vessels. The arterial inflow pressure to the hind limb was lowered from 110 mmHg to 20 mmHg in steps and the arterial and venous resistance calculated. In 75% of the dogs there was a progressive fall in arterial resistance with lowering of the arterial pressure, but, in 25% of the dogs, there was a progressive rise in arterial resistance over the whole range of pressure reduction. The interesting finding in their experiments was a progressive increase (as much as 360% at 30 mmHg) in venous resistance in all experiments as the arterial pressure was reduced. This increase in venous resistance could not be eliminated by denervation or by adrenergic blockade with phenoxybenzamine. However, repetitive muscular contractions by electrical stimulation of the muscle branches of the sciatic nerve did abolish the venous resistance response.

This phase of the review has been focussed on the responses of the precapillary and postcapillary resistance vessels to severe hypotension. In summary, it would seem that there is some evidence to show that the precapillary vessels are more susceptible to loss of their reactivity than the postcapillary vessels. The reactivity of the postcapillary vessels seems to be quite resistance to the effects of hypotension.

Of interest in regard to the capacitance vessels - which are considered to be chiefly the venous system beyond the postcapillary resistance vessels, as

opposed to the smaller component of the capacitance system, which is in the arterial tree - are the papers by Alexander (1955) and Bartelstone (1960).

Alexander studied venomotor tone in hemorrhagic shock by using an injection technique to measure the distensibility in intestinal loops of anesthetized dogs, and thereby obtained an index of venomotor tone during hemorrhagic hypotension. In his experiments he claimed to have shown the development of a serious deficiency in venomotor tone, which could possibly account for pooling of blood in the venous system. The problem of 'pooling', of course, has gained greatest prominence in extracorporeal circulation experiments (Najafi, Battung, Sarfatis, Hirose & DeWall, 1966).

Bartelstone cites Franklin (1937) as introducing what might be termed the capacity concept of venous function: "In the body, the musculature of the veins controls the volume of a large part of the venous system . . . and hence it influences the venous return and heart minute volume." Bartelstone (1960) used a technique of simultaneously clamping the inferior vena cava (close to the atrium) and the descending aorta; in this way the head circulation was preserved. Then, by means of studying the arterial and venous (mainly) run-off pressures he considered that he was able to show that the 'central venous conduit' (inferior vena cava and contiguous veins) was mainly a passive reservoir, whereas, the remainder of the bed back to the capillaries was the 'reactive venous reservoir', responsible largely for the movement of blood from the venous system under sympathetic stimulation. He viewed the former bed as passive, and containing 18 % of the blood volume, and the latter reactive, and containing 45 % of the total blood volume, citing Milnor & Bertrand (1958) to substantiate the blood volume partitioning. It is difficult to conceive that the large veins can be completely passive, but the evidence is convincing that there was a movement of blood from the smaller veins to the larger during carotid occlusion.

As noted above, in the broadest sense the term 'capacitance vessels' also refers to the arterial side of the circulation, but since the volume of blood contributed by the arterial side of the tree during vascular adjustments is probably small the term is usually associated with only the venous side of the circulation. One difficulty, however, is that, although it may be reasonable to assume that arterial adjustments are small, there is actually no way to evaluate them. It is usually implicitly understood that any large alterations will be accounted for by the venous circulation. Yet, it is now recognized that precise filling of the arterial tree may be critical in reduced circulatory states (Simeone, 1963), and, it is ironical that no one has yet been able to make so vital a measurement.

Vascular Responses to Various Vasoactive Factors

Vascular responses to alterations in pH, O_2, CO_2, metabolites, ionic substances, catecholamines and vasoactive peptides form a broad and complex subject and only the salient features can be reviewed here.

Perfusion of muscle with oxygen deficient blood causes vascular dilatation, and Carrier, Walker & Guyton (1964) in the case of isolated vessels believe this is due to oxygen deficiency per se. It is difficult to establish this point and Olsson (1964) contends for instance, in coronary reactive hyperemia which is preceded by an interval of anoxia, that the hypothetical dilator responsible for the reactive hyperemia is a metabolite. Skinner & Powell (1967) have shown, during constant perfusion in a dog gracilis muscle preparation with desaturated blood, that increasing the K^+ concentration from 1.95 to 6.15 mEq /liter causes a steady fall in vascular resistance, thus indicating an interrelationship between the vasodilator effects of O_2 and K^+. Even at normal blood O_2 tensions an increase in the K^+ can cause a reduction in vascular resistance. So, as the above authors point out, if the interstitial K^+ increased in reduced circulatory states, where there is already reduced blood flow and O_2 tension, this could act to decrease the precapillary resistance.

The peripheral vascular effects of CO_2 are usually described as vasodilator, although in perfusion fluids saturated with CO_2 the vasodilator properties are most often attributed to the changes in pH (Rushmer, 1965). In man, hyperventilation has been reported to cause constriction of the hand vessels (Stewart, 1911) and contraction of the large arteries (Christensen, 1945).

Changes in pH above or below 7.4 produce vasodilation in hind limb preparations (Kester, Richardson & Green, 1952). But to produce substantial increments in blood flow required rather extreme changes in pH beyond the physiological range. Carrier, Cowsert, Hancock & Guyton (1964) utilizing isolated artery segments confirmed qualitatively these findings.

Metabolic acidosis is accompanied by the accumulation of acid metabolites. Fleisch & Sibul (1933) investigated the vasoactive properties of a number of organic acids, such as lactic and acetic acid and found that the free acids produce some vasodilatation, whereas the sodium salts had little effect on hind limb blood flow. The changes were therefore considered to be due to the change in pH rather than to the specific anion.

Of the several naturally occurring vasoactive substances, namely, angiotensin, bradykinin, histamine, noradrenaline, adrenaline, serotonin and vasopressin, the two catecholamines have received by far the widest attention.

Noradrenaline is the neuro-humoral transmitter at the sympathetic nerve endings (Euler, 1956). Arteriolar constriction resulting from sympathetic activity was suspected of causing deleterious effects (Freeman, 1933), and an entire new concept based on blocking its effects has arisen (Nickerson, 1962). Celander (1954) showed conclusively that the constriction resulting from release of noradrenaline by stimulation of the sympathetic nerves to organs was far in excess of that caused by catecholamines secreted from the adrenals. Celander therefore looked upon the medullary secretion as subserving metabolic needs and subordinate to the sympathetic innervation as far as constrictor needs were concerned.

The possible role of the adrenals in shock received attention quite some time ago. Bedford, employing a biological assay technique, gave the following conclusions in the American Journal of Physiology in 1917, quote:

> "1. That increased quantities of epinephrin are thrown into the blood during conditions of low blood pressure and shock.
>
> 2. That this increased amount of epinephrin found in the blood is accompanied by a hyper-activity of the adrenal gland and is not simply the result of the release of epinephric material stored in the gland.
>
> 3. That the epinephric content of the blood increases only after a somewhat prolonged continuation of the conditions leading to shock.
>
> 4. That the quantity of epinephric material in the blood increases with the prolongation of the period of low blood pressure and shock.
>
> 5. That this increased output of epinephrin into the blood may be a last effort on the part of the organism to resist the forces that are tending toward a fatal degree of low blood pressure."

G. N. Stewart had apparently been invited to become a member of the Sub-Committee on Shock (Medical Division of the National Research Council) in World War 1 and had been assigned the task of investigating the output of epinephrine in this condition. Stewart & Rogoff (1919) summarized their report to the Committee by a paper in the American Journal of Physiology, as follows:

> "The results of this investigation may be summed up in a sentence. In none of our experiments has evidence been obtained that any sensible change occurs in the rate of output of epinephrin from the adrenals in conditions of continued low blood pressure."

What authority was ascribed to this statement is difficult to evaluate. In any event, the problem has now been more thoroughly investigated, predominantly,

by the chemical assay technique utilizing differential fluorometric analysis. Lund (1951), using his fluorometric technique, showed in dogs that both noradrenaline and adrenaline were elevated in the suprarenal venous blood following hemorrhage, and that the noradrenaline levels were constantly about 50% of the adrenaline levels. Watts (1956) using a bioassay method demonstrated a 22-fold increase in arterial plasma adrenaline after hemorrhage. Others, using the chemical fluorometric method confirmed the observations of higher levels of adrenaline than noradrenaline during severe hypotension (Manger, Bollman, Maher & Berkson, 1957; Millar & Benfey, 1958; Walker, Zileli, Reutter, Shoemaker, Friend & Moore, 1959). However in these experiments, before the severe levels of hypotension are reached which seem to be necessary before the catecholamines rise (especially noradrenaline), reflex sympathetic responses will have undoubtedly been invoked; yet, at this stage, the noradrenaline blood levels are not detectably altered. It would seem that H^3-noradrenaline studies might give more meaningful results at the intermediary stages of hypotension (Rosell, Kopin & Axelrod, 1963).

Angiotensin is the most potent pressor agent yet discovered (Page, 1961). Renin output (Skinner, McCubbin & Page, 1964) and the concentration of angiotensin in the blood (Regoli & Vane, 1966) are increased when renal arterial pressure is decreased. Regoli & Vane showed that following hemorrhage the rate of production of angiotensin was 0.5 to 1 ug/min, when assayed by the rat colon (Vane, 1966). Hodge, Lowe & Vane (1966) claim, however, that blood volume changes are more important in the generation of angiotensin than changes in arterial pressure; there appeared to be an inverse relationship between central venous pressure and angiotensin blood concentration but not with systemic arterial pressure; the efferent limb of the reflex appeared to be associated with the renal nerves; the afferent limb remained unidentified.

The roles that the three vasoactive substances - histamine (Barger & Dale, 1910; Riley & West, 1953), bradykinin and kinins (Rocha e Silva, Beraldo & Rosenfeld, 1949; Schachter & Thain, 1954; Schachter, 1968) and serotonin (Rapport, Green & Page, 1948) - have in the various kinds of shock are not clear, except perhaps in the case of histamine, which is known to be one of the main toxic agents in allergic shock (Halpern, 1962). In endotoxin shock, it could not be established that bradykinin was a significant contributing factor (Erdös & Miwa, 1968). In dogs, however, Corrado, Reis, Carvalho & Diniz (1966) concluded that the release of peptides of the bradykinin type was an important factor in the hypotension produced by proteolytic enzymes. Emerson (1967), utilizing a 'venous return preparation' of the type described by Weil, MacLean, Visscher & Spink (1956) observed after bradykinin infusion dilation of resistance vessels and an increase in the reservoir blood volume. The latter change was interpreted as evidence of a translocation of blood from arteries to veins. One cannot discount the possible importance of these substances. For example, in hemorrhagic shock in dogs, metabolic deterioration in the mucosa apparently occurs, rendering the mucosal cells permeable to proteolytic enzymes such as trypsin (Bounous, Hampson & Gurd, 1964). The intestinal hemorrhagic necrosis commonly observed in this condition has been attributed to this mechanism. The proof that this probably is so was presented by Bounous, Brown, Mulder, Hampson & Gurd (1965) who showed that in dogs with ligated pancreatic ducts the necrosis did not occur.

Interrelationships of Endocrine Control in Hypotensive States

Catecholamines (as noted above) and 17 hydroxycorticosteroids became elevated following hemorrhage in dogs (Hume, 1961). Aldosterone is also elevated after hemorrhage, even in the absence of the pituitary (Ganong, 1967). The evidence is that aldosterone appears to be linked to the renin-angiotensin system, because in nephrectomized, hypophysectomized dogs, administration of angiotensin II increases aldosterone output (Ganong & Mulrow, 1962; Mulrow

& Ganong, 1962). The importance of the adrenalcortical hormones, with respect to the vascular system, lies in the fact that adrenalectomized animals withstand trauma and hemorrhage poorly; it is probable that the vascular collapse is due to the poorly maintained vascular tone in the absence of cortical hormones (Ganong, 1967). Halpern (1962) refers to their earlier work on mice (Halpern, Benacerraf & Briot, 1952) in which they describe that cortisone and hydrocortisone potentiate the effect of adrenaline on peripheral vascular tone. This would possibly be an important mechanism in hypotension for increasing vascular tone. Vasopressin (antidiuretic hormone) and aldosterone are capable of influencing blood volume by means of their effect on the tubular reabsorption of the kidney (Davson, 1964; Ganong, 1967).

CHAPTER III

Experimental Methods, Techniques and Materials

The experiments were performed on a total of 61 mongrel dogs. The average weight for the entire group was 12.24 kg (S.D. = 0.65 kg; - Table I, Appendix). The dogs were selected without regard to age or sex and retained in isolation for approximately two weeks. During this interval they were dewormed and fed a nutritious diet.

Procedure Followed in Experiments.

The following procedure was used in each experiment: The day before an experiment the dog was allowed to eat and was given water ad libitum the remainder of the day and evening. The morning of the experiment the dog's lower bowel was cleansed by means of an enema. The gross body weight was determined to the closest 10 g. A small catheter was introduced into a foreleg vein and the dog anesthetized via this route with sodium pentobarbital (30 mg/kg) and heparinized (2 to 3 mg/kg). The dog's hair was removed by a clipper and the hair collected by means of a vacuum cleaner hose attached to the clipper. The average weight of the hair for the 61 dogs was 221 g (S.D. = 83 g). The weight of hair was subtracted from the gross body weight and the resultant net weight was the value used for the weight of the dogs in the results of all the experiments. The dog was transferred to an operating room table and secured in the dorsal position with the right chest slightly uppermost. A cuffed endotracheal tube was introduced and taped securely.

Figure III - 1 illustrates schematically the venous return preparation used in these experiments. The surgical and implantation procedures were as follows: The right chest was opened through the fourth interspace. An adequate exposure

was achieved without cutting across the latissimus dorsi muscle and the deep pectoral muscle. This helped to reduce blood loss, which was further minimized by using the electro-cautery on the intercostal muscles and at the angles of the incision. All major bleeding points were clamped and ligated. The internal mammary artery was left intact. The azygos vein was ligated and heavy black silk ligatures placed about the venae cavae. The pericardial sac was left intact. Small incisions were made in the neck and right groin for the catheter implantations; these were performed after the chest was opened as the absence of negative intrapleural pressure minimized the chances of an air embolus. The tubing connecting the reservoir bottle to the latex rubber pump tubing and the inflow tubing into the right atrium were primed with 75 to 100 ml of normal saline (in four experiments Dextran was used and in the same quantity). On the other hand, the caval drainage tubes were filled with blood from the dog at the time of the catheter implantations and clamped. The dogs were ventilated with oxygen at the rate of 10 to 12 respirations per minute from the time the chest cavity was opened until the end of the experiment. Oxygen was admitted during inspiration under positive pressure so that there was satisfactory inflation of the lungs within the chest cavity. During expiration, the artificial means of oxygenation was such that the lungs were allowed to deflate on their own. Sodium pentobarbital was intravenously administered in approximately 30 mg doses as necessary as judged by the movements of the dog and its light reflex response.

Sterile instruments, techniques and procedures were not used in these experiments. At the end of the procedure the tubings were immediately flushed out by repeated washings with cold water. No detergent was used. New tubings and catheters were not used for each experiment but were replaced as necessary.

Calibration of Sigmamotor Pump

The Sigmamotor pump was calibrated with normal saline early in the morning prior to the experiment. The degree of occlusion by the fingers of the

pump was checked in the following way: The fingers of the pump head were set to compress the latex tubing against the back-plate just to the extent that the level of a column of fluid in the cardiac inflow tube (Fig. III - 1) would not change when the tube was held above the pump head 30 cm. A further degree of occlusion was not necessary as the pump was operating only against a pressure of 30 cm of water. The pump was set at a pre-determined rate based on the weight of the dog and the approximate range of constant venous return desired for that particular experiment. It was calibrated over one minute intervals until the required rate was obtained. After each experiment, the pump was immediately recalibrated, utilizing the blood in the reservoir bottle. The duration of the calibration interval was one minute. This calibrated value of pump output was used for the value of constant venous return for that particular experiment.

Procedure of Starting Constant Venous Return Period

The period of constant venous return was commenced by releasing the clamps on the caval drainage tubes. After a 10 to 15 sec delay, the Sigmamotor pump was turned on. The reservoir, which had previously been empty, now filled during this interval with 100 to 200 ml of blood from the dog, the volume varying somewhat with the pump rate setting. The Sigmamotor pump was intermittently flicked off and on until the normal saline had been pumped out of the tubes connecting the pump and reservoir to the dog. After this, it was left on at the preset rate for the duration of the two-hour constant venous return period. As soon as the reservoir had been primed with blood and the saline ejection maneuver completed, the ligatures around the venae cavae were tightened and tied. In the intervals, before the pump was turned on and during the constant venous return period, the temperature of the normal saline and blood in the respective tubes was maintained by the heat from an infra red lamp (Fig. III - 1). A second infra red lamp was used to maintain the temperature of the dog (not shown in Fig. III - 1).

Blood Volume Determinations

In seven experiments the plasma blood volumes were estimated by the T - 1824 dye technique (Dawson, Evans & Whipple, 1920; Gregersen & Rawson, 1959). The determinations were made before, and 45 minutes after, the start of the constant venous return period. Hemodilution was also assessed by determining the hematocrit values during the period of constant venous return in three dogs that were splenectomized 6, 7 and 12 days prior to the experiments; the plasma blood volumes were determined before the period of constant venous return with T - 1824, but the 45 minute values were obtained by substituting the hematocrit values in a formula, assuming that the red cell volume remained essentially constant (Table XXV, Appendix).

A 5 % stock solution of T - 1824 dye was used for all determinations. For the values determined before the onset of the constant venous return period, exactly one ml of the stock dye solution was measured out in a micrometer syringe, injected into a jugular catheter and flushed into the dog with normal saline. A sample of blood for the plasma blank was taken just before the dye injection. Three to four samples were taken at 15 minute intervals and the optical densities of the plasma determined, using a Beckman Model - B spectrophotometer. These densities were plotted on graph paper and extrapolated back to determine the optical density at time zero. This value was then used to calculate the plasma blood volume from the standard curve (Fig. III - 2).

In the case of the plasma blood volumes determined 45 minutes after the start of the constant venous return period (i.e., in the non-splenectomized dogs) the following procedure was used: The optical density of the plasma sample from the femoral vein catheter obtained 45 minutes after the start of the pump was employed as the blank. Immediately after obtaining this sample exactly one ml of the T - 1824 stock dye solution was injected into the jugular caval drainage catheter. Two samples were taken from the femoral caval drainage catheter 15 and 25

minutes after the dye solution was injected. The value of the optical density at the 15 minute mark on this decay curve was plotted back to the 45 minute mark, using the decay rate from the curve determined on the samples taken before the peried of constant venous return; this value of optical density was then used to calculate the plasma blood volume from the standard curve of Figure III - 2. An example of this procedure is noted in Figure III - 3. Hematocrit values were obtained on the majority of blood samples taken from the plasma volume determinations.

Recording Equipment

The output from the Statham pressure transducer was amplified and recorded by means of a Gilson Polyviso pen-writer recorder. In the majority of dogs the systemic arterial pressure was obtained from the abdominal aorta via a femoral artery catheter; however, in a few dogs the pressure was obtained from a catheter in one of the common carotid arteries. The mean arterial pressure was obtained by the electronic integrator circuit of the recorder and continuously recorded throughout the period of constant venous return; at frequent intervals the stopcock on the Statham transducer was opened to the atmospheric pressure of the room and the zero pressure obtained. The transducer was calibrated against a known pressure of mercury. The gain of the Gilson recorder was not changed throughout the experiment.

Arterial and venous blood samples for the measurement of pH and partial pressure of CO_2 and O_2 were obtained from the pressure tube in the femoral artery and the femoral drainage caval catheter. The pH was measured by a Beckman Micro Blood pH Assembly No. 46850, using a Glass Electrode No. 39070. The Beckman Thermomatic constant temperature block was used. The partial pressure of CO_2 was measured by the Severinghaus electrode; the electrode was calibrated against known concentrations of carbon dioxide. The partial pressure of O_2 was measured by the Beckman Oxygen Micro-Electrode No. 161-950.

Method of Determining Average and Interpolated Values of Mean Arterial Pressure and Reservoir Blood Volume.

The data for the values of arterial pressure and reservoir blood volume were recorded and arranged in the following manner: Measurements of mean arterial pressure and reservoir blood volume were made at approximately 5 minute times during the first 30 minutes of the constant venous return period and at 10 minute times during the last 90 minutes of the two-hour period. The values of the reservoir blood volume measurements were converted to ml/kg/min, utilizing the value for the dog's net body weight. The curves for these two variables were then plotted on a 120 minute time scale. It will be realized that these points did not necessarily fall at the 5 or 10 minute times. However, interpolated values at these points were obtained from these two curves. As a result, in every experiment there was derived a value for mean arterial pressure and reservoir blood volume for each 5 minute time in the (0 to 30) minute period and for each 10 minute time in the (30 to 120) minute period. The curve in the case of the mean arterial pressure was commenced at zero time, using the control value of arterial pressure obtained just prior to starting the pump. The curve for the reservoir blood volume was also started at zero time, but at zero volume, because just before the pump was turned on there was no blood in the reservoir bottle. The average values for the above two variables during the (0 to 30) minute period were determined from the areas under the respective curves; the average values for the two variables for the (30 to 120) minute period were determined by averaging the 10 minute interpolated values.

The heart rate was determined from the pulsatile blood pressure trace taken approximately as noted above at the 5 or 10 minute times throughout the (0 to 120) minute interval. The control heart rate was determined just before the onset of the venous return period.

Lean Body Mass and Surface Area

The lean body mass was determined from the specific gravity of the body (Behnke, Feen & Welham, 1942; Bard, 1961). The specific gravity was measured after the experiment by weighing the dog first in air, then in water. After obtaining the value for the specific gravity, the percent of body fat was obtained, using the formula derived by Rathbun & Pace (1945). The measurements and calculations involved in this procedure are given for one of the experiments in Table VIA (Appendix). The specific gravity of the reservoir blood was determined by the copper sulfate method (Hawk, Oser & Summerson, 1951).

The Meeh-Rubner formula (cited by Cowgill & Drabkin, 1927) was used for estimating the surface area of the dogs, e.g., $S_{sq\ cm} = 11.2 \times Weight_g^{2/3}$. Body weight of the dogs was also expressed in several of the correlations as a power function (Kleiber, 1961).

Catecholamine Determinations

Adrenaline and noradrenaline blood plasma concentrations were determined by the spectrophotofluorometric assay technique, the details of which are presented in the Appendix. The 20 ml samples of whole blood were collected from the femoral venous catheter before the start of the constant venous return period and at the one- and two-hour times during the period. The catecholamines were absorbed onto alumina (Aronow & Howard, 1955; Cohen & Goldenberg, 1957b). Fluorescence was developed by the iodine oxidation method (Euler & Hamberg, 1949; Shore & Olin, 1958; and, essentially as described by Chang, 1964). The concentrations of the adrenaline and noradrenaline were estimated by substituting the galvanometric readings of fluorescence in simultaneous equations and solving as shown by Cohen & Goldenberg (1957a).

Phenoxybenzamine (Dibenzyline)

Phenoxybenzamine powder was dissolved in alcohol (100 mg/ml) and diluted up to 10 ml normal saline. It was given intravenously over a 10 to 12 minute

interval in 5 mg/kg and 1 mg/kg doses, respectively, in Groups VI and VII experiments. It was given approximately one hour prior to the start of the constant venous return period.

Statistical Methods

Standard statistical procedures were used in the calculations of S.D. regression equations, coefficients of correlation, and testing of significant differences between means (Kenney & Keeping, 1954; Bailey, 1959). The significance of any observed correlation coefficient was tested by Table X in Quenouille (1952). The 'z' transformation test was used to test differences between coefficients of correlation (Quenouille, 1952). The P values corresponding to the calculated 't' values were determined from Table II (Kenney & Keeping, 1954), using a one-tailed test.

Figure III - 1. Diagram of the 'venous return preparation'. The venous blood was prevented from returning to the heart by the circumferential sutures about the cavae at (1) and (2). The azygos vein (3) was ligated. The blood from the superior vena cava was collected via a catheter (18 or 20 F) in the right jugular vein (4) and drained by tube (5) into the one liter reservoir bottle (6). The blood from the inferior vena cava was collected via catheter (7) and tube (8) also into reservoir (6). Catheter (7) was introduced through the right femoral vein. A Model T-MI Sigmamotor pump (9) was used to return the blood into the right atrium; the pump head had 12 fingers and was approximately 7 1/2 inches in length. The latex rubber pump tubing (10) was approximately 12 inches long (I.D. 5/8 inch). The blood from the reservoir was returned via tube (11) and catheter (17) into the right atrium. Catheter (12) was introduced via the left jugular vein beyond the circumferential suture (1); it was 16 to 20 F. Conduits (5) (8) and (11) were plastic vinyl tubings (I.D. 1/4 inch). A PE - 240 polyethylene tube (13) was introduced into the right femoral artery and into the abdominal aorta; it was connected to a Statham transducer (14). An infra red lamp (15) was used to maintain the temperature of the reservoir blood and another (not shown) was directed on the dog at an appropriate distance. Reservoir bottle (6) was 30 cm below level of the heart. Preliminary reports of this method were made by Elliot (1962a) and Elliot & Heath (1964).

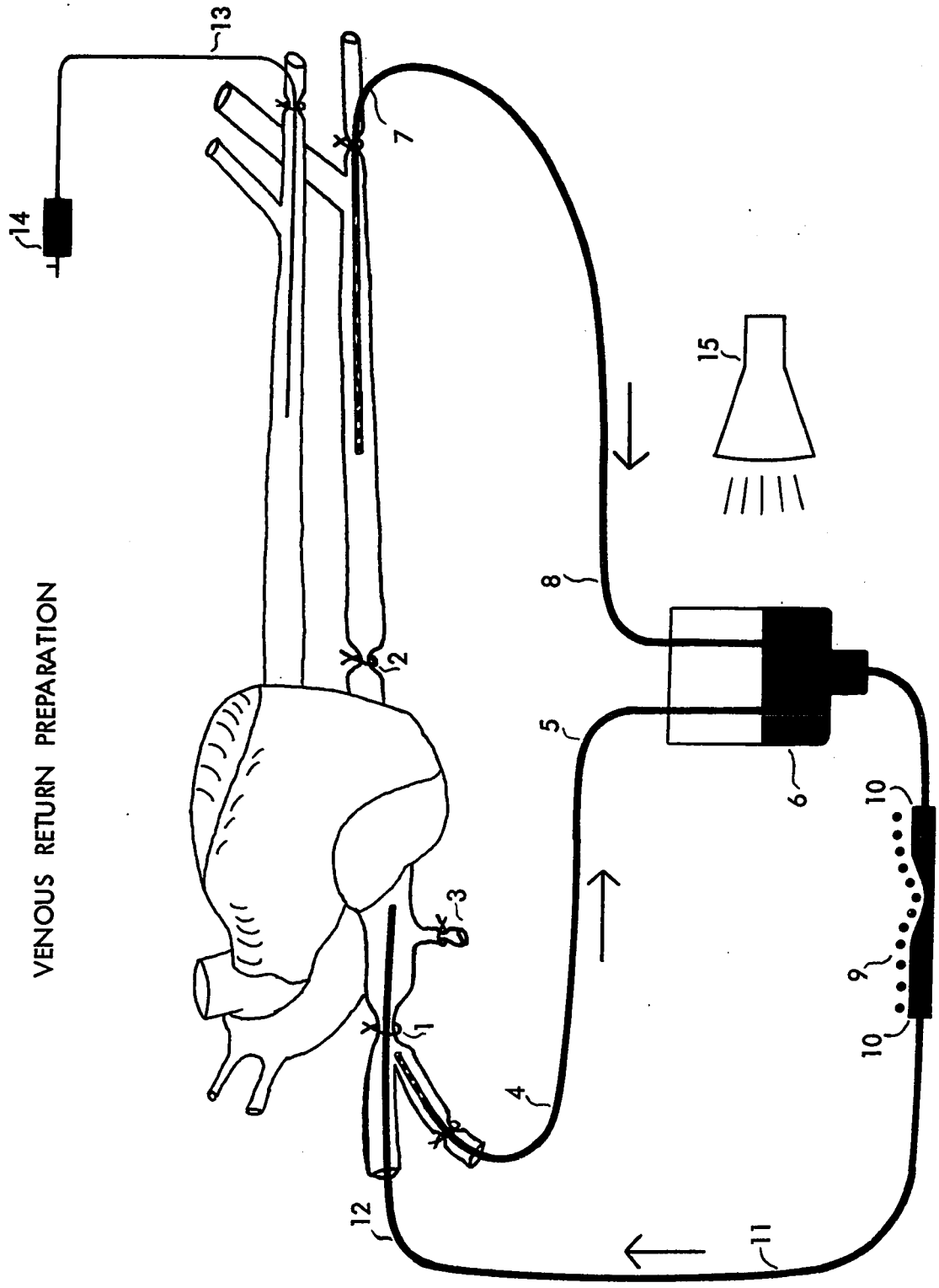
VENOUS RETURN PREPARATION
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Figure III - 2. Standard Curve used in the blood volume determinations. Further details appear in Table XXXI. (Appendix).

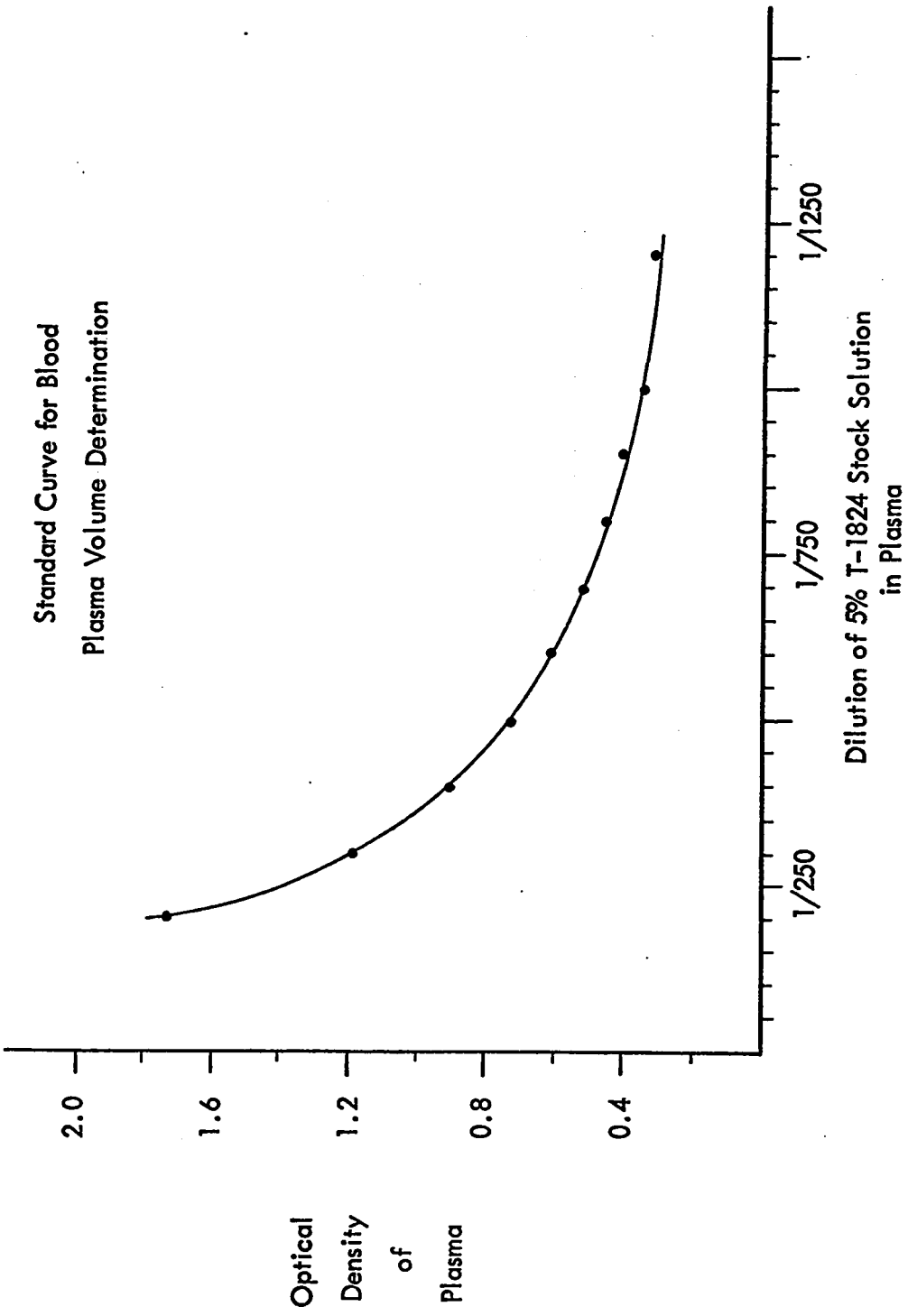
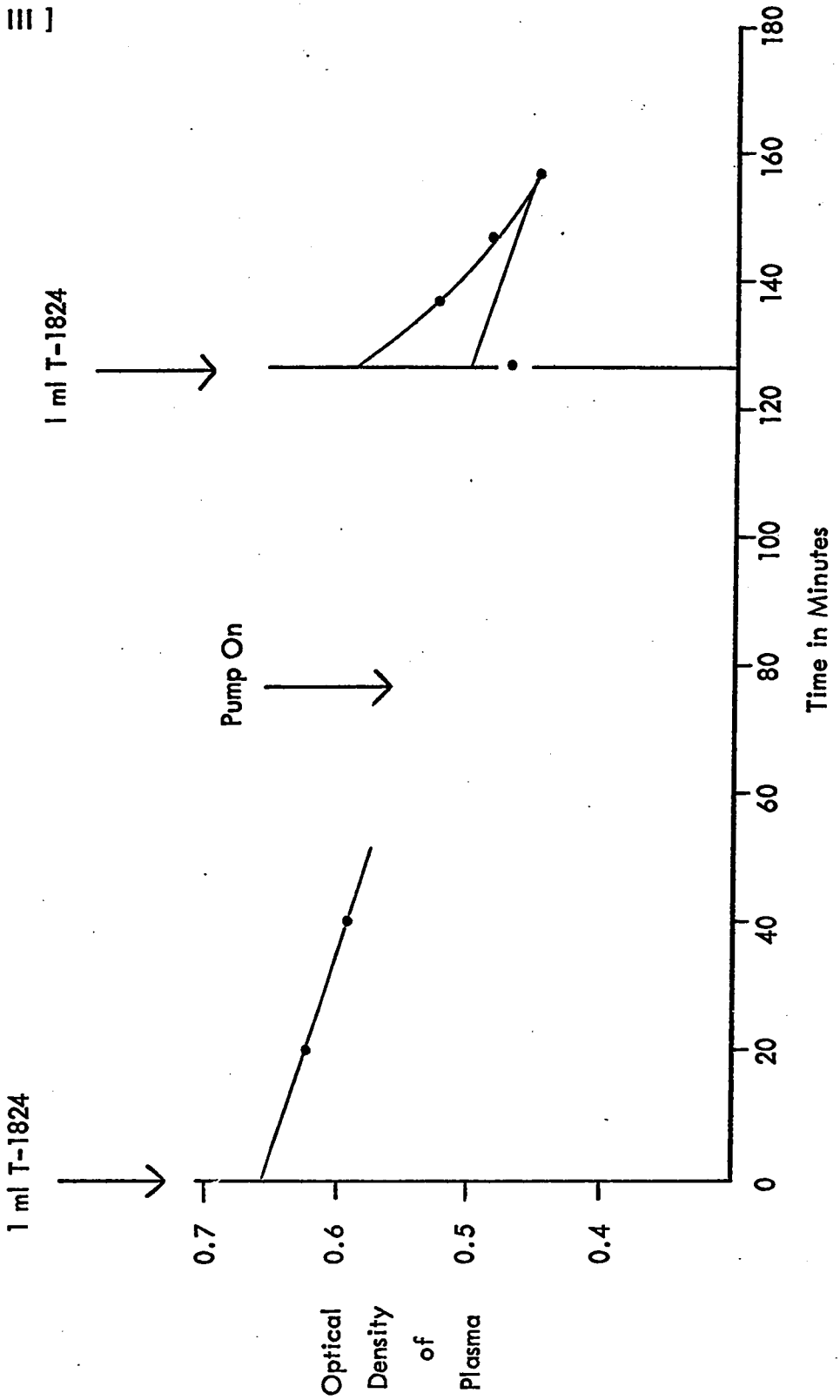

Standard Curve for Blood
Plasma Volume Determination
Optical Density of Plasma
2.0
1.6
1.2
0.8
0.4
1/250
1/750
1/1250
Dilution of 5% T-1824 Stock Solution in Plasma

Figure III - 3. Graph shows the method used for blood volume determinations 45 minutes after start of constant venous return period. Data in graph are from experiment No. 579. Dye used was from 5% stock solution of T-1824.


1 ml T-1824
1 ml T-1824
Pump On
0.7
0.6
0.5
0.4
Optical Density of Plasma
0
20
40
60
80
100
120
140
160
180
Time in Minutes

CHAPTER IV

Critique of Methods

Venous Return Preparation

In the preparation used in these experiments, there was no necessity to perform a pericardotomy or right atriotomy to place the catheters in the cavae. This reduced considerably the amount of surgical trauma and from this point of view was an advantage over the technique described earlier (Elliot, 1961b). Because the catheters had to be introduced through the jugular and femoral veins this limited their size and therefore the amount of blood that could be drained. Although the upper limit was not precisely determined it was approximately one liter/min. This system provided adequate drainage for the range of flows used.

The 'caval long-circuit' technique reported by Greenway & Howarth (1963) used the same placement of the caval catheters; in fact, it would appear that their method was even less traumatic because, by using catheters with inflatable cuffs, the technique could be carried out in closed-chest dogs. However, the advantage in using the open-chest approach was that the azygos vein could be ligated; since low flows were used in many of the experiments the blood flow through a patent azygos vein might have been significant.

Lean Body Mass and Surface Weight

Venous return to the heart was related to body weight and expressed in ml/kg. This decision was largely governed by the fact that this convention had already appeared extensively in the literature; the reasoning behind this stems from the fact that metabolism is related to body weight and surface area. It was considered important to measure the weight of the dogs as accurately as possible. Hair which is not metabolically active was therefore removed. In 61 dogs the hair averaged 221 g (S.D. = 83), Table I (Appendix). Although hair of the 12 kg dog represents less than 2 % of its total weight, nevertheless, if in addition to this the bowel and

bladder contents had also been ignored, an error of upwards of one kg could have resulted. Removal of hair can increase heat-loss; however, the rectal temperature was not observed to drop more than 2 to 3° C during an experiment. The temperature was not measured in each dog, but the method for maintaining the temperature was constant from dog to dog (see Chapter III).

Since fat is a poorly perfused tissue, it was thought that it would be more meaningful to express venous return in terms of lean body mass. Various attempts to do this (Table VI, Appendix) effected some improvement in correlation coefficients. Because this improvement was not significant, venous return was simply related to the value of net body weight in all subsequent experiments.

Exclusion of Coronary Venous Return

In earlier experiments (Elliot, 1961a, 1961b) the coronary flow had been estimated and added to the value of venous return for a more precise value of the cardiac output. To simplify the procedure in the present experiments, only the value of the constant venous return to the heart was used. Unless one were to cannulate the coronary sinus, which would involve extra surgery and still only account for a percentage of the total coronary venous return (Gregg & Shipley, 1947), there would be no way to include the coronary return with the caval drainage in this type of preparation. The benefits of such a cannulation would be questionable. The objective was to control the inflow into the arterial circulation at a known rate, and this was done, because the coronary venous return flowing into the right side of the heart, although added to the inflow from the Sigmamotor pump, was immediately subtracted again from the cardiac output just beyond the aortic valve as the coronary arterial inflow.

Sigmamotor Pump and Hemolysis Factor

The Sigmamotor pump was usually calibrated prior to the constant venous return period (see Chapter III) so that the venous return rate would be within the desired range. However, precise calibration of the Sigmamotor pump was carried out at the end of the experiment utilizing the blood from the reservoir bottle. The reputed reliability of the Sigmamotor pump had been assumed (Lillehei, Cohen,

Warden & Varco, 1955). However, in several experiments it was subsequently found that there was a fall of approximately 15 ml/min in the flow rate between the pre- and post-calibrations. Since the mean arterial pressure response in many experiments was opposite to what would be expected from a reduction in pump rate, it is unlikely that this change in pump rate had any significant influence on the physiological responses observed.

Another factor relating to the pump was the amount of hemolysis which the Sigmamotor pump is known to cause (Elliot & Callaghan, 1958b). The Model T - MI pump used in the present experiments had 12 fingers in the pump head and, therefore, allowed a relatively slow action of the fingers even at the higher flow rates in Group III experiments. The latex rubber pump tubing was of sufficient internal diameter (5/8 inch) that this also favoured a slow action. It could be observed from samples of blood plasma obtained as a result of centrifuging blood samples for hematocrit values and samples for catecholamine determinations that the gross hemolysis in the blood plasma at the end of the two hours was almost negligible.

Reservoir Blood Volume Measurements

Blood volumes read from calibrations on the reservoir bottle were within 2.5 ml of the volume measured by emptying the reservoir into a graduated cylinder (S.D. of the Differences = 5.5 ml; see Table II, Appendix). Because the volume of blood contained in caval drainage tubes, latex rubber pump tube and arterial inflow tube was constant from experiment to experiment, it was necessary only to record the volume of blood in the reservoir bottle during the experiments.

Ventilation with Oxygen at Atmospheric Pressure

In 28 determinations, the Pa_{O_2} values averaged 375 mmHg (S. D. = 75; Table IIA, Appendix). Because of these high arterial oxygen tensions, the possibility of oxygen toxicity must be considered. However, it would appear that following ventilation with oxygen at atmospheric pressure, some days of exposure are required before toxic effects occur (Gerschman, 1963; Bean, 1963; Gyllensten, 1959).

This should not be interpreted to mean that important physiological dysfunctions might not have occurred. For instance, oxygen at atmospheric pressure causes cerebral vasoconstriction (Kety & Schmidt, 1948). These aspects are discussed in Chapter VI.

Plasma Catecholamine Determinations

Known quantities of noradrenaline and adrenaline were added to the control samples of plasma and satisfactory recoveries were obtained. Recovery tests were not performed in each experiment because, where they were done, the recoveries were consistently good and the steps in the chemical determinations had become well standardized. In eight recovery tests the retrieval of noradrenaline and adrenaline averaged 77 % (S.D. = 20) and 74 % (S.D. = 15) respectively (Table III, Appendix). These recoveries compared favourably to those reported by others, e.g., Millar & Benfey (1958) - 50 to 75 %. In the above tests the amounts of catecholamines added to the 10 ml aliquots of plasma ranged from 0.05 to 0.1 ug in the case of noradrenaline, and from 0.05 to 1.0 ug in the case of adrenaline, and were therefore equivalent to the range of experimental observations in the majority of instances.

The method was apparently not sensitive enough to measure the levels of catecholamines in the plasma samples obtained prior to starting the pump. As can be seen in Tables IV and V (Appendix) the galvanometric readings were sometimes higher than the controlplasma readings, even when, in the oxidation process, the reagents (alkaline sulfite and iodine) were added in inverse order. Catecholamine content of the control samples may have been extremely low. Sodium pentobarbital anesthesia is reputed to cause a lowering of the plasma catecholamine levels. Walker, Zileli, Reutter, Shoemaker & Moore (1959) showed in dogs, that following sodium pentobarbital anesthesia there was a 96 % and 44 % reduction respectively in the adrenaline and noradrenaline concentrations in the adrenal blood. Since the dogs in the venous return experiments were also anesthetized with sodium pentobarbital there is the possibility that it had a similar effect.

CHAPTER V

Results

The results are based on 61 experiments in each of which the rate of venous return to the heart was held constant for an arbitrary interval of two hours. One dog was used for each experiment.

GROUPS I, II AND III EXPERIMENTS

There were 42 experiments in these three groups and the presentation of the data is divided into three parts: 1.) Basis for division of experiments into three groups; 2.) Mean arterial pressure, reservoir blood volume and heart rate changes in Groups I, II and III experiments; 3.) Additional relationships in the 42 experiments.

1.) Basis for Division of Experiments into Three Groups.

The experiments were divided into three groups on the basis of the mean arterial pressure response. The first 18 experiments of the investigation are presented in Figures V - 1 through V - 4 and it is evident from the pressure curves in these graphs that the responses were essentially of two kinds. In the eight experiments at the lower range of venous return (Figs. V - 1 and V - 2) the arterial pressure dropped to very low levels and remained low for the rest of the experiment. This is referred to as a 'flat type' of response. In contrast, in the second group (Figs. V - 3 and V - 4), the initial fall in arterial pressure was less and in the majority of experiments a 'progressive rise' occurred throughout the rest of the two-hour interval.

From these first few experiments it was evident that, although changes in peripheral resistance which seemed dependent on the values of constant venous return appeared to occur, more experiments were needed to delineate the responses. After an additional 24 experiments had been

performed, the same general trend was again exhibited, namely, one group of experiments in which the 'flat type' of response occurred and another group of experiments, in which there was observed the 'rising type' of pressure response during the latter part of the two-hour interval. The total of 42 experiments was then arranged in ascending order of increasing values of constant venous return and were divided into the following three groups on the basis of the mean arterial pressure response: Group I. Eighteen experiments at the lowest values of constant venous return which showed a 'flat type' response. Group II. Nine experiments with intermediate values of constant venous return, which had a variable response in arterial pressure. Group III. Fifteen experiments at the highest values of constant venous return which gave a 'rising type' of arterial pressure response in the last 90 minutes of constant venous return.

2.) Mean Arterial Pressure, Reservoir Blood Volume and Heart Rate Changes in Groups I, II and III Experiments.

These data of the above three groups of experiments were analyzed by the method of averaging the values for the variables for the first 30 and last 90 minutes of the two-hour period of constant venous return. The details of this method have been outlined in Chapter III.

Group I Experiments

The values of constant venous return to the heart in these eighteen experiments averaged 15.3 ml/kg/min (range - 13.2 to 17.4).

a) Mean Arterial Pressure. Mean arterial pressure data are presented in Figure V - 5 and Table V - 1. At the start of the constant venous return period the arterial pressure

fell to low values. It averaged 34 mmHg for the first 30 minute period and did not change during the next 90 minutes ($P = 0.35$).

b) Reservoir Blood Volume. Reservoir blood volume data are presented in Figure V - 6 and Table V - 1. It can be seen from the graph that the reservoir blood volume curve rose rapidly during the (0 to 30) minute interval but more gradually in the (30 to 120) minute interval. It averaged 26.5 ml/kg in the first 30 minutes and rose by 12.6 ml/kg in the last 90 minutes ($P < 0.005$).

c) Heart Rate. Heart Rate data are summarized in Table V - 1. The control heart rate before the onset of the constant venous return period averaged 141 beats/min. The rate fell by 22 beats/min during the (0 to 30) minute interval to an average of 119 beats/min ($P < 0.01$). The rate rose again during the (30 to 120) minute interval to an average of 133 beats/min, a significant increase over the value in the first 30 minute interval ($P < 0.05$).

Summary

The pressure fell immediately to low levels with the start of the pump (34 mmHg in the (0 to 30) minute interval) and did not change thereafter. The most rapid rise in blood volume occurred in the (0 to 30) minute interval. The heart rate fell significantly during the (0 to 30) minute interval from control but rose again in the (30 to 120) minute interval.

Group II Experiments

In these nine experiments the constant venous return rate averaged 20.6 ml/kg/min (range - 17.9 to 24.6).

a) Mean Arterial Pressure. Mean arterial pressure data are presented in Table V - I. The apparent increase of 6.7 mmHg in average mean arterial pressure for the (30 to 120) minute interval over that of the (0 to 30) minute interval pressure was not significant ($P = 0.3$).

b) Reservoir Blood Volume. Reservoir blood volume data are presented in Table V - I. The average reservoir blood volume during the (0 to 30) minute interval of 20.1 ml/kg rose to 33 ml/kg for the (30 to 120) minute interval ($P < 0.005$).

c) Heart Rate. Heart rate data are presented in Table V - I. The heart rate averaged 143 beats/min before the venous return period was started and decreased to 125 beats/min during the (0 to 30) minute period ($P < 0.025$). The heart rate rose again during the (30 to 120) minute interval to an average of 143 beats/min ($P < 0.025$).

Summary

The apparent rise in pressure in the (30 to 120) minute interval was not significant. The blood volume changes again showed a fast rise in the (0 to 30) minute interval and also a significant rise in the (30 to 120) minute interval. The heart rate in the (0 to 30) minute interval fell significantly from control and rose again during the (30 to 120) minute interval.

Group III Experiments

In the 15 experiments of this group the constant venous rate averaged 32.6 ml/kg/min (range - 27.0 to 45.3).

a) Mean Arterial Pressure. Mean arterial pressure data are presented in Figure V - 5 and Table V - 1. There was an obvious change in the mean arterial pressure response in this group of experiments, compared to that of Group I experiments. The average mean arterial pressure during the (0 to 30) minute interval was 62.3 mmHg, almost double the value for the corresponding interval in Group I experiments ($P < 0.005$). The average mean arterial pressure during the (30 to 120) minute interval increased by 13.2 mmHg above the value in the (0 to 30) minute interval ($P < 0.005$).

b) Reservoir Blood Volume. Reservoir blood volume data are presented in Figure V - 6 and Table V - 1. The curve denoting the average reservoir blood volume changes for this group of experiments was obviously lower than the corresponding curve for Group I experiments. The average reservoir blood volume during the (0 to 30) minute interval was 17.6 ml/kg. The volume increased during the (30 to 120) minute interval to 27.4 ml/kg ($P < 0.005$).

c) Heart Rate. Heart rate data are presented in Table V - 1. The changes in heart rate in this group of experiments were less dramatic. The rate before the venous return period was started averaged 150 beats/min, but the fall to 137 beats/min during the (0 to 30) minute interval was not significant nor the rise to 152 beats/min in the (30 to 120) minute interval ($P = 0.1$).

Summary

The pressure curve was obviously at a higher level compared to Group I experiments (Fig. V - 5) and also the blood volume curve was obviously lower (Fig. V - 6). The heart rate did not fall significantly from control.

3.) Additional Relationships in the 42 Experiments.

Several relationships are now presented by considering in each relationship the observations of the entire 42 experiments, as opposed to dividing them into groups.

a) Relationship Between the Average (0 to 30) and (30 to 120) minute Mean Arterial Pressure and Constant Venous Return Rate. The plot of this relationship appears in Figures V - 7 and V - 8. Each closed circle in both graphs represents an experiment. The graphs show that there is a relationship between these two variables, the coefficients of correlation 'r' being respectively 0.77 and 0.75 ($P < 0.01$). In comparing these graphs it can be observed that, at constant venous return rates below 20 to 25 ml/kg/min, the values of mean arterial pressure were clustered above the same level of pressure, but, at higher rates, the values for the (30 to 120) minute mean arterial pressures were noticeably higher than the (0 to 30) interval pressures. This accounts for the greater rise in the slope of the regression line in Figure V - 8.

The above findings are expressed differently in Figure V - 9. The differences between the mean arterial pressure of (30 to 120) and (0 to 30) minute intervals were determined and plotted against the corresponding values

of the constant venous return rate. It can be seen again that, above constant venous return rates of 20 to 25 ml/kg/min the average values of the (30 to 120) minute mean arterial pressures exceeded the average values for the first 30 minutes. This graph emphasizes the fact that at constant venous return rates above 25 ml/kg/min, average pressures rose during the (30 to 120) minute interval. Below these flows it was, on the average, unchanged.

b) Relationship Between the Average (0 to 30) and (30 to 120) Minute Reservoir Blood Volume and Constant Venous Return Rate. The plot of this relationship is presented in Figures V - 10 and V - 11. There is shown to be a negative correlation between these variables ($r = -0.57$ and -0.51, respectively; $P < 0.01$). The rate of increase in reservoir blood volume was the same in both intervals; the regression equation in Figure V - 11 lies above that in Figure V - 10 because more blood collected in the reservoir in the (30 to 120) minute interval.

c) Relationship Between the Average (0 to 30) and (30 to 120) minute Reservoir Blood Volume and Mean Arterial Pressure. Since there was shown to be a relationship between the arterial pressure and venous return and also between reservoir blood volume and venous return, it was of interest to note the relationship between reservoir blood volume and mean arterial pressure. These data are presented in Figures V - 12 and V - 13. There is a negative relationship in the two plots ($r = -0.52$ and -0.50; $P < 0.01$)but the degree of correlation was of

the same order as between arterial pressure and venous return and reservoir blood volume and venous return.

Summary

From these data above it was established that in the 42 experiments that the mean arterial pressure and reservoir blood volume appeared to be dependent upon the corresponding values of constant venous return rate.

d) Three Graphs of Coefficients of Correlation Plotted at Frequent Times During the Two-hour Experimental Period

In the first two graphs (Figs. V - 14 and V - 15) the correlations were determined between the mean arterial pressure and constant venous return rates. In the third graph (Fig. V - 16) the correlations were determined between the reservoir blood volume and constant venous return rate.

In Figure V - 14, the correlations were based on the entire 42 experiments of Groups I, II and III, whereas in Figure V - 15 the correlations were restricted to the 15 experiments of Group III. It can be seen in Figure V - 14 that the correlations were essentially unchanged from the 10 minute time onward; at the five minute time, the best correlation was observed with 'r' = 0.86. In contrast to this, in Figure V - 15 the correlation coefficient 'r' = 0.36 at the 5 minute time was the only significant correlation observed in the entire (0 to 120) minute interval ($P<0.05$). The curve of correlation in this graph showed a tendency to reverse signs; for example, during the 5 to 30 minute interval the sign decreased in value, then remained essentially unchanged in the (20 to 90) minute interval, but finally became negative in (90 to 120) minute interval.

In the third graph (Fig. V - 16), relating to the correlations between reservoir blood volume and constant venous return the data were obtained from the 42 experiments of Groups I, II and III, and in this graph the correlations were all observed to be negative. The best correlation was observed early in the 30 minute interval. The correlations in this graph were all significant ($P < 0.01$).

GROUPS IV, V, VI AND VII EXPERIMENTS

Having determined the pattern of responses that could be expected at various levels of constant venous return, further experiments were performed to try and shed some light on the underlying mechanisms that might be operative. In Groups IV, V and VI experiments the following determinations were carried out: Plasma catecholamines, pH and P_{CO_2} determinations, mean arterial pressure and reservoir blood volume measurements, under conditions of constant venous return. In addition, in Groups VI and VII experiments the effects of adrenergic blockade were tested at 5 mg/kg and 1 mg/kg doses, respectively.

Since Groups IV and V experiments differ from Groups I and III experiments only in respect to the additional measurements that were made, they were included in Groups I and III. The data can be found separately for these experiments from Tables X, XII, XIII and XIV (Appendix) - the relevant experiment numbers being given in Tables XIX and XX (Appendix).

The mean arterial pressure and reservoir blood volume determinations, in Groups IV, V and VI experiments, were analyzed in the same manner as in Groups I, II and III experiments (see Methods, Chapter III).

Plasma Catecholamines, pH and P_{CO_2} Determinations, Mean Arterial Pressure and Reservoir Blood Volume, under Conditions of Constant Venous Return

Group IV Experiments (Flow rate equivalent to Group I experiments).

These seven experiments did not differ from the Group I experiments in regard to constant venous return ($P = 0.15$), mean arterial pressure ($P = 0.30$ and 0.20 respectively, for the (0 to 30) and (30 to 120) minute intervals) and reservoir blood volume ($P = 0.25$ and 0.45 respectively, for the two intervals).

a) Venous Plasma Catecholamine Levels. The catecholamine levels became markedly elevated; the adrenaline levels averaged 95.6 and 116.1 ug/liter of plasma, while the noradrenaline levels average 8.8 and 10.0 ug/liter of plasma, at the end of one and two hours of constant venous return, respectively (Fig. V - 17 and Table V - IV).

b) pH and P_{CO_2} Determinations. The arterial and venous pH values fell to low levels; the averaged values were 7.1 and 6.9 respectively at the end of two hours of constant venous return. The average arterial P_{CO_2} remained low at the one and two hour intervals (19.6 mmHg and 20.2 mmHg, respectively), whereas, the venous P_{CO_2} rose to an average value of 57.4 mmHg at the end of one hour, and to an average value of 72.6 mmHg at the end of two hours (Fig. V - 17 and Table V - IV).

Summary

Noradrenaline and especially adrenaline blood levels became markedly elevated. The venous P_{CO_2} values were markedly elevated; in the presence of low arterial P_{CO_2} and low arterial pH this would indicate the presence of metabolic acidosis.

Group V Experiments (Flow rate equivalent to Group III experiments).

These five experiments did not differ from Group III experiments with respect to venous return ($P = 0.2$), mean arterial pressure ($P = 0.2$ and 0.5 respectively for the (0 to 30) and (30 to 120) minute intervals) and reservoir blood volume ($P = 0.2$ and 0.1 respectively, for the two intervals).

a) Venous Plasma Catecholamine Levels. The average values for the adrenaline plasma levels at the one- and two-hour intervals of the constant venous return period were 15.0 and 13.5 ug/liter respectively, and these were significantly lower than the corresponding values in Group IV experiments ($P < 0.005$ in both instances, Table V - IV). The average values for the noradrenaline plasma levels at the one-and two-hour intervals were 0.73 and 0.66 ug/liter respectively; these values were also significantly less than the corresponding values in Group IV experiments ($P < 0.01$ and 0.005 respectively; Table V - IV). These comparisons can also be observed in Figure V - 17.

b) pH and P_{CO_2} Determinations. The pH and P_{CO_2} determinations were limited to arterial measurements in this group of experiments. The P_{CO_2} values were not significantly different from those in Group IV experiments at the one- and two-hour intervals of the constant venous return period ($P = 0.4$ for both intervals). Although the average pH values at the one- and two-hour intervals of 7.3 and 7.33 respectively, were higher than the corresponding values in Group IV experiments, they were not significantly higher ($P = 0.1$ for both intervals, Figure V - 17 and Table V - IV).

Summary

Both the noradrenaline and adrenaline plasma levels were significantly lower than in Group IV experiments. The venous P_{CO_2} measurements were not available in this group of experiments and thus the presence of metabolic acidosis could not be determined. However, judging from the values of arterial pH, it is unlikely that there was metabolic acidosis.

Group VI Experiments (Effect of Adrenergic Blockage (phenoxybenzamine) - Flow rate equivalent to highest constant venous return rate).

The values of constant venous return in this group were not significantly different from the values in the experiments of Groups III and V (P values being respectively = 0.25 and 0.35). The average value for the mean arterial pressures just prior to starting the sigmamotor pump in this group of experiments was 80.2 mmHg, which was significantly lower than the corresponding values in Groups III and V (P < 0.005, in both instances, Table V - I). Phenoxybenzamine (5 mg/kg) was administered in all these dogs before the constant venous return period was commenced and would appear to be the cause of the lower control mean arterial pressures in this group.

a) Mean Arterial Pressure. The mean arterial pressures remained low during the (0 to 30) and (30 to 120) minute intervals averaging respectively 35.8 mmHg and 30.0 mmHg for the two intervals; both these values were not significantly different from the corresponding values in Group I experiments (P values being respectively 0.35 and 0.25 for the two intervals; compare Figure V - 5 and V - 18; Table V - 1). However, it can be seen by comparing the average pressure curves in Figures V - 5 and V - 18, that the arterial pressure response in Group VI experiments was obviously lower than that in Group III experiments (P < 0.005 for the (0 to 30) and (30 to 120) minute intervals); these lower arterial pressures were registered, in spite of the fact the values of constant venous return in Group VI experiments were not different from those in Group III experiments.

b) Reservoir Blood Volume. The reservoir blood volumes averaged respectively 27.3 ml/kg and 41.5 ml/kg in the (0 to 30) and (30 to 120) minute intervals and these values were significantly higher than the corresponding values in Group III in spite of the fact that the venous return rates were comparable ($P < 0.005$, for the two intervals; compare Figures V - 6 and V - 19; Table V - I). When this same comparison, in respect to the (0 to 30) and (30 to 120) minute intervals, is made with Group I experiments, wherein there is a significant difference between constant venous return rates, there is observed no difference between the corresponding average values of reservoir blood volume ($P = 0.4$ and 0.25, respectively, for the two intervals; compare Figs. V - 6 and V - 19; Table V - 1). In comparing the reservoir blood volume curves in Figures V - 6 and V - 19, it is seen that the curve for Group VI experiments continues to rise at the 80, 100 and 120 minute times, whereas the curve in Group I experiments plateaus during the (100 to 120) minute interval. But even where the separation of the curves is greatest, namely, at the 120 minute time the difference is not significant ($P = 0.1$, Table V - III).

c) Blood Plasma Catecholamine Levels. The blood plasma catecholamine levels were elevated in Group VI experiments (Tables V - IV and V - VI). The adrenaline plasma levels averaged at the one and two hours, 24.9 and 26.9 ug/liter, respectively, and the noradrenaline

plasma levels at these two times averaged respectively, 3.96 and 4.3 ug/liter. In comparing the plasma catecholamine levels between Groups VI and V (Table V - VI), there was observed no significant difference between the values, except in the case of the noradrenaline determinations at the two-hour time period. The Group VI catecholamine plasma levels, however, were significantly less than the levels in Group IV experiments (Table V - VII), except in the case of noradrenaline determinations at the one hour time.

d) pH and P_{CO_2} Determinations. When comparing Group VI and IV experiments with respect to the pH and P_{CO_2} determinations, it is first pointed out that the levels of hypotension in the (0 to 30) and (30 to 120) minute intervals were comparable in these two groups ($P = 0.45$ and 0.1 for the two intervals, respectively; Fig. V - 17; Table V - 1; Tables XIX and XXIII, Appendix). Despite the comparable levels of hypotension in these two groups the arterial pH of Group VI experiments was significantly elevated above the corresponding two-hour average value of Group IV experiments (Table V - V), whereas, the venous pH was significantly elevated at both the one-and two-hour times (Table V - V). There is no difference between the arterial P_{CO_2} values in these two groups (Table V - V), in contrast to this there was a significant difference between the venous P_{CO_2} values at the two-hour time. However, there was no difference at the one-hour time (Table V - V).

Summary

In spite of the fact that the constant venous return rates were not different from Group III experiments, the arterial pressures were the same as in Group I experiments. Also the reservoir blood volumes were the same as those in Group I experiments. Thus, the administration of phenoxybenzamine prior to the constant venous return period appeared to convert the Group III experiments into Group I type experiments in regard to the mean arterial pressure and reservoir blood volume. The noradrenaline and adrenaline plasma levels were intermediate between those of Groups IV and Group V experiments. In spite of the fact that the degree of hypotension was not different from that in Group IV experiments, the arterial pH in Group VI experiments was significantly elevated over that in Group IV experiments. Also, there was a significant difference in the two-hour venous P_{CO_2} values, the value in the Group VI experiments being less.

Group VII Experiments. (Effect of Small Dose of Phenoxybenzamine).

In these five experiments phenoxybenzamine was administered before the start of the constant venous return period in the dosage of 1 mg/kg. The salient data of the experiments are presented in Table XXVI (Appendix). It was concluded, especially from experiment No. 558, that the blockade was incomplete, because there was a pressure rise in the (30 to 120) minute interval. In subsequent experiments (see Group VI experiments) the dosage of phenoxybenzamine was increased to 5 mg/kg. In experiment No. 556, at the end of two hours of constant venous return at the rate of 15.7 ml/kg/min, the heart was observed to be greatly dilated and the heart beat very feeble.

GROUPS VIII, IX, X AND XI EXPERIMENTS

The following procedures were carried out in these four groups of experiments: 1.) Plasma blood volume and hematocrit determinations before and after constant venous return period in non-splenectomized dogs; 2.) Hematocrit determinations before and after constant venous return period in splenectomized dogs; 3.) Supramaximal administration of noradrenaline at end of constant venous return period; 4.) Effect of administration of THAM on mean arterial pressure response.

1.) Plasma Blood Volume and Hematocrit Determinations Before and After Constant Venous Return Period in Non-splenectomized Dogs.

Group VIII Experiments

In these seven experiments the blood plasma volumes were determined before and approximately 45 minutes after the onset of the constant venous return period. In conjunction with these determinations a control venous hematocrit was also obtained before, and serial hematocrits obtained during, the constant venous return period. The results are presented in Table XXVII (Appendix). The experiments were not performed specifically for this purpose, but rather the determinations were incorporated into several of the experiments of Groups I, II and III. The greatest increase in percentage of plasma volume gain over control occurred in the four dogs with the lowest values of constant venous return, namely, experiments Nos. 575, 576, 577 and 579. In none of the dogs was there any appreciable decrease in the hematocrit values during the first 30 minutes of the constant venous return period; in fact, there were only two dogs in which there was a decrease at the end of two hours, namely, experiments Nos. 576 and 577. In one dog there was an increase in the hematocrit by the end of the two hours (experiment No. 575).

2.) Hematocrit Determinations Before and During Constant Venous Return Period in Splenectomized Dogs.

Group IX Experiments

In three dogs the spleen was removed and in several days when the dogs had recovered from the operation the constant venous return experiment was performed. These experiments were done specifically to observe the serial hematocrit values during the constant venous return period. It can be observed from Table XXVIII (Appendix) that there was a progressive decrease in the hematocrit values in all three dogs during this period. Only the control plasma volume was obtained, subsequent serial plasma volumes being calculated by utilizing the hematocrit values in a formula (see Table XXVIII, Appendix).

3.) Supramaximal Administration of Noradrenaline at the End of the Constant Venous Return Period.

Group X Experiments

In the three dogs of this group the constant venous return experiment was carried out and the pertinent data are presented in Table XXIX (Appendix). Continuous infusion of noradrenaline (one ml of Levophed in 500 ml of 5% dextrose in saline) at the rate of 3.3 ug of Levophed base/min had no effect on the arterial pressure (experiment No. 551); the infusion at this rate was started at the 90 minute point in the constant venous return period. In each experiment at the end of the constant venous return period a dose of 2000 ug of Levophed base was injected into the reservoir bottle. The mean arterial pressure response was marked in experiment No. 548, less so in experiment No. 551, while in experiment No. 553 there was only a feeble response. There was a marked rise in the reservoir blood volume in experiment No. 548 and a small increase in experiment No. 551; unfortunately, the reservoir

blood volume was not recorded in experiment No. 553, after the noradrenaline injection.

4.) Effect of Administration of THAM on Mean Arterial Pressure Response

Group XI Experiments

In three dogs the venous return to the heart was severely reduced so that there would be low values of arterial pressure and pH. THAM (Nahas, 1963) was then added to the reservoir bottle and the blood agitated to ensure mixing. Sufficient THAM (0.3 Molar solution) was added to raise the pH to approximately 7.4. The results are presented in Table XXX (Appendix). The return of pH to approximately 7.4 from the 7.04 to 7.1 range, did not appear to influence the arterial pressure response, at least the pressure did not rise. As the arterial pH rose after the administration of THAM there occurred a concomitant fall in the arterial P_{CO_2}. In the third experiment, the noradrenaline and adrenaline values remained low, at least in comparison to the first two experiments of this group, and also, for instance, in comparison to the values of Group IV experiments (see Table XXI, Appendix).

Summary

In the non-splenectomized dogs the hematocrit values remained unchanged during the constant venous return period but the plasma volumes determined by T - 1824 dye increased. In the splenectomized dogs there was a progressive reduction in the hematocrit values during the constant venous return period. In the experiments with very low constant venous return rates and low arterial pressure there was still a response to supramaximal doses of noradrenaline at the end of the two hours of constant venous return. Correcting the metabolic acidosis by the administration of THAM (judged by the return of pH to normal levels) did not appear to influence the arterial pressure in experiments with very low constant venous return rates.

DEVELOPMENT OF SET OF CURVES

The objective in this section is to develop a set of curves in order to represent the average arterial pressure and reservoir blood volume responses at different levels of constant venous return for the entire 42 experiments. The 18 experiments presented in Figures V - 1 through V - 4 were determined from the interpolated values of the data presented in Tables X, XI and XII (Appendix), and it will now be demonstrated how the data for the pressure and volume curves for the 42 experiments can be arranged into a family of curves.

a) Mean Arterial Pressure. The values for the mean arterial pressure at each of the 5 and 10 minute times in Tables X, XI and XII (Appendix) were combined into a single column of figures making a total of 40 to 41 observations in each of the 16 columns. For each value of mean arterial pressure in a column there was a different value of constant venous return, (Col (2) in Tables VII, VIII and IX, Appendix). In essence then, there were 16 different plots of mean arterial pressure (y) versus constant venous return (x). The regression equations of arterial pressure on constant venous return for each of these plots were then calculated and the coefficients of correlation obtained. These are the coefficients of correlation 'r' which appear in Figures V - 14and V -15 (in Figure V -15 the plots were restricted to Group III experiments). The data for these regression equations and their coefficients of correlation as well as the S.D. of y and S.E. of b appear in Tables XVI and XVII (Appendix).

By substituting values for seven different levels of venous return from 15 through 45 ml/kg/min in each of the 16 different regression equations (Table XVI, Appendix) a corresponding set of Y values or mean arterial pressures was obtained. These were calculated for each level of constant venous return and formed the set of curves illustrated in Figure V - 20.

b) Reservoir Blood Volume. The raw data of the interpolated values of reservoir blood volume at the 5 and 10 minute intervals of the constant venous return period are given in Tables XIII, XIV and XV (Appendix). These data were treated in the same way as were those for arterial pressures and the 16 regression equations for reservoir blood volume on constant venous return are given in Table XVIII (Appendix). The set of curves for the reservoir blood volumes at the seven different levels of constant venous return were calculated and appear in Figure V - 21.

c) Times of Maximal Pressure and Volume Changes. If in Figure V - 20 the best fit line is drawn through each curve starting at the 20 minute interval, a set of curves is obtained as in Figure V - 22. Above each curve is an arrow which indicates the point at which the maximum mean arterial pressure occurred. It may be observed that the maximum pressure response occurred further along in each curve, the higher the level of constant venous return.

Figure V - 21 is plotted logarithmically and the curves are exponential for approximately the first 40 to 60 minutes; this logarithmic plot is given in Figure V - 23. During the last 60 minutes of the constant venous return period the reservoir blood volume tended to plateau and therefore the curves were not exponential. It may be seen both in Figures V - 21 and V - 23 that the maximal reservoir blood volume changes occurred at approximately the same time in each curve, i.e. during the 80 to 100 minute interval.

d) Interrelationship Between Mean Arterial Pressure and Reservoir Blood Volume Changes. In Figure V - 24, the mean arterial pressure curves from Figure V - 22 were superimposed on the corresponding reservoir blood volume curves of Figure V - 21 so that each pair of curves intersects at the 40 time.

These curves show that at the lower levels of constant venous return, the reservoir blood volume continues to increase beyond the point where the pressure curves plateau. At the level of 30 ml/kg/min constant venous return the two curves from the 40 minute time on are almost perfectly superimposed. Above this level of constant venous return the relationship in each pair of curves reverses itself compared to the lower levels.

TABLE V - I - Summary of Data, of Groups I through VI Experiments, for the Average Values of Mean Arterial Pressure, Reservoir Blood Volume and Heart Rate - During the (0 to 30) and (30 to 120) minute Intervals.

Groups of Experiments	Net Weight in Kilograms (1)	Value of Constant Venous Return Rate ml/kg/min (2)	Control Mean Arterial Pressure mmHg (3)	Average Mean Arterial Pressure During (0 to 30)' Interval mmHg (4)	Average Mean Arterial Pressure During (30 to 120)' Interval mmHg (5)	Difference Between Average (30 to 120)' - (0 to 30)' Mean Arterial Pressure mmHg (6)
Group I						
N	18	18	18	16	16	16
$\bar{x}$ and S.E.	12.38 ±0.5	15.3 ±0.31	108 ±5.28	34.1 ±1.87	32.9 ±1.94	-1.25 ±0.75
Group II						
N	9	9	9	9	9	9
$\bar{x}$ and S.E.	11.15 ±0.97	20.6 ±0.72	118 ±6.93	40.1 ±2.92	46.7 ±6.24	+4.78 ±5.24
Group III						
N	15	15	15	15	15	15
$\bar{x}$ and S.E.	12.11 ±0.51	32.6 ±1.37	121 ±3.1	62.3 ±2.65	74.7 ±2.93	+13.20 ±3.11
Group IV						
N	9	9	9	9	9	9
$\bar{x}$ and S.E.	12.61 ±0.85	14.6 ±0.53	102 ±8.1	36.6 ±3.60	36.7 ±3.49	+0.14 ±2.61
Group V						
N	5	5	5	5	5	5
$\bar{x}$ and S.E.	11.7 ±0.84	30.3 ±0.85	118 ±3.16	67.6 ±3.96	73.8 ±3.33	+6.20 ±3.77
Group VI						
N	6	6	6	6	6	6
$\bar{x}$ and S.E.	11.47 ±0.30	30.8 ±0.55	80.2 ±2.03	35.8 ±1.82	30.0 ±1.51	-5.80 ±2.11

TABLE V - I - Continued

Groups of Experiments	Average Reservoir Blood Volume During (0 to 30)' Interval ml/kg (7)	Average Reservoir Blood Volume During (30 to 120)' Interval ml/kg (8)	Difference Between Average (30 to 120)' - (0 to 30)' Reservoir Blood Volume ml/kg (9)	Control Heart Rate Beats/min (10)	Average Heart Rate During (0 to 30)' Interval Beats/min (11)	Average Heart Rate During (30 to 120)' Interval Beats/min (12)	Difference Between Average (30 to 120)' - (0 to 30)' Heart Rate Beats/min (13)
Group I							
N	16	16	16	16	16	16	16
$\bar{x}$ and S.E.	26.5 ±1.22	39.1 ±2.08	+12.7 ±1.28	141 ±6.32	119 ±4.47	133 ±5.85	+13.68 ±3.87
Group II							
N	9	9	9	9	9	9	9
$\bar{x}$ and S.E.	20.1 ±2.52	33.0 ±2.54	+12.9 ±2.70	143 ±6.10	125 ±3.83	143 ±5.83	+18.3 ±3.22
Group III							
N	15	15	15	15	15	15	15
$\bar{x}$ and S.E.	17.6 ±1.79	27.27 ±2.26	+9.60 ±1.17	150 ±5.52	137 ±5.29	152 ±7.02	+15.6 ±3.25
Group IV							
N	7	7	7				
$\bar{x}$ and S.E.	28.2 ±2.02	38.2 ±3.46	+9.93 ±2.26				
Group V							
N	5	5	5				
$\bar{x}$ and S.E.	14.5 ±1.23	21.3 ±2.69	+6.78 ±2.05				
Group VI							
N	6	6	6	4	6	6	6
$\bar{x}$ and S.E.	27.3 ±2.63	41.5 ±3.00	+13.88 ±1.07	177 ±9.9	160 ±6.77	166 ±6.33	+6.3 ±4.44

TABLE V - II - Summary of the Data for Groups I, II, III and IV Experiments for the Average Values of the Interpolated Mean Arterial Pressures at the five and 10 minute Times During the Constant Venous Return Period.

Minutes	Control	2-3	5	10	15	20	25	30	40	60	80	100	120
Groups of Experiments													
Group I													
N	18	17	17	17	17	17	17	17	17	17	16	16	16
$\bar{x}$	108.5	24.7	28.6	30.9	29.8	28.7	30.5	33.0	33.6	34.0	33.2	31.4	29.6
s^2	502.136	21.9	35.30	80.06	78.88	67.85	79.42	121.176	114.94	104.35	52.33	49.74	63.73
S.D.	22.41	4.685	5.94	8.94	8.88	8.23	8.91	11.01	10.72	10.22	7.22	7.05	7.98
Group II													
N	9	9	9	9	9	9	9	9	9	9	9	9	9
$\bar{x}$	117.9	30.2	36.3	41.8	39.3	37.8	38.5	41.7	47.9	49.5	49.5	46.2	42.7
s^2	433.2	84.17	109.0	127.51	89.78	76.1	96.7	136.89	294.75	388.03	541.54	744.25	345.78
S.D.	70.8	9.17	10.44	11.29	9.47	8.72	9.84	11.7	17.16	19.7	23.26	27.28	18.6
Group III													
N	15	15	15	15	15	15	15	15	15	15	15	15	15
$\bar{x}$	120.6	39.3	57.9	61.7	60.6	61.2	63.1	65.5	68.8	74.6	77.2	78.3	79.5
s^2	145.44	87.96	129.53	213.53	144.64	117.23	119.40	141.99	138.82	152.37	154.56	203.02	229.32
S.D	12.06	9.37	11.38	14.6	12.03	10.83	10.94	11.92	11.77	12.35	12.43	14.25	15.14
Group VI													
N	6	6	6	6	6	6	6	6	6	6	6	6	6
$\bar{x}$	80.2	30.2	31.0	33.2	32.8	32.3	32.0	32.0	32.0	30.5	30.3	28.2	27.2
s^2	247.14	12.47	19.3	39.14	29.13	25.89	27.33	25.0	16.67	8.58	15.89	32.4	47.50
S.D	15.72	3.53	4.39	6.25	5.4	5.09	5.23	5.0	4.08	2.93	3.98	5.69	6.89

TABLE V - III - Summary of the Data for Groups I, II, III and VI Experiments for the Average Values of the Interpolated Reservoir Blood Volumes at the five and 10 minute Times During the Constant Venous Return Period.

Minutes	Control	5	10	15	20	25	30	40	60	80	100	120
Groups of Experiments												
Group I												
N	16	16	16	16	16	16	16	16	16	16	16	16
$\bar{x}_2$	0	23.9	27.32	29.25	31.03	34.2	35.3	37.56	39.5	40.0	40.0	39.69
s^2	0	20.31	27.67	38.18	40.08	57.77	59.93	73.68	90.75	93.95	79.09	69.89
S.D.	0	4.51	5.24	6.18	6.32	7.6	7.74	8.58	9.52	9.69	8.89	8.36
Group II												
N	9	9	9	9	9	9	9	9	9	9	9	9
$\bar{x}_2$	0	14.6	19.2	21.8	24.6	25.8	27.5	30.6	33.9	34.8	33.9	33.9
s^2	0	32.44	36.39	50.76	72.48	78.099	71.56	53.98	63.39	86.94	84.58	123.44
S.D.	0	5.7	6.03	7.12	8.51	8.83	8.46	7.34	7.96	9.32	9.2	11.11
Group III												
N	15	15	15	15	15	15	15	15	15	15	15	15
$\bar{x}_2$	0	15.8	18.06	19.57	21.4	23.1	24.51	26.17	27.1	27.9	28.2	27.83
s^2	0	49.03	67.655	82.62	77.39	71.66	65.119	75.47	78.44	85.04	80.83	90.63
S.D	0	7.0	8.22	9.09	8.79	8.47	8.069	8.69	8.86	9.22	8.99	9.52
Group VI												
N	6	6	6	6	6	6	6	6	6	6	6	6
$\bar{x}_2$	0	22.4	27.0	29.3	31.0	32.7	34.2	37.1	40.1	42.7	44.8	46.4
s^2	0	32.45	49.25	51.31	50.0	52.15	57.39	42.54	60.95	65.90	64.47	45.70
S.D.	0	5.7	7.0	7.16	7.07	7.22	7.57	6.52	7.8	8.12	8.03	6.76

TABLE V - IV - Summary Data for Groups IV, V and VI Experiments for Values of Arterial and Venous pH & P_{CO_2} Determinations, and Venous Noradrenaline & Adrenaline Blood Plasma Determinations - At One and Two Hours After the Start of the Constant Venous Return.

Groups of Experiments	pH		P_{CO_2}		Catecholamines		pH		P_{CO_2}		Catecholamines	
	Art	Ven	Art	Ven	NA	A	Art	Ven	Art	Ven	NA	A
Group IV												
N	7	5	7	5	9	9	6	5	6	5	7	7
$\bar{x}$	7.22	7.06	19.64	57.4	8.8	95.6	7.06	6.94	20.17	72.6	10.0	116.1
s^2	0.00775	0.0042	150.84	376.3	31.6	2925.46	0.00428	0.0081	50.05	626.6	23.69	3185.23
S.D.	0.088	0.0648	12.28	19.40	5.62	54.1	0.0648	0.09	7.07	25.02	4.86	56.44
Group V												
N	4		5		5	5	5		5		5	5
$\bar{x}$	7.3		21.75		0.73	15.0	7.33		21.8		0.66	13.5
s^2	0.00765		28.69		0.2842	42.6	0.008416		85.66		0.0025	20.661
S.D.	0.0874		5.36		0.533	6.53	0.0917		9.25		0.05	4.55
Group VI												
N	6	4	6	5	6	6	6	4	6	5	6	6
$\bar{x}$	7.30	7.185	21.83	42	3.96	24.9	7.22	7.11	20.33	44.2	4.3	26.9
s^2	0.005	0.00003	38.81	60	24.2922	174.66	0.0055	0.0071	60.56	96.56	11.673	233.801
S.D.	0.07	0.0054	6.23	7.74	4.93	13.22	0.0742	0.0842	7.78	9.83	3.42	15.28

TABLE V - V - Average Values of pH and P_{CO_2} Determinations At the One and Two Hour Times After the Start of the Constant Venous Return Period are Compared Between Groups IV and VI Experiments.

Experiment Group	pH		P_{CO_2}		pH		P_{CO_2}	
	Art	Ven	Art	Ven	Art	Ven	Art	Ven
IV	7.216	7.06	19.64	57.4	7.06	6.94	20.17	72.6
VI	7.3	7.185	21.84	42	7.22	7.11	20.33	44.2
P Value	0.1	0.01	0.4	0.1	0.01	0.025	0.45	0.05

TABLE V - VI - Average Values of Adrenaline and Noradrenaline At the One and Two Hour Times After the Start of the Constant Venous Return Period are Compared Between Groups VI and V Experiments.

Experiment Group	A	NA	A	NA
VI	24.9	3.96	26.9	4.3
V	15.0	0.73	13.5	0.65
P Value	0.15	0.15	0.1	0.05

TABLE V - VII - Average Values of Adrenaline and Noradrenaline At the One and Two Hour Times After the Start of the Constant Venous Return Period are Compared Between Groups VI and IV Experiments.

Experiment Group	A	NA	A	NA
VI	24.9	3.96	26.9	4.3
IV	95.6	8.8	116.1	10.0
P Value	0.01	0.1	0.005	0.025

Figure V - 1. Graph demonstrates the mean arterial pressure curves for four experiments at low values of constant venous return rate, for the two-hour experimental period. Control values of mean arterial pressure before start of constant venous return period are shown at the right of the ordinate near the top; these points (symbols) also serve as a key to denote the different curves in the graph; the two numbers beside each symbol are respectively the experiment number and the value of constant venous return (the latter being the one in brackets). - (Data obtained from Tables X, XI and XII, Appendix).

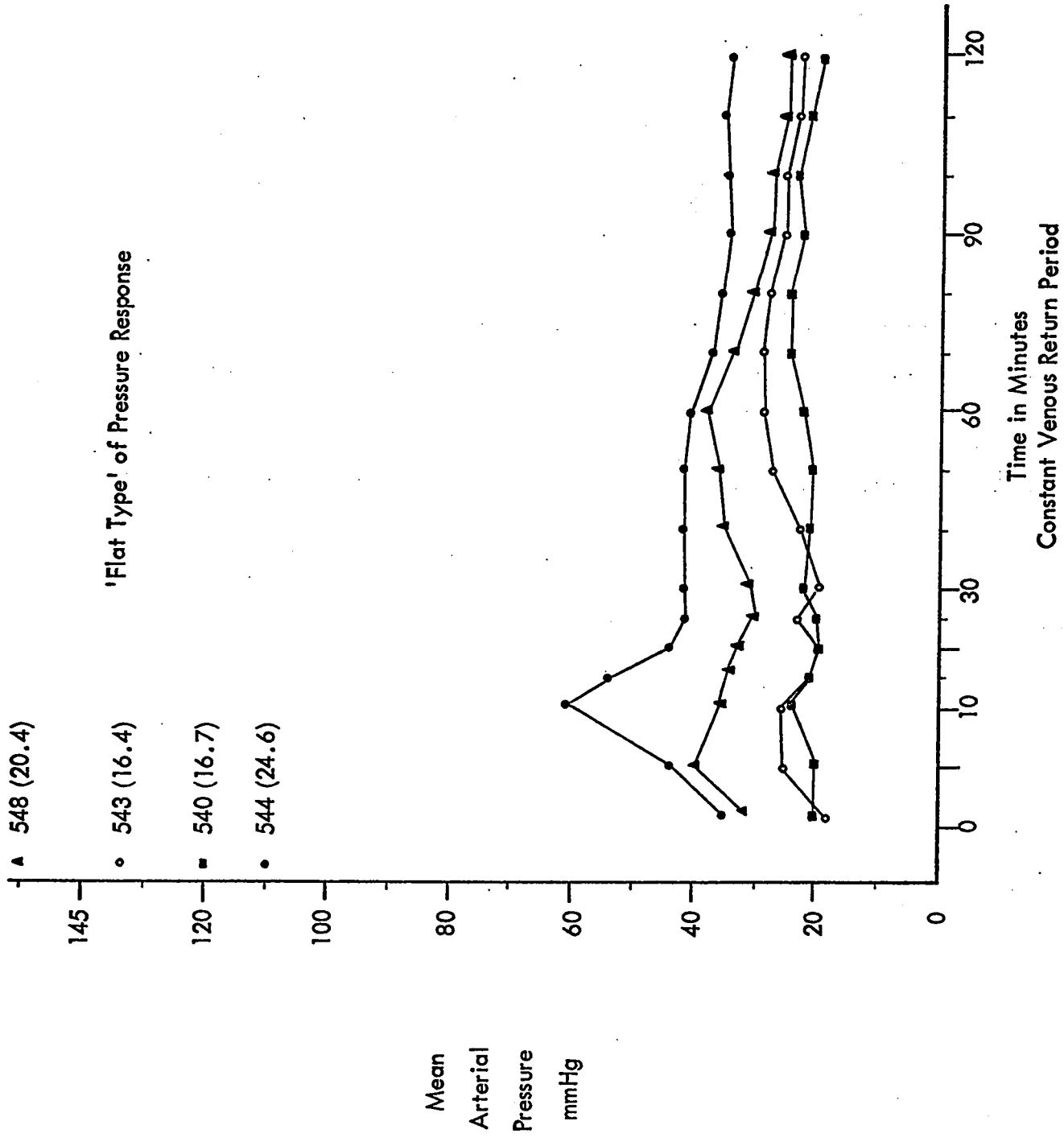

'Flat Type' of Pressure Response
▲ 548 (20.4)
○ 543 (16.4)
■ 540 (16.7)
● 544 (24.6)
Mean Arterial Pressure mmHg
145
120
100
80
60
40
20
0
0
10
30
60
90
120
Time in Minutes
Constant Venous Return Period

Figure V - 2. Graph demonstrates the mean arterial pressure curves for four experiments at low values of constant venous return rate, for the two-hour experimental period. Same explanation pertains as given in legend for Figure V - 1 in regard to the symbols for the control values at the right of ordinate near top. (Data obtained from Tables X, XI and XII, Appendix).

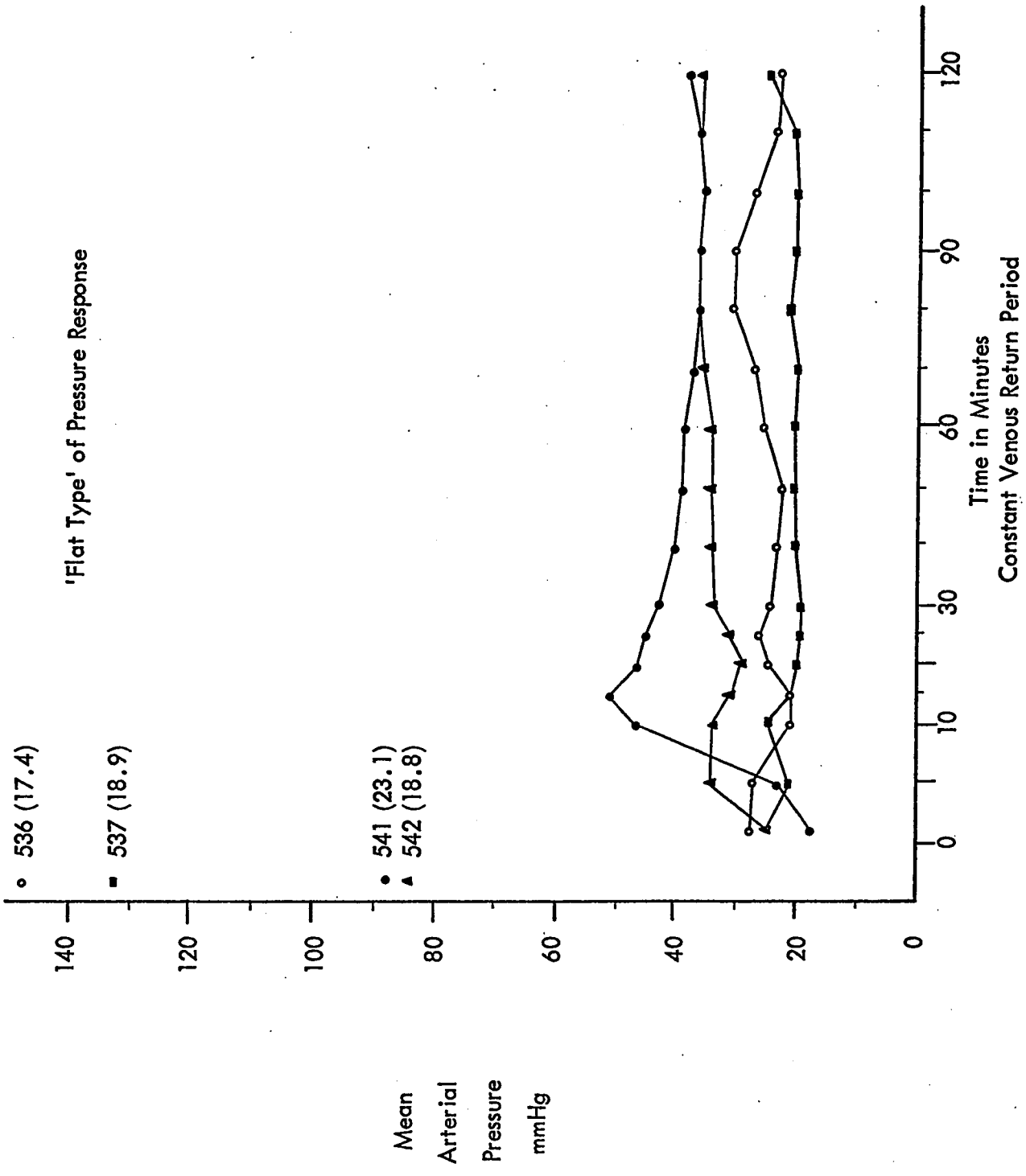

'Flat Type' of Pressure Response
○ 536 (17.4)
■ 537 (18.9)
● 541 (23.1)
▲ 542 (18.8)
Mean Arterial Pressure mmHg
140
120
100
80
60
40
20
0
0
10
30
60
90
120
Time in Minutes
Constant Venous Return Period

Figure V - 3. Graph demonstrates the mean arterial pressure curves for five experiments at higher values of constant venous return rate, for the two-hour experimental period. Same explanation pertains as given in legend for Figure V - 1 in regard to the symbols for the control values at the right of ordinate near top (Data obtained from Tables X, XI and XII, Appendix).

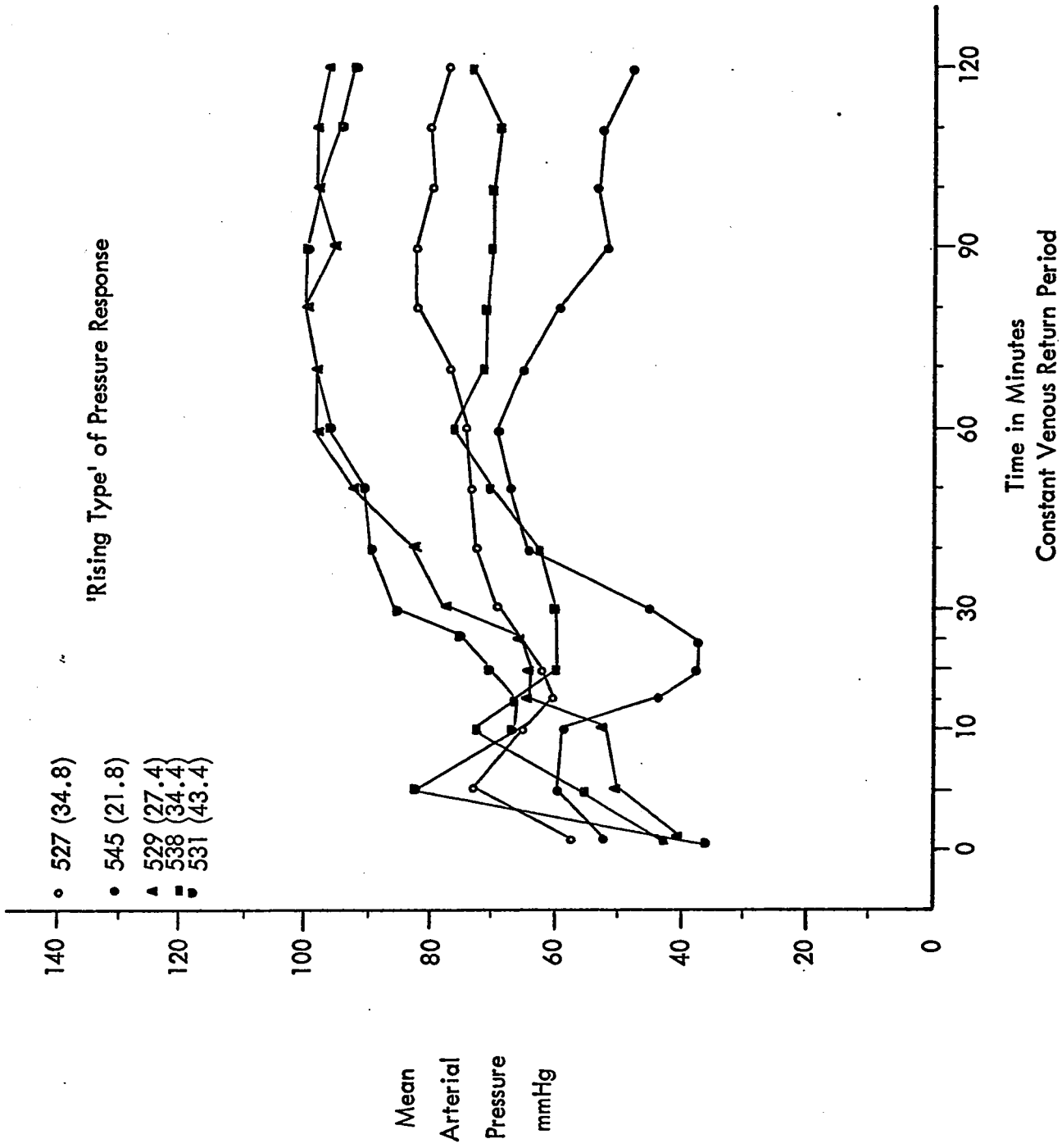

'Rising Type' of Pressure Response
527 (34.8)
545 (21.8)
529 (27.4)
538 (34.4)
531 (43.4)
Mean Arterial Pressure mmHg
140
120
100
80
60
40
20
0
0
10
30
60
90
120
Time in Minutes
Constant Venous Return Period

Figure V - 4. Graph demonstrates the mean arterial pressure curves for five experiments at higher values of constant venous return rate during two-hour experimental period. Same explanation pertains as given in legend for Figure V - I in regard to the symbols for the control values at the right of the ordinate near the top. (Data obtained from Tables X, XI and XII, Appendix).

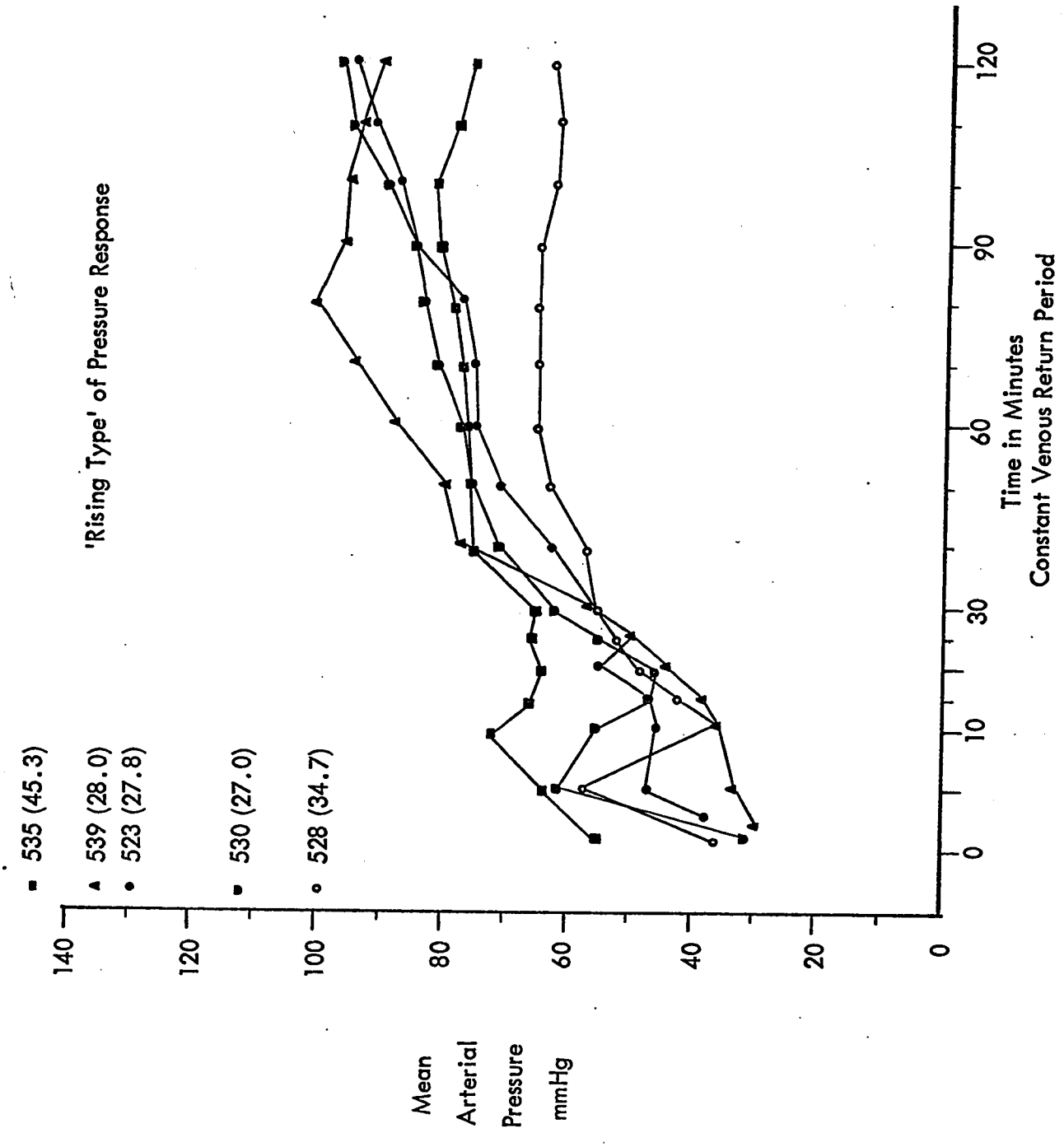

'Rising Type' of Pressure Response
▪ 535 (45.3)
▲ 539 (28.0)
● 523 (27.8)
▪ 530 (27.0)
○ 528 (34.7)
Mean Arterial Pressure mmHg
140
120
100
80
60
40
20
0
0
10
30
60
90
120
Time in Minutes
Constant Venous Return Period

Figure V - 5. Two curves in graph represent the average responses in mean arterial pressure for Groups I and III experimental period. Points represent the average values with S.D. (vertical lines) - (Data obtained from Table V - II; Tables X and XII, Appendix).

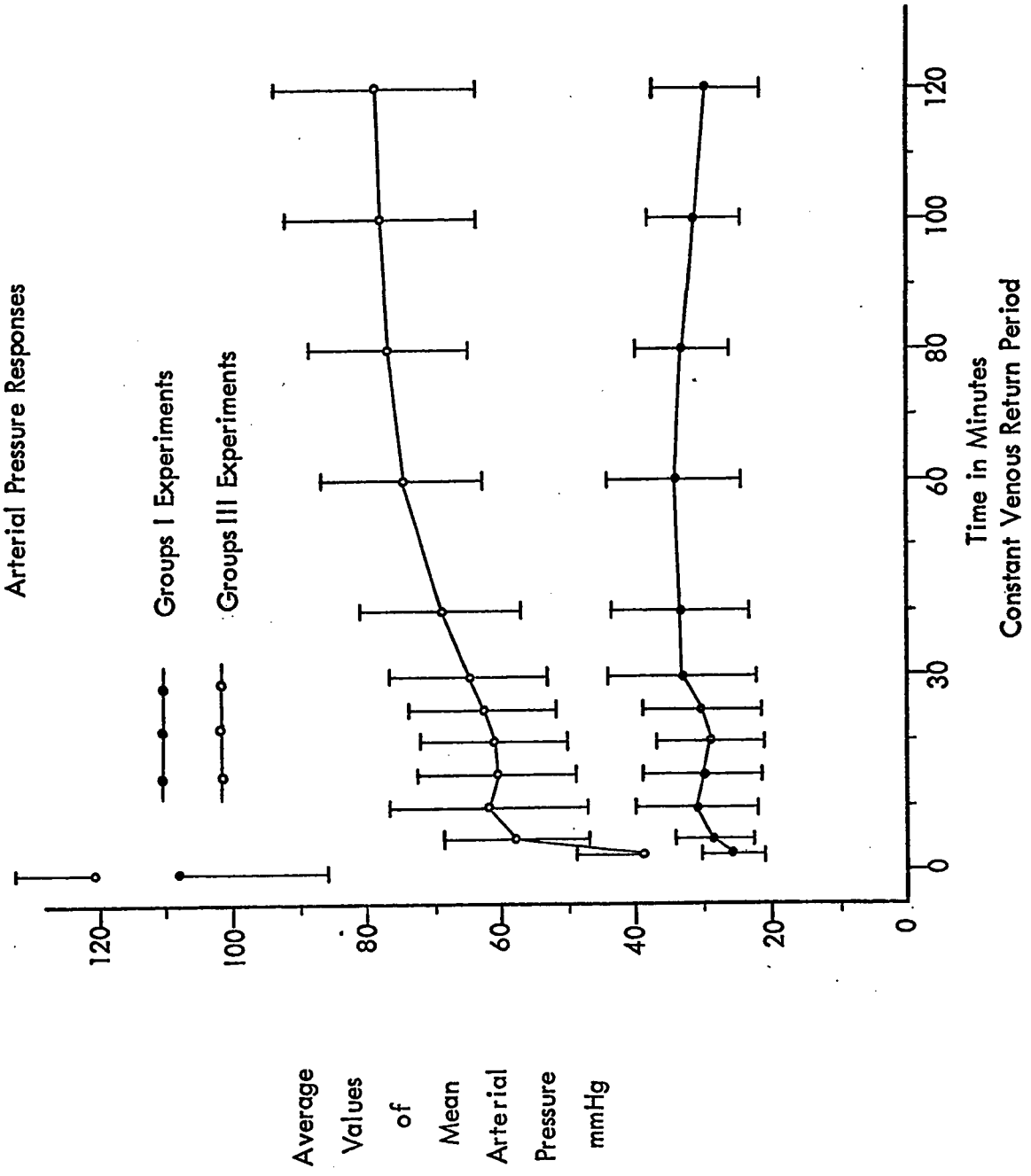
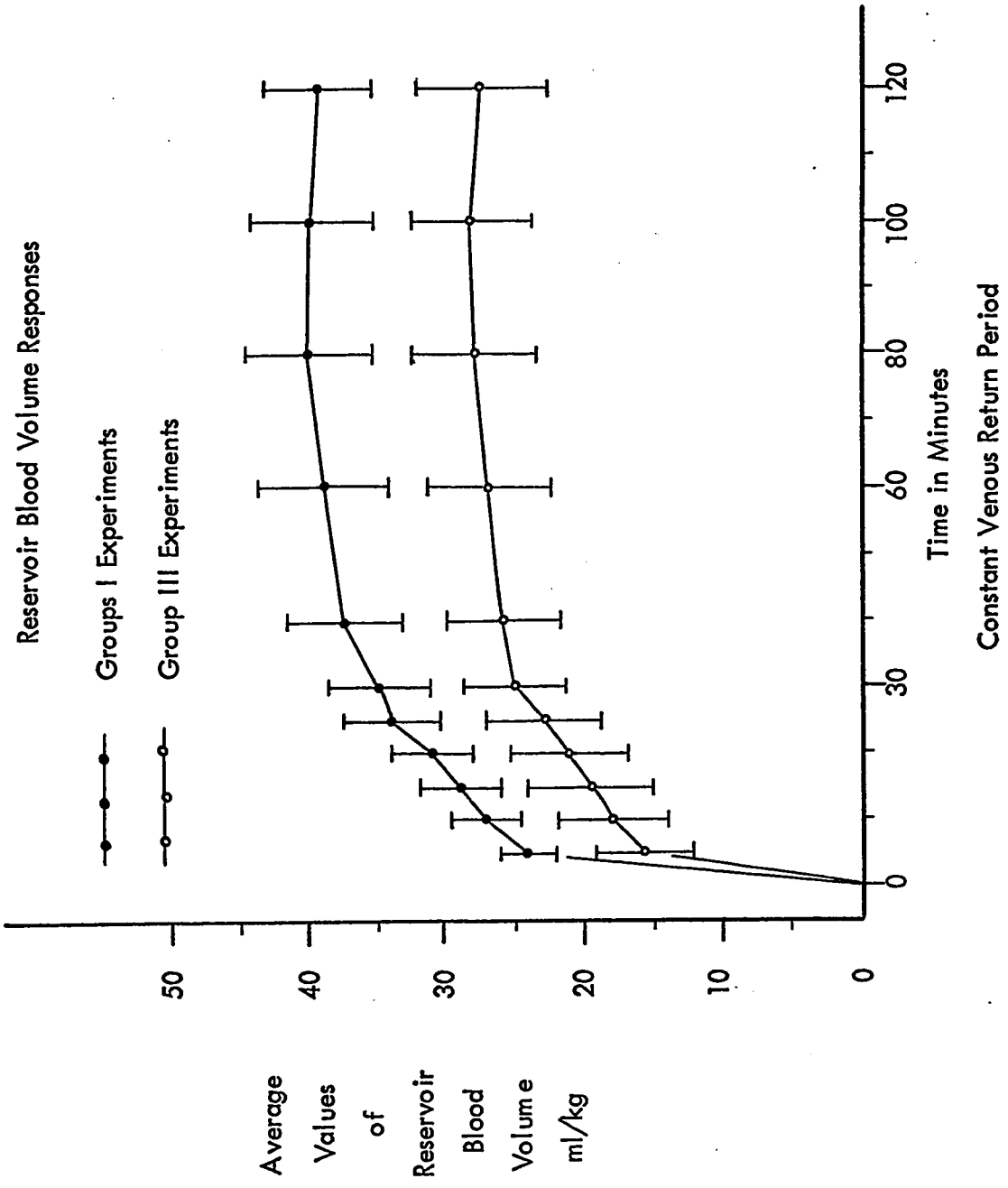

Arterial Pressure Responses
Groups I Experiments
Groups III Experiments
Average Values of Mean Arterial Pressure mmHg
120
100
80
60
40
20
0
0
30
60
80
100
120
Time in Minutes
Constant Venous Return Period

Figure V - 6. Two curves in graph represent the average responses in reservoir blood volume for Groups I and III experiments during the two-hour experimental period. Points represent the average values with S.D. (vertical lines) - (Data obtained from Table V - III; Tables XIII and XV, Appendix).


Reservoir Blood Volume Responses
Groups I Experiments
Group III Experiments
Average Values of Reservoir Blood Volume ml/kg
0
10
20
30
40
50
0
30
60
80
100
120
Time in Minutes
Constant Venous Return Period

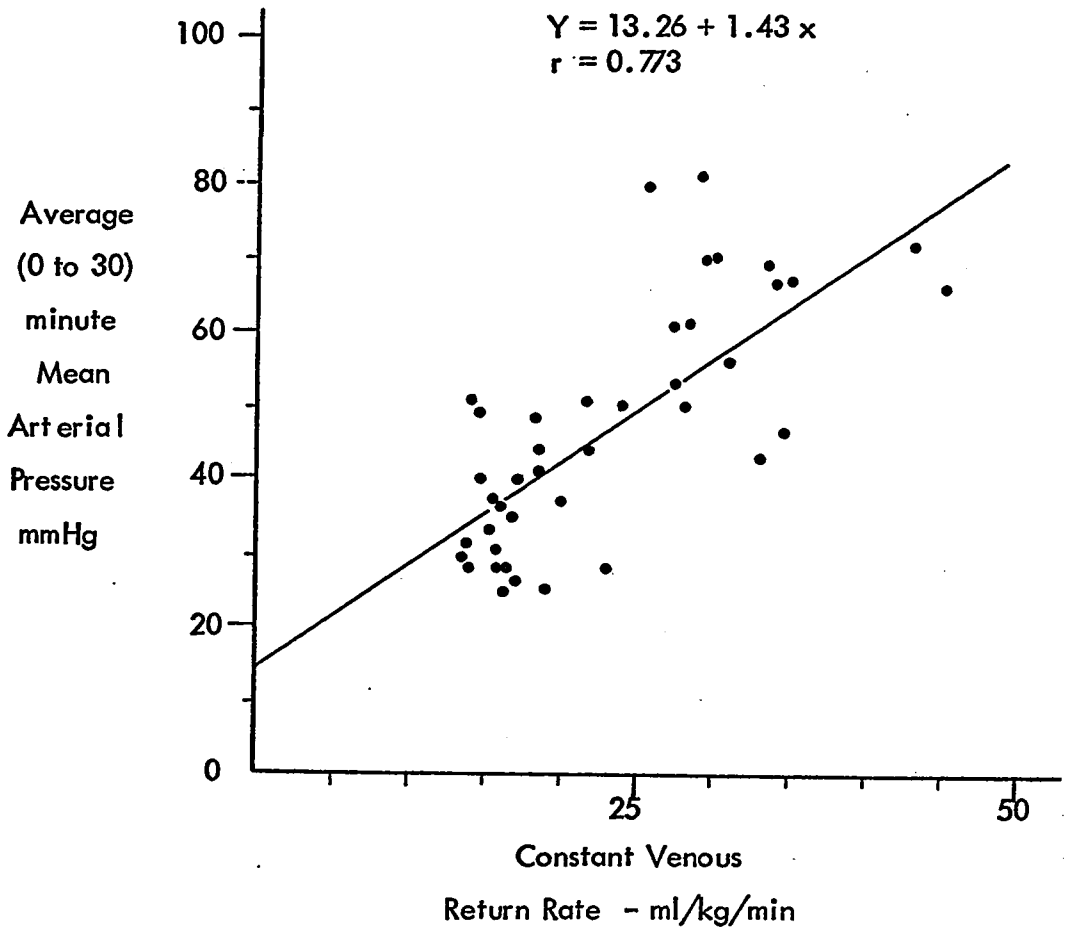


Figure V - 7. Graph shows the relationship between the average (0 to 30) mean arterial pressures and the corresponding values of constant venous return rate, for data from Groups I, II and III experiments (Data obtained from Cols (2) and (4) in Tables VII, VIII and IX, Appendix).

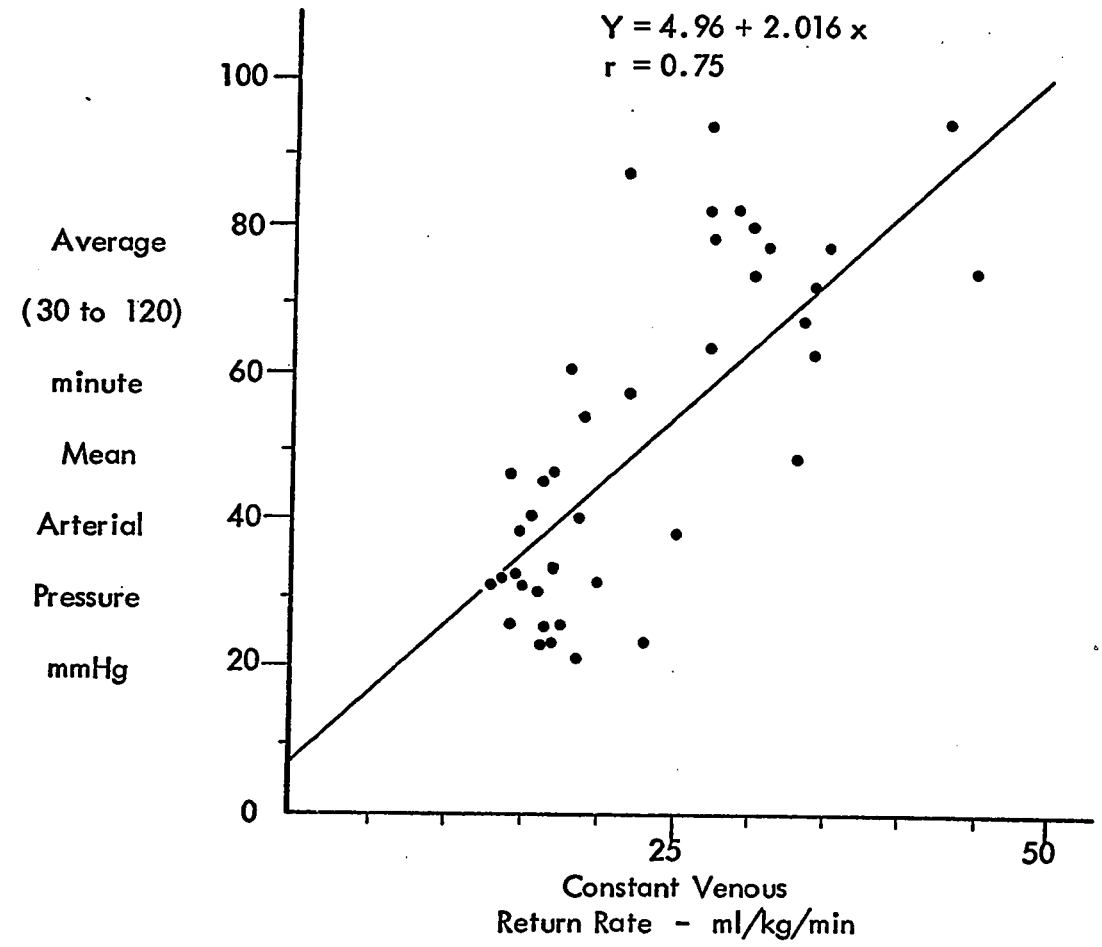


Figure V - 8. Graph shows the relationship between the average (30 to 120) minute mean arterial pressures and the corresponding values of constant venous return rate, for data from Groups I, II and III experiments (Data obtained from Cols (2) and (5) in Tables VII, VIII and IX, Appendix).

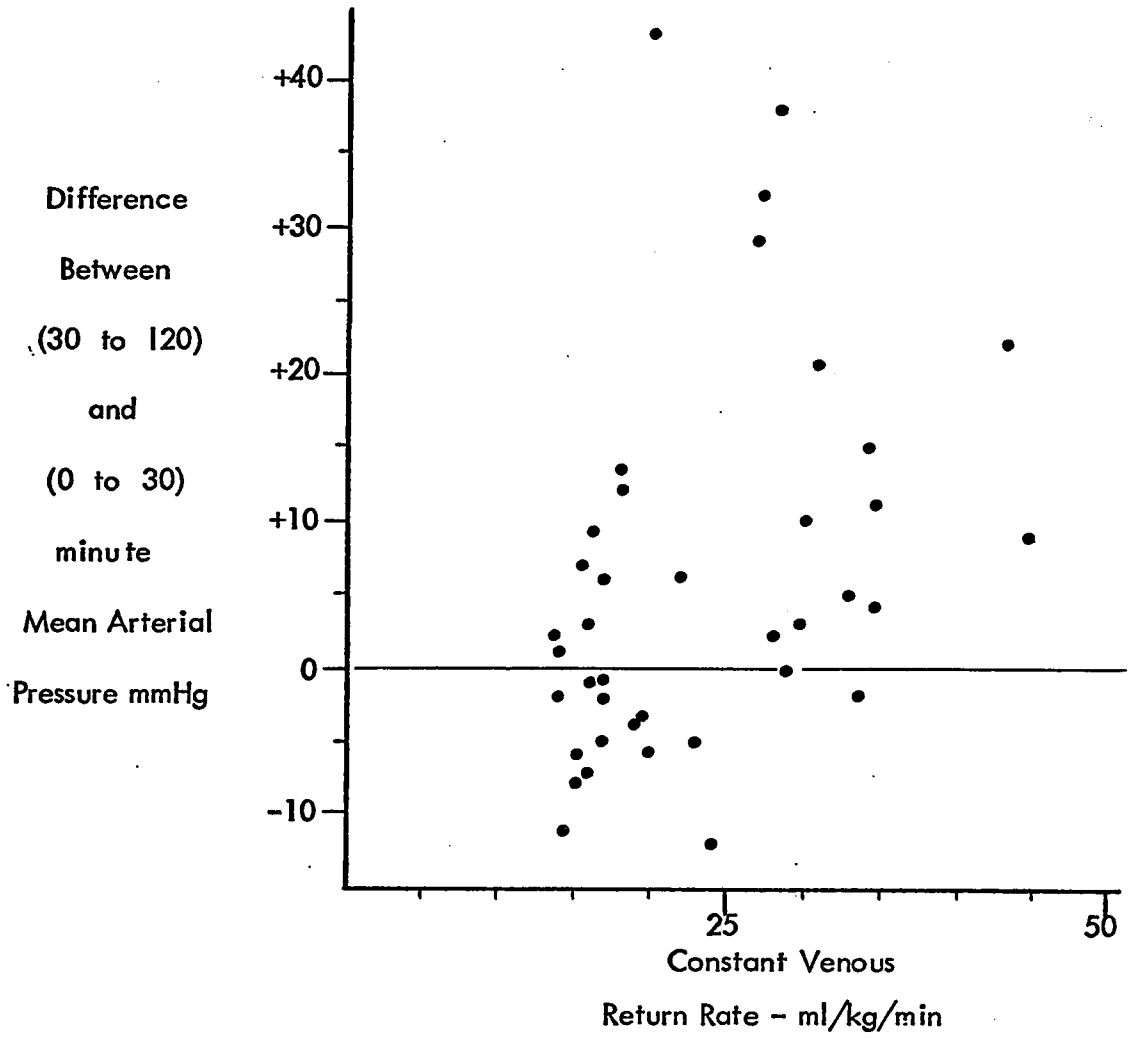


Figure V - 9. Graph shows the relationship between the differences of the average (30 to 120) and (0 to 30) minute mean arterial pressures and the corresponding values of constant venous return, for data from Groups I, II and III experiments. (Data obtained from Cols (2) and (6) in Tables VII, VIII and IX, Appendix).

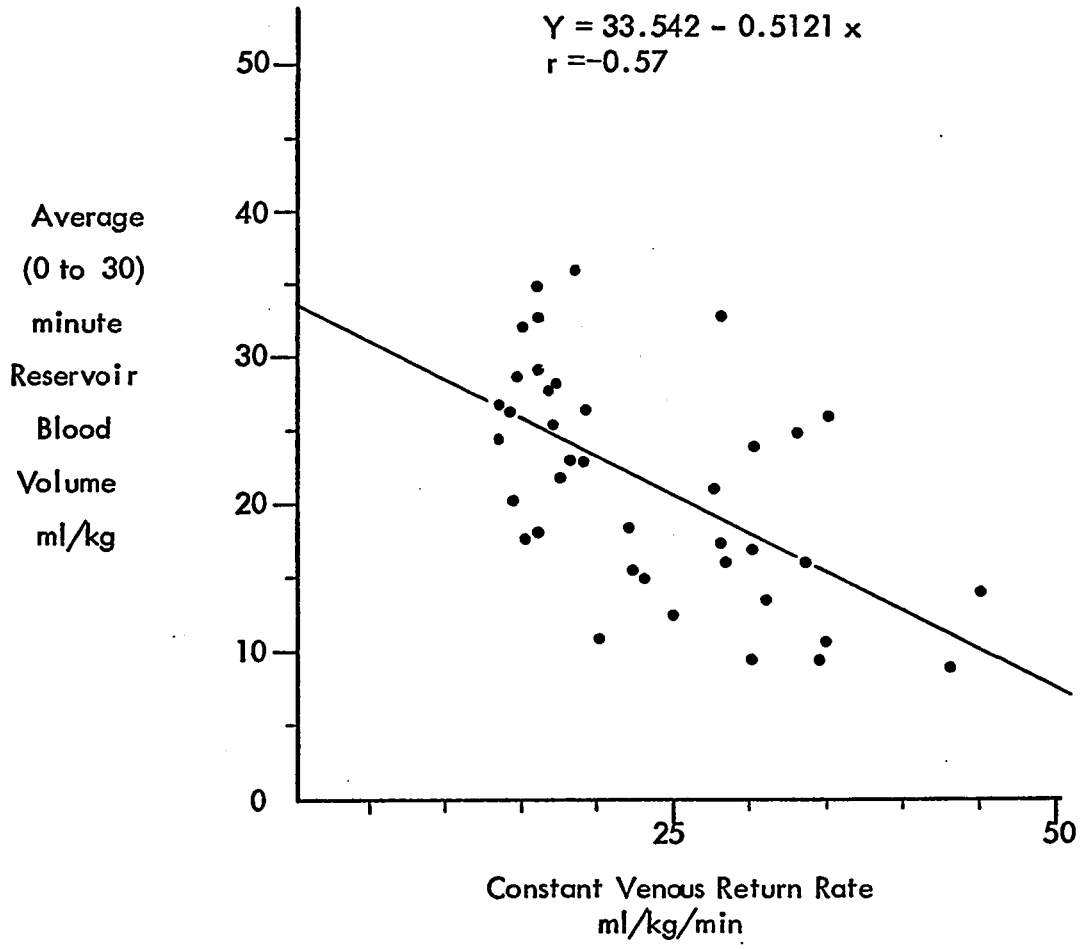


Figure V - 10. Graph shows the relationship between the average (0 to 30) minute reservoir blood volumes and the corresponding values of constant venous return rate, for data from Groups I, II and III experiments (Data obtained from Cols (2) and (7) in Tables VII, VIII and IX, Appendix).

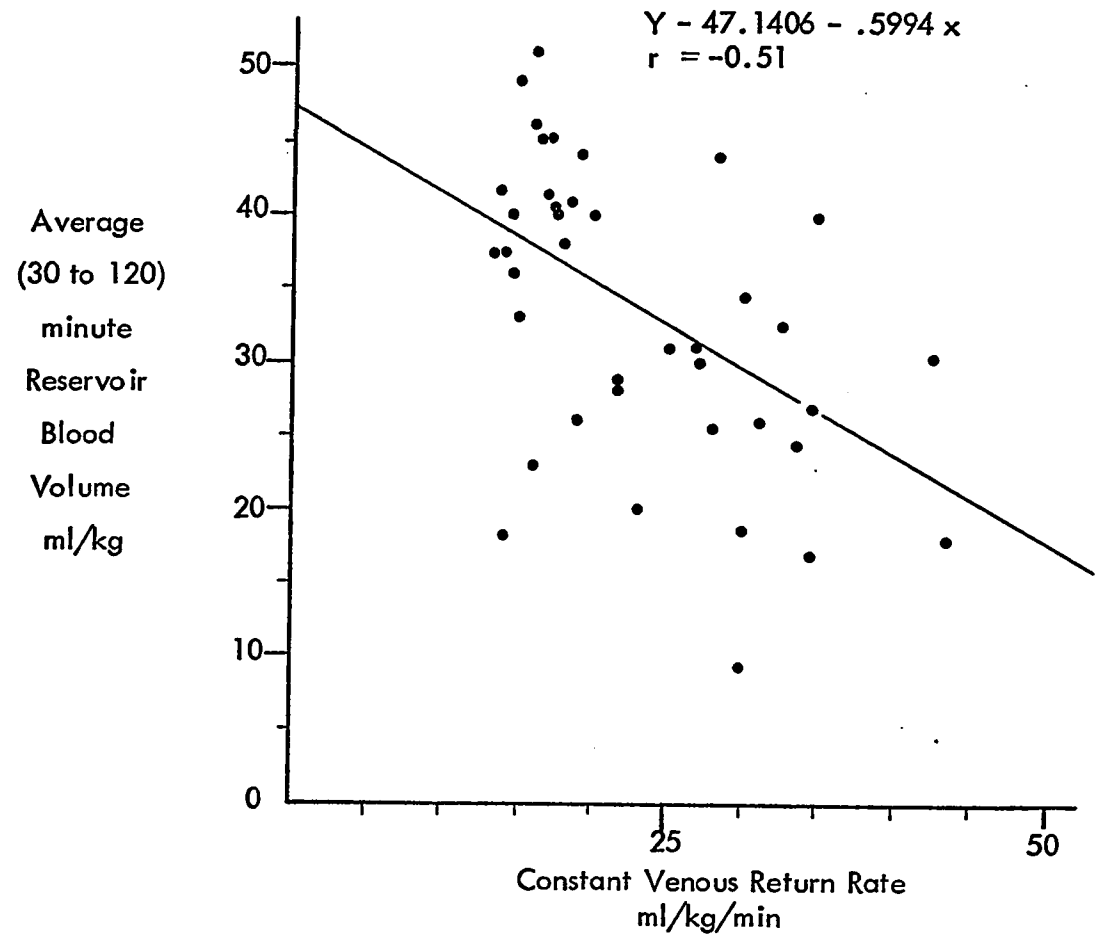


Figure V - 11. Graph shows the relationship between the average (30 to 120) minute reservoir blood volumes and the corresponding values of constant venous return rate, for data from Groups I, II and III experiments (Data obtained from Cols (2) and (8) in Tables VII, VIII and IX, Appendix).

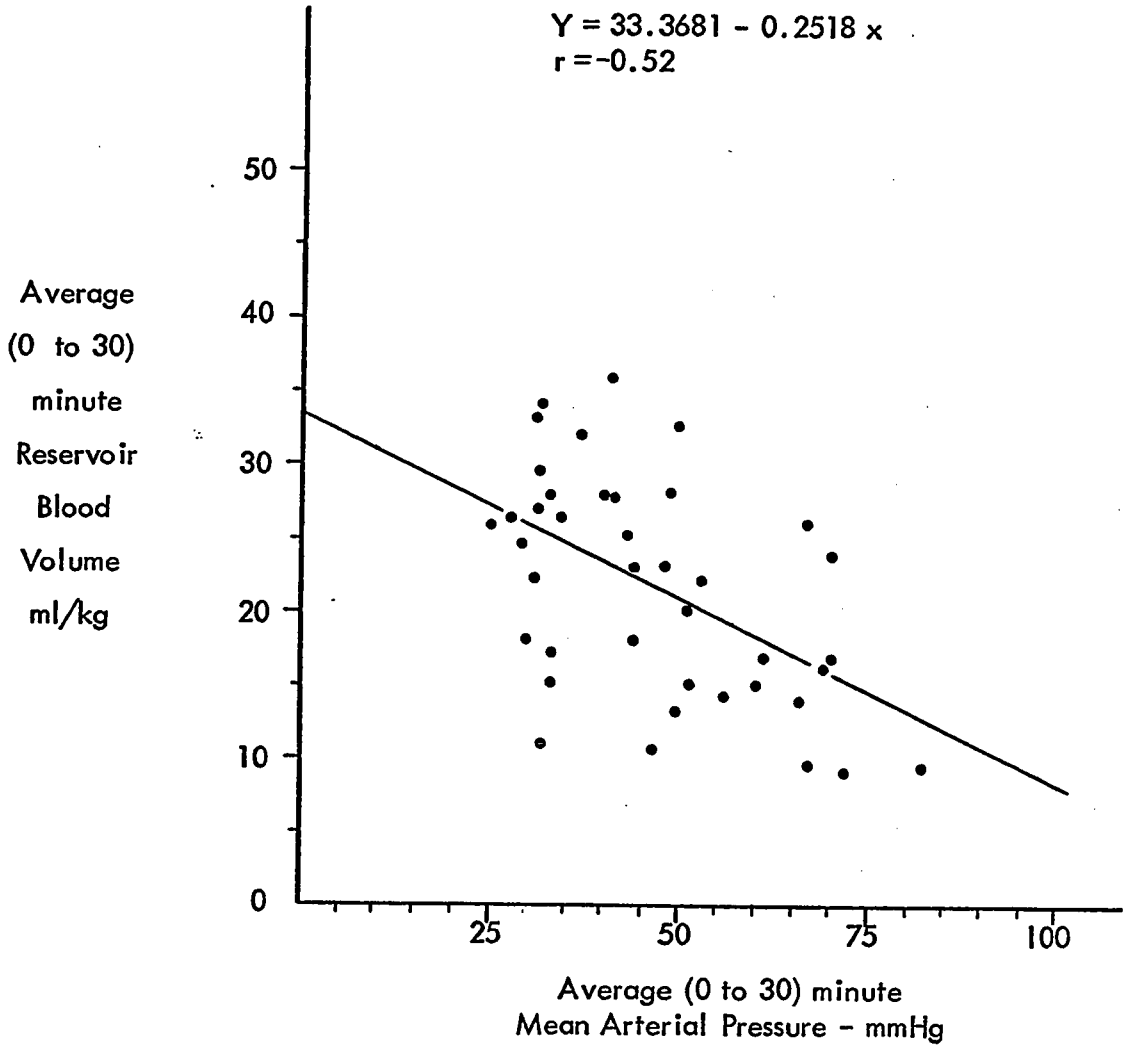


Figure V - 12. Graph shows the relationship between the average (0 to 30) minute reservoir blood volumes and the corresponding values of the average (0 to 30) minute mean arterial pressure, for data from Groups I, II and III experiments (Data obtained from Cols (4) and (7) in Tables VII, VIII and IX, Appendix).

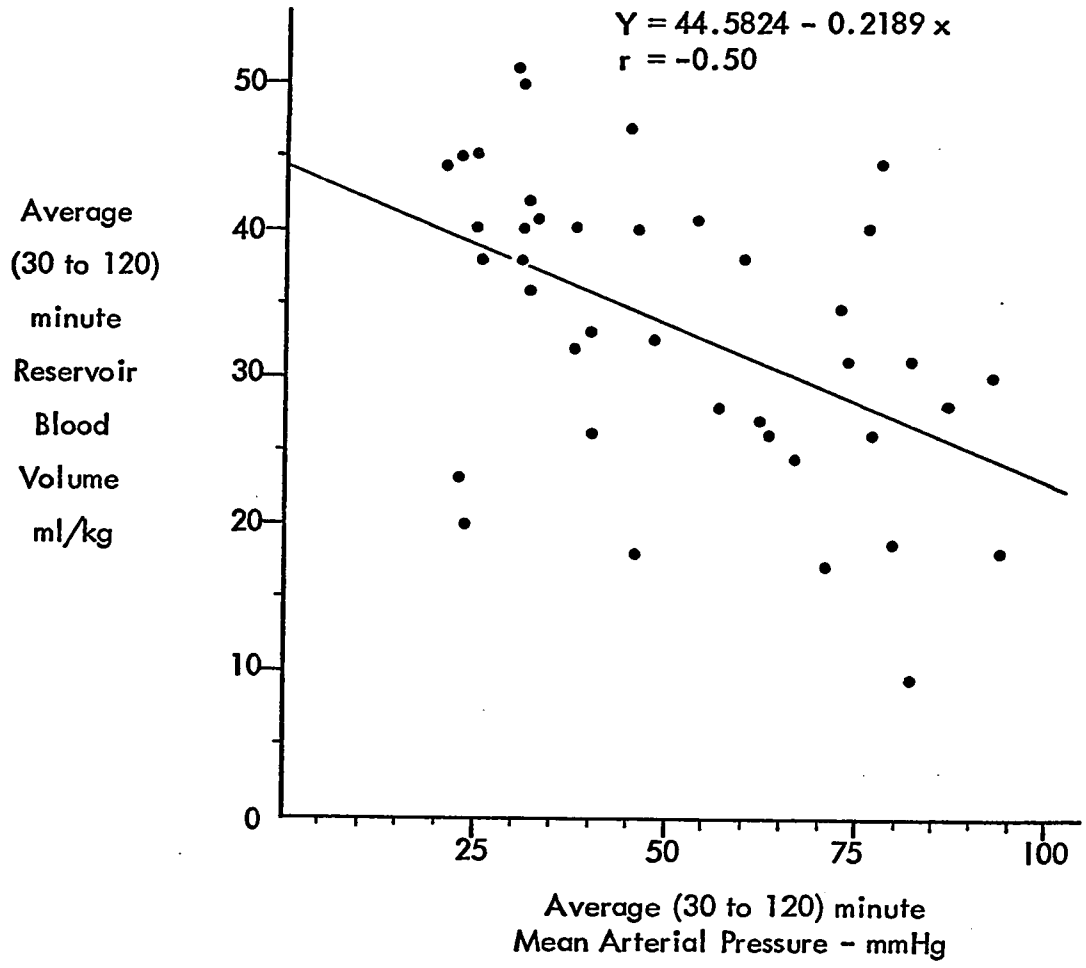


Figure V - 13. Graph shows the relationship between the average (30 to 120) minute reservoir blood volumes and the corresponding values of average (30 to 120) minute mean arterial pressure, for data from Groups I, II and III experiments (Data obtained from Cols (5) and (8) in Tables VII, VIII and IX, Appendix).

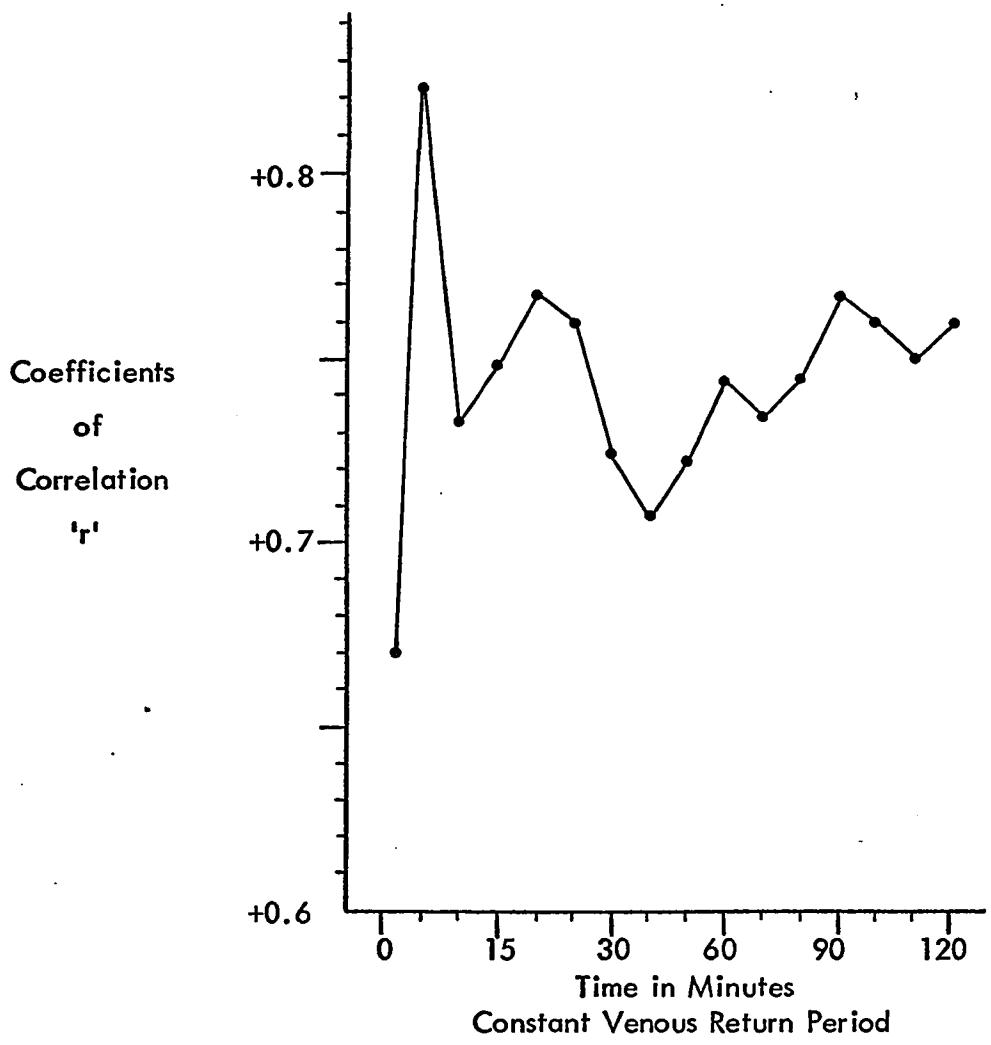


Figure V - 14. Graph of coefficients of correlation 'r' plotted at the 5 and 10 minute times throughout the two-hour experimental period. Data obtained from Groups I, II and III experiments. Each value of 'r' represents a plot between mean arterial pressure and constant venous return (See Development of Set of Curves, Chapter V).

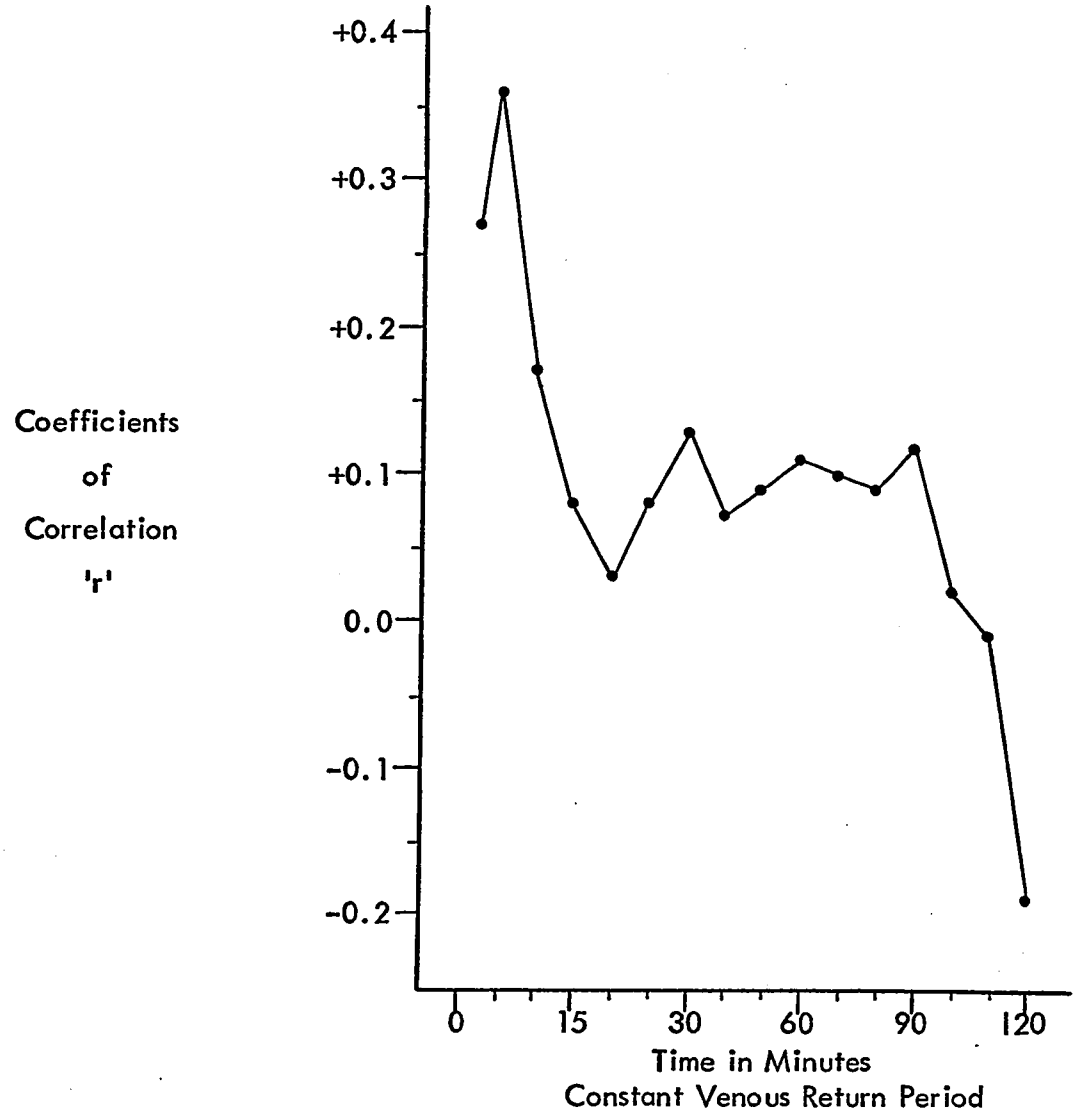


Figure V - 15. Graph of coefficients of correlation 'r' plotted at the 5 and 10 minute times throughout the two-hour experimental period. Data obtained from Group III experiments. Each value of 'r' represents same plot as described in legend of Figure V - 14 (See Development of Set of Curves, Chapter V).

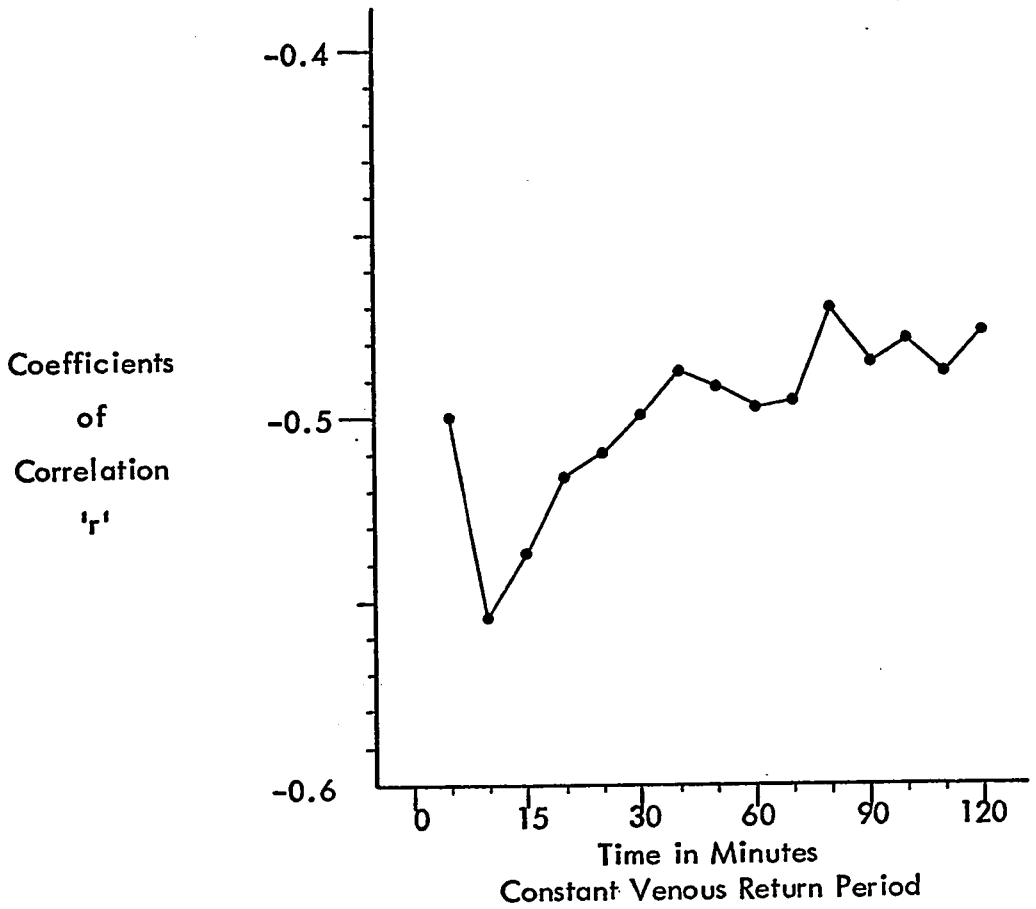


Figure V - 16. Graph of coefficients of correlation 'r' plotted at the 5 and 10 minute times throughout the two-hour experimental period. Data are from Groups I, II and III experiments. Each value of 'r' represents a plot between reservoir blood volume and constant venous return (See Development of Set of Curves, Chapter V).

Figure V - 17. Graph shows the average values of catecholamines, pH and P_{CO_2} determinations at the one- and two-hour times of the experimental period for Groups IV, V and VI experiments. (Data obtained from Tables XXI, XXII and XXV, Appendix).

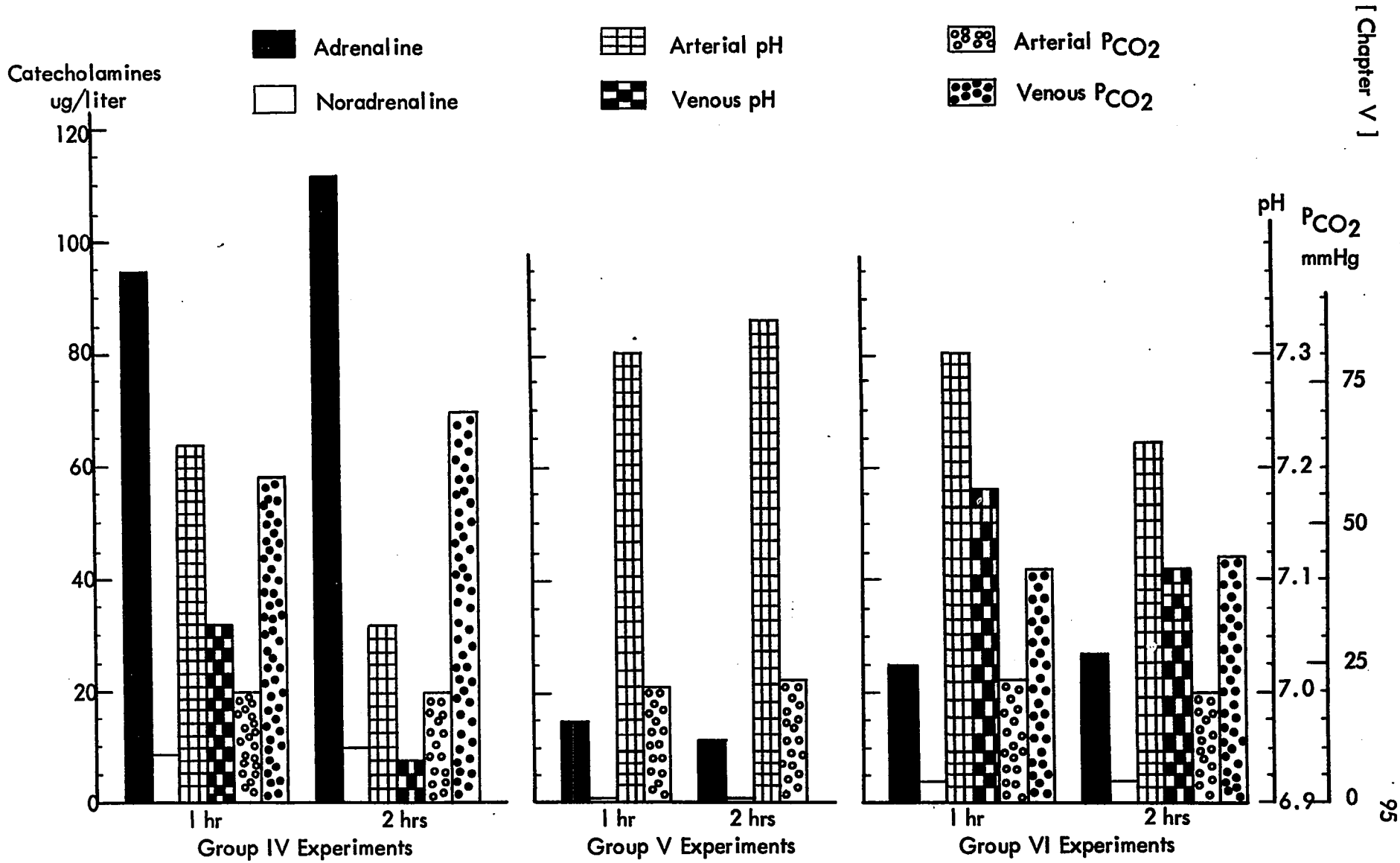

Adrenaline
Noradrenaline
Arterial pH
Venous pH
Arterial P_{CO_2}
Venous P_{CO_2}
Catecholamines ug/liter
120
100
80
60
40
20
0
pH
P_{CO_2} mmHg
7.3
7.2
7.1
7.0
6.9
75
50
25
0
1 hr
2 hrs
Group IV Experiments
Group V Experiments
Group VI Experiments

Figure V - 18. Curve in graph represents the average response in mean arterial pressure for Group VI experiments. Each point is an average value with S.D. (vertical lines) - (Data obtained from Table V - 11; Table XXIV, Appendix).

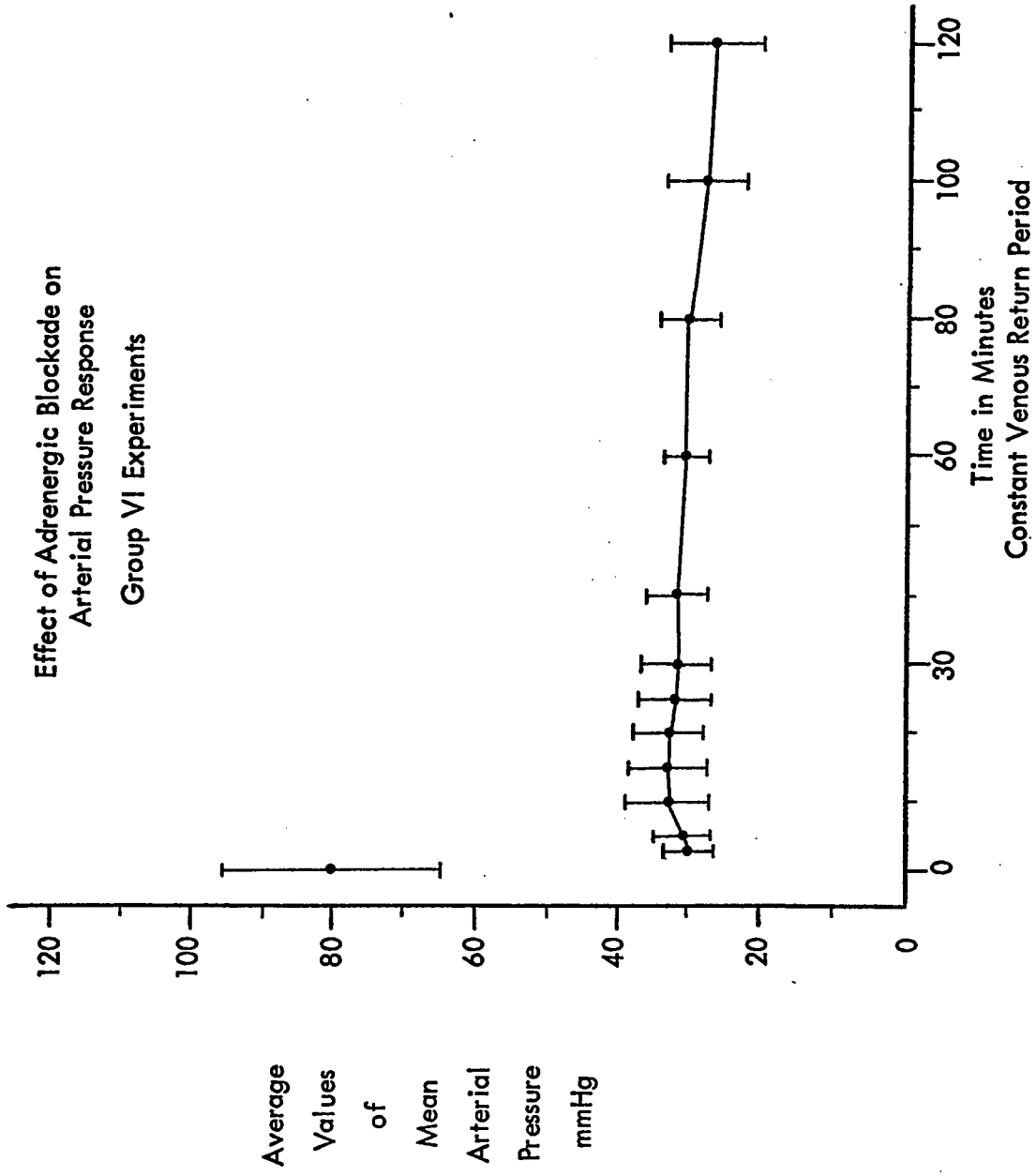

Effect of Adrenergic Blockade on
Arterial Pressure Response
Group VI Experiments
Average Values of Mean Arterial Pressure mmHg
120
100
80
60
40
20
0
0
30
60
80
100
120
Time in Minutes
Constant Venous Return Period

Figure V - 19. Curve in graph represents the average response in reservoir blood volume for Group VI experiments. Each point is an average value with S.D. (vertical lines) - (Data obtained from Table V - III; Table XXIV, Appendix).

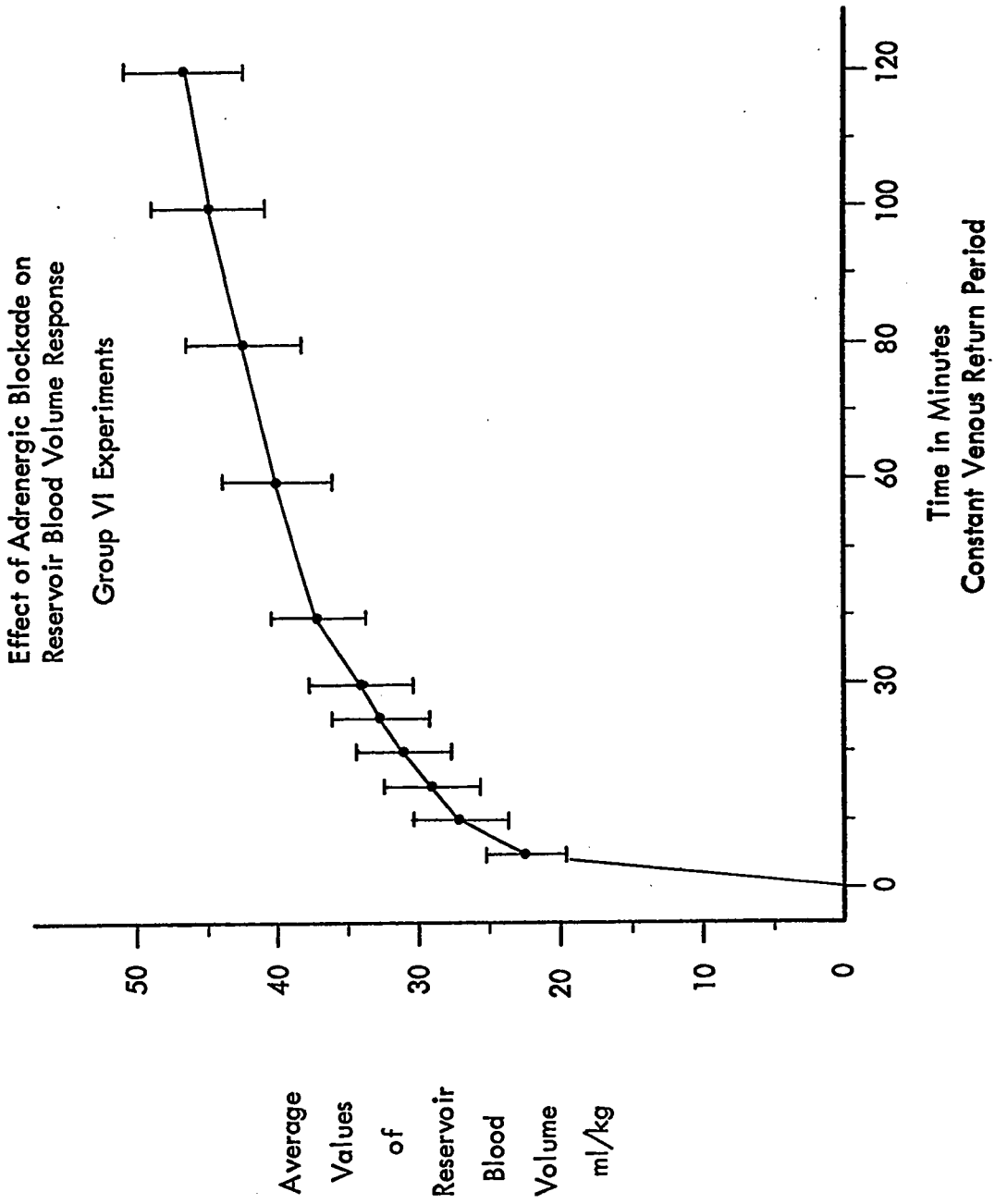

Effect of Adrenergic Blockade on
Reservoir Blood Volume Response
Group VI Experiments
Average Values of Reservoir Blood Volume ml/kg
0
10
20
30
40
50
0
30
60
80
100
120
Time in Minutes
Constant Venous Return Period

Figure V - 20. Set of curves to represent the mean arterial pressure response in Groups I, II and III experiments during the two-hour experimental period, at seven different levels of constant venous return from 15 to 45 ml/kg/min; these values of constant venous return appear in the brackets above and at the right side of each curve. (See Development of Set of Curves, Chapter V).

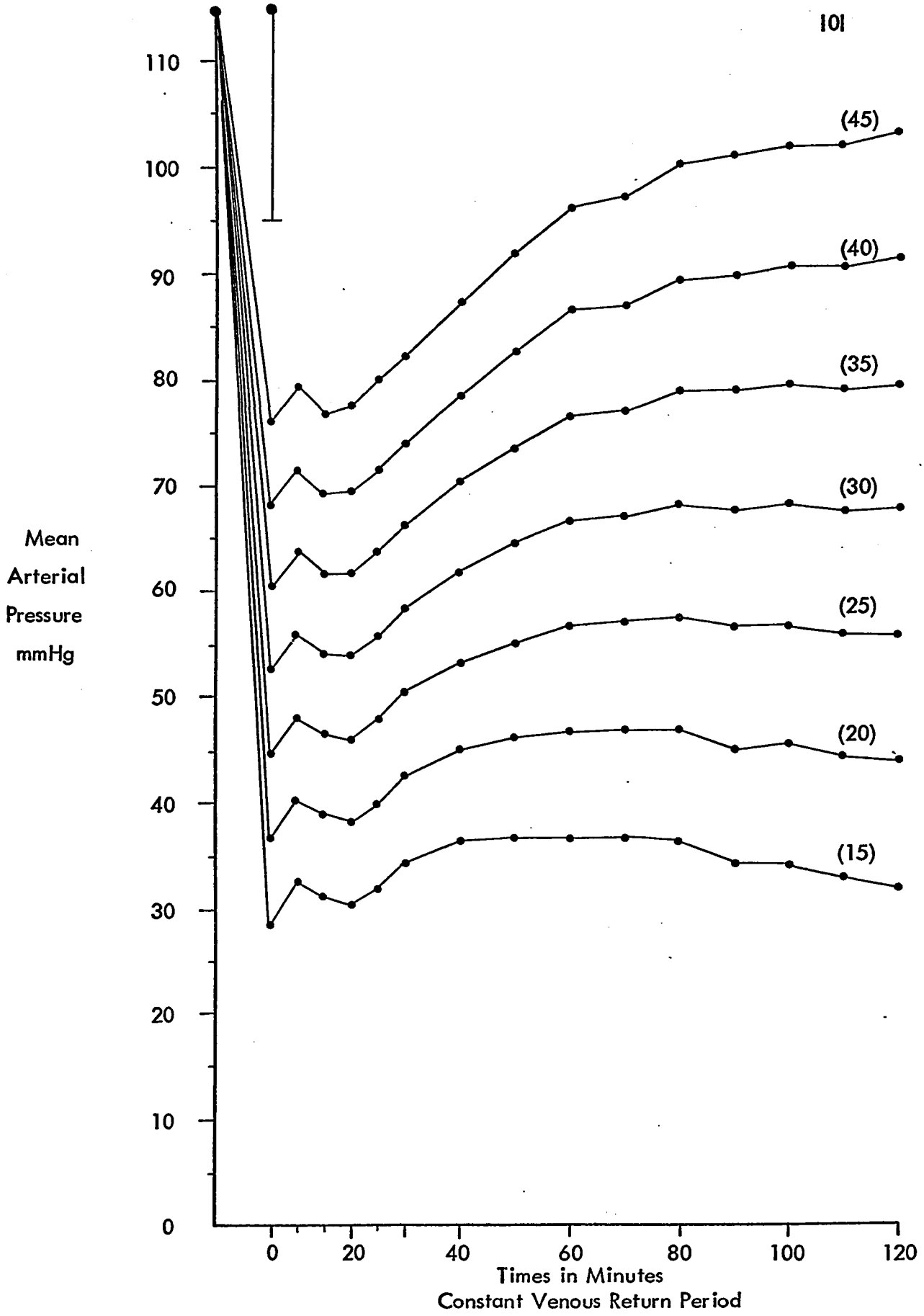

110
100
90
80
70
60
50
40
30
20
10
0
(45)
(40)
(35)
(30)
(25)
(20)
(15)
Mean
Arterial
Pressure
mmHg
0
20
40
60
80
100
120
Times in Minutes
Constant Venous Return Period

Figure V - 21. Set of curves to represent the reservoir blood volume changes in Groups I, II and III experiments during the two-hour experimental period at seven different levels of constant venous return, from 15 to 45 ml/kg/min; these values of constant venous return appear in the brackets above and at the right side of each curve. (See Development of Set of Curves, Chapter V).

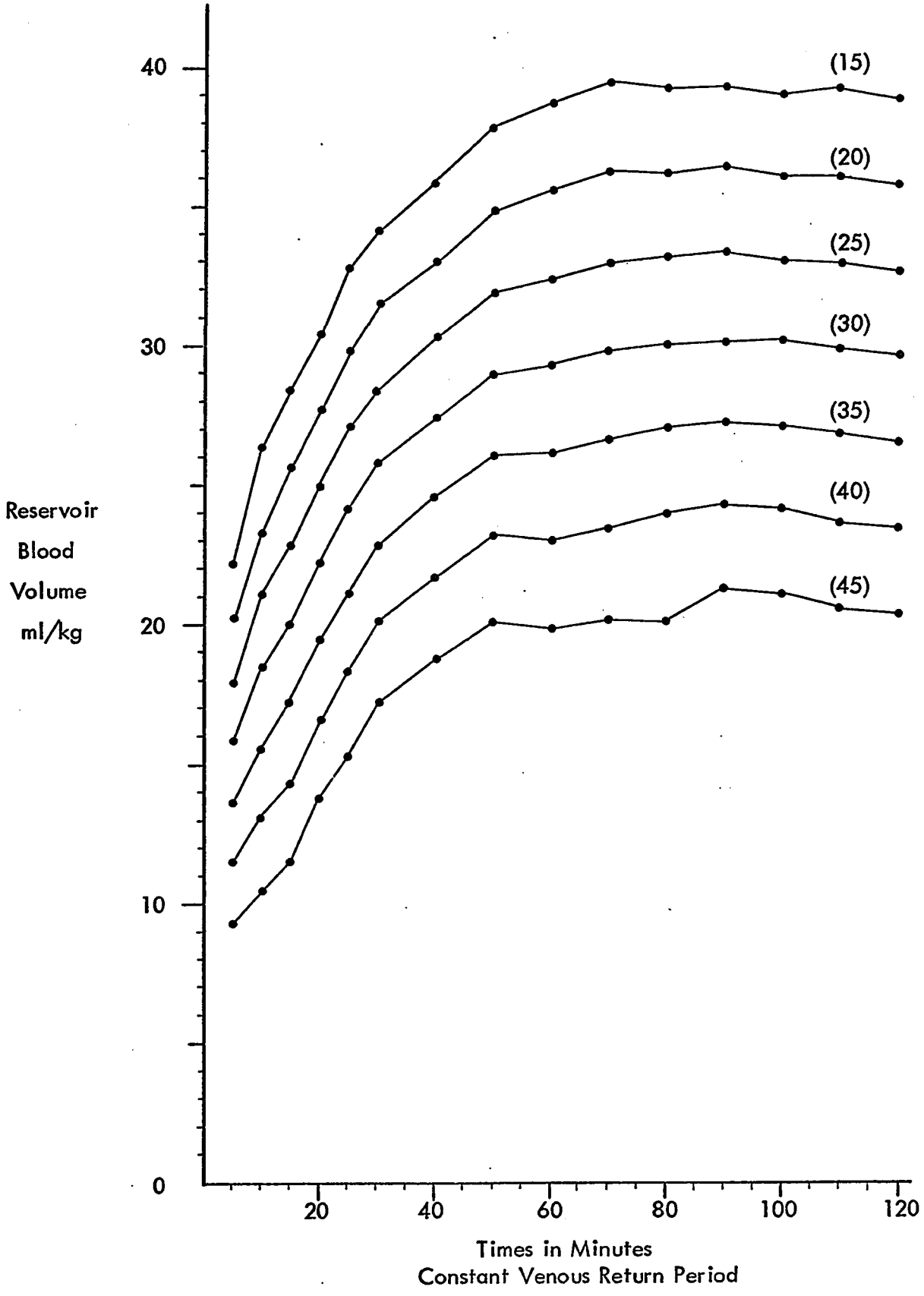

40
30
20
10
0
(15)
(20)
(25)
(30)
(35)
(40)
(45)
Reservoir
Blood
Volume
ml/kg
20
40
60
80
100
120
Times in Minutes
Constant Venous Return Period

Figure V - 22. Mean arterial pressure curves showing time of maximal response (at arrows) during two-hour experimental period at different levels of constant venous return. Curves were obtained by best fit lines drawn through curves of Figure V - 20. Value of constant venous return appear in brackets at left end of curves. (See Development of Set of Curves, Chapter V).

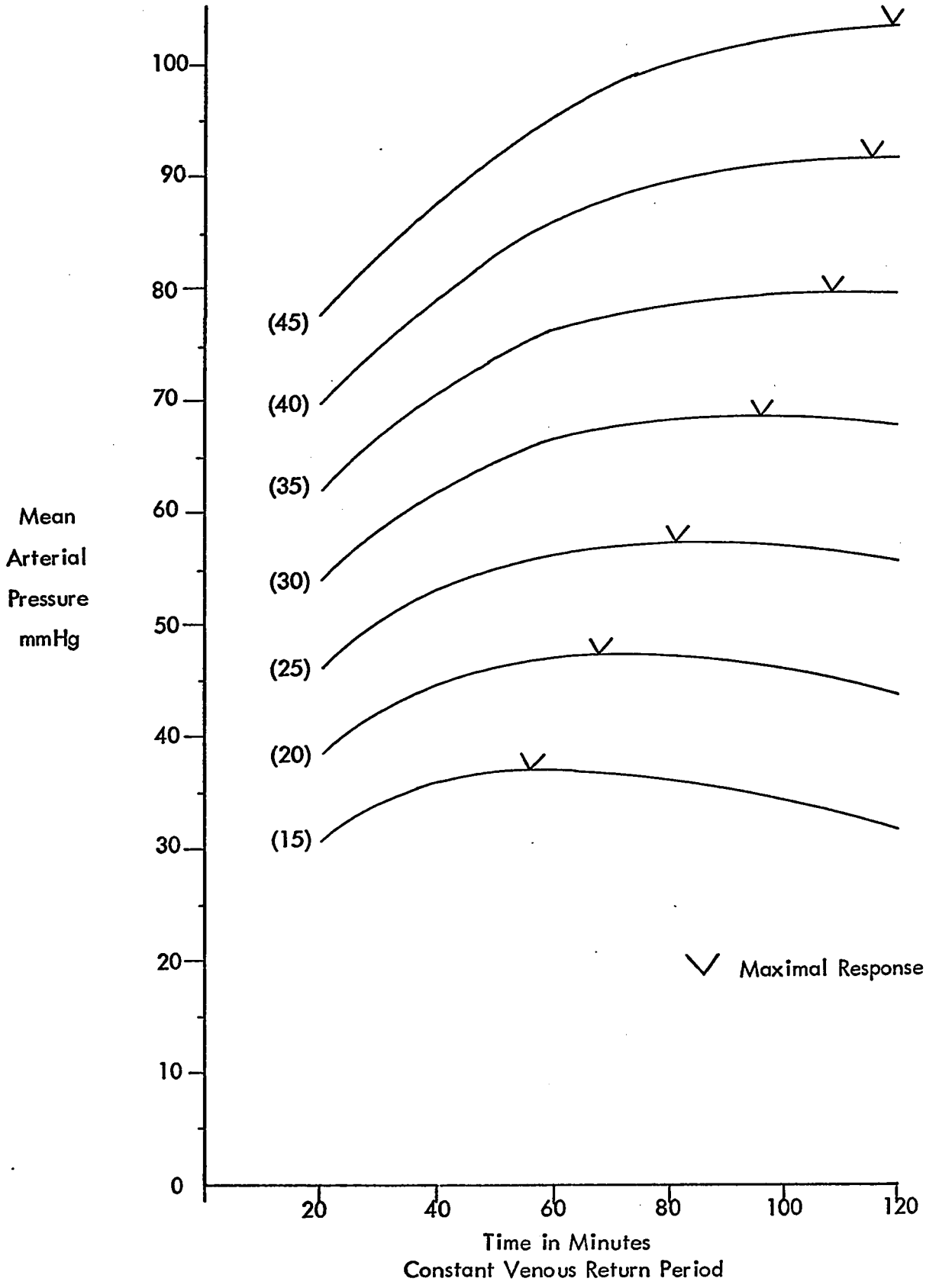

Mean
Arterial
Pressure
mmHg
100
90
80
70
60
50
40
30
20
10
0
(45)
(40)
(35)
(30)
(25)
(20)
(15)
Maximal Response
20
40
60
80
100
120
Time in Minutes
Constant Venous Return Period

Figure V - 23. Reservoir blood volume curves showing time of maximal response (at arrows). The time scale is logarithmic (ln) to show the exponential relationship in the (10 to 60) minute period. Numbers in brackets at left side of curves refer to the values of constant venous return rate. (See Development of Set of Curves, Chapter V).

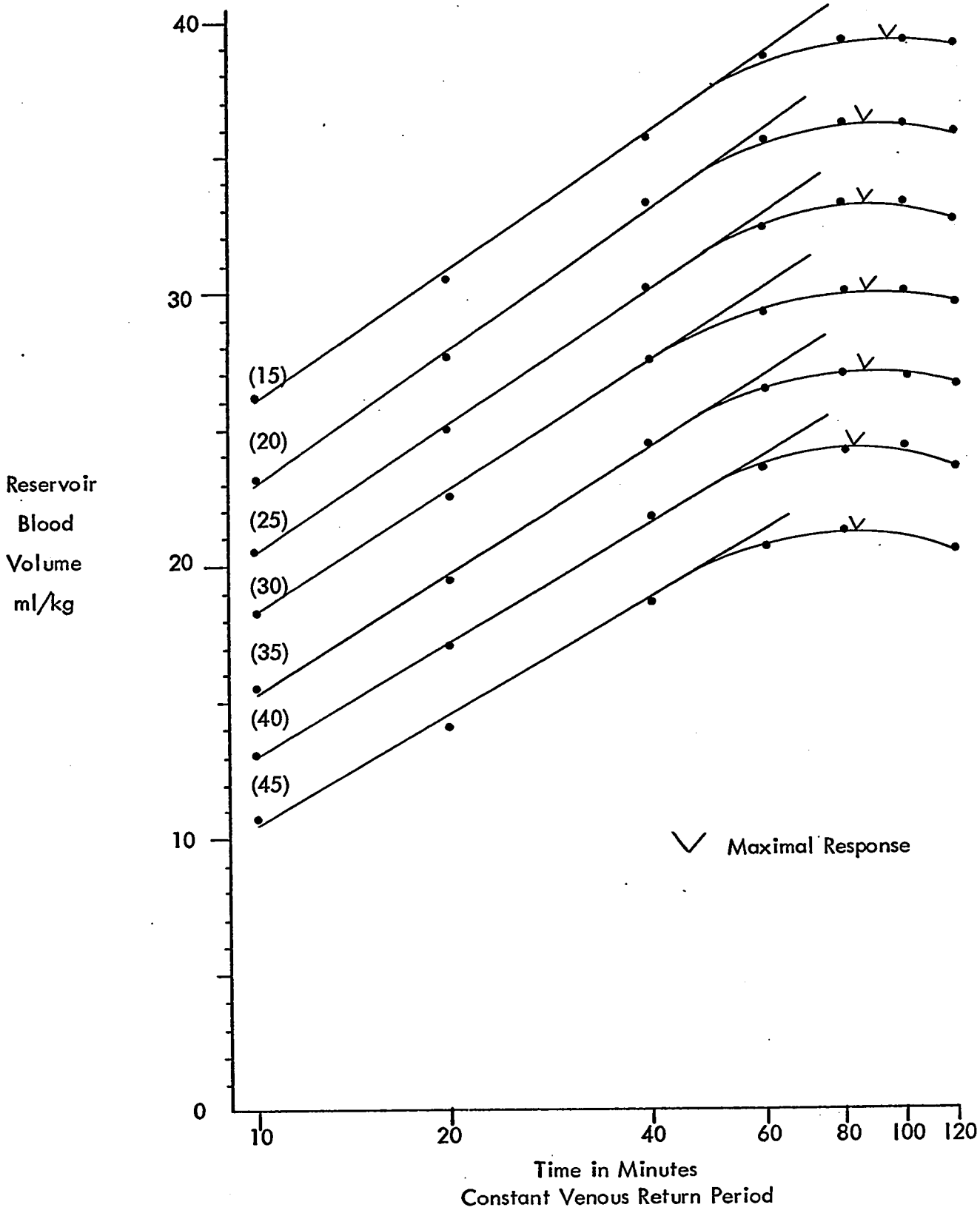
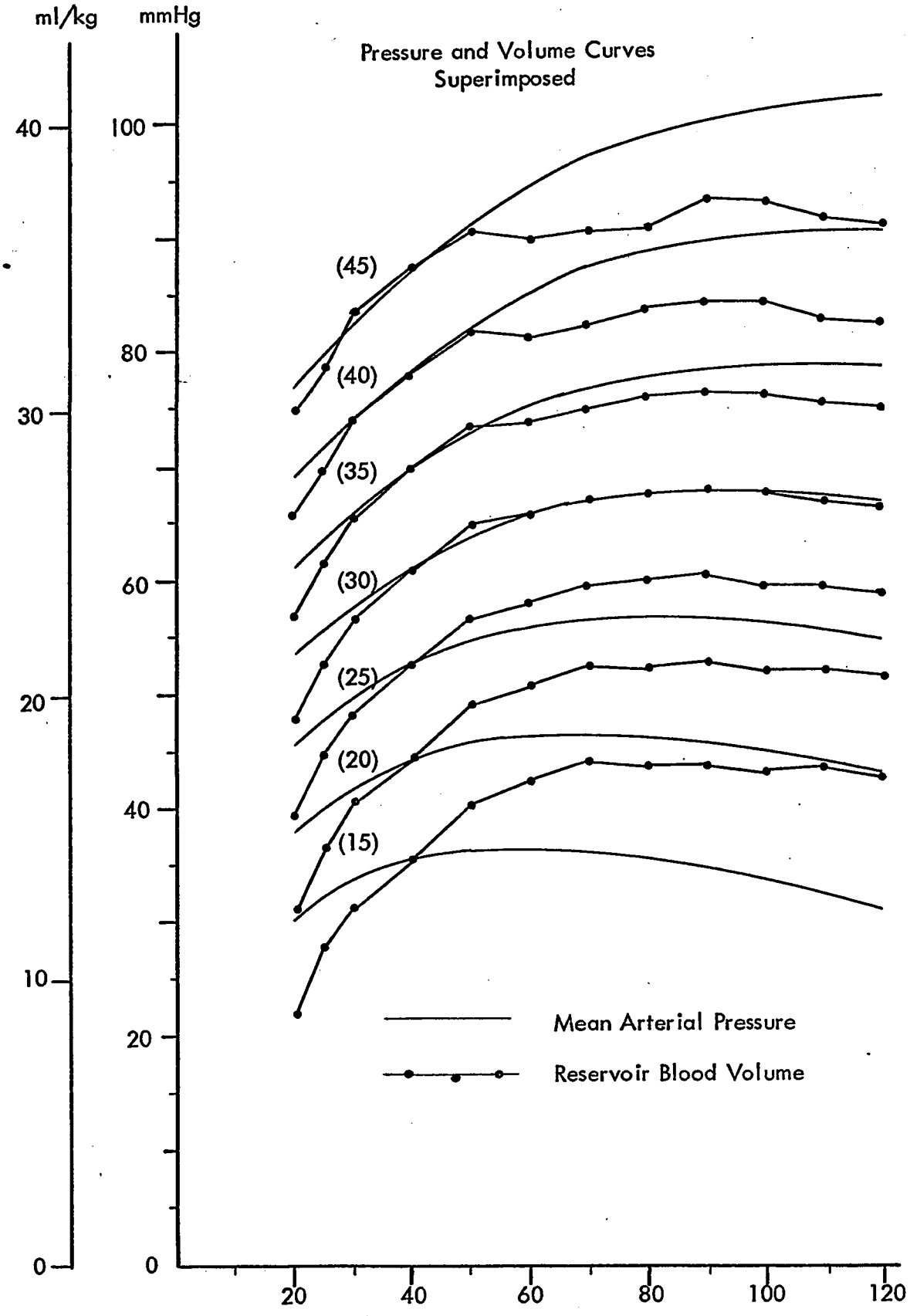

40
30
20
10
0
(15)
(20)
(25)
(30)
(35)
(40)
(45)
Reservoir
Blood
Volume
ml/kg
Maximal Response
10
20
40
60
80
100
120
Time in Minutes
Constant Venous Return Period

Figure V - 24. Graph demonstrates interrelationship between mean arterial pressure and reservoir blood volume curves. The curves of Figures V - 21 and V - 22 were superimposed to intersect at the 40 minute time; the values of constant venous return are in brackets and placed above each pair of curves at the 40 minute time. (See Development of Set of Curves, Chapter V).


ml/kg
mmHg
Pressure and Volume Curves
Superimposed
40
30
20
10
0
100
80
60
40
20
0
(45)
(40)
(35)
(30)
(25)
(20)
(15)
Mean Arterial Pressure
Reservoir Blood Volume
20
40
60
80
100
120

CHAPTER VI

Discussion

METHODS

Effects of Sodium Pentobarbital Anesthesia

Anesthesia is a complicating factor in animal experimentation that is difficult to assess because there are few comparable experiments in the conscious and anesthetized states. Sodium pentobarbital has been widely used as an anesthetic in dogs, probably because of its convenience. A dose of 25 to 30 mg/kg administered intravenously has become generally accepted. When pentobarbital is used in this way several changes appear regularly and possibly the most consistent of these is an increase in heart rate. This effect has been compared in magnitude to either that of atropinization, or cooling of the vagi (Steiner & Calvin, 1967). Tachycardia following pentobarbital is a well confirmed finding by others (Barlow & Knott, 1964; Gilmore, 1965; Olmsted & Page, 1966).

Two studies are especially important because the investigators used trained dogs (Olmsted & Page, 1966; Steiner & Calvin, 1967). This permitted obtaining reliable control values of heart rate, blood pressure and cardiac output in the conscious state. After sodium pentobarbital in the usual dosage the heart rate increased and the increase was maintained. This resulted in a decreased stroke volume, although the mean arterial pressure and cardiac output were essentially unchanged from control levels. However, Olmsted & Page found during the anesthetized state that over a two- to four-hour period there was a gradual increase in mean arterial pressure "due to increase either in peripheral resistance or in cardiac output, but not simultaneous elevations of both." During this two- to four-hour period it was found that tachycardia and reduced stroke volume persisted.

It should be mentioned that pentobarbital anesthesia leads to hemodilution due to splenic sequestration (Hausner, Essex & Mann, 1938; Hahn, Bale & Bonner, 1943; Barlow & Knott, 1964).

In the 42 dogs of Groups I, II and III (Tables VII, VIII & IX, Appendix) control heart rate and mean arterial pressure determined just before the start of the constant venous return period were respectively, 145 beats/min (S.D. = 23) and 115 mmHg (S.D. = 20). These results are comparable to those of Steiner & Calvin (1967) using seven dogs in which the heart rate and mean arterial pressure 30 minutes after sodium pentobarbital anesthesia averaged respectively, 140 beats/min (S.D. = 29) and 112 mmHg (S.D. = 14).

Effect of Thoracotomy on Cardiac Output

Thoracotomy reduces the cardiac output in open-chest dogs (Ferguson, Shadle & Gregg, 1953; Rushmer, 1961; Caldini, Ho & Zingg, 1963; Formoso, Richardson & Guyton, 1964). This reduction from control ranged from 19 to 45 %. In the experiments reported in this thesis the chest was open before the commencement of the constant venous return period for approximately 30 to 45 minutes and probably longer in some of the experiments. It is reasonable to assume that similar reductions in cardiac output occurred during this time. Furthermore, the chief abnormalities after opening the chest reported by Fermoso, Richardson & Guyton (1964) appear to be a 3 to 4 mmHg increase in right atrial pressure, an increase in the A-V oxygen difference and a fall in cardiac output, although the oxygen consumption remained essentially the same. In open-chest dogs, Ferguson, Shadle & Gregg (1953) found the stroke volume index (cc/M^2) to be reduced and Rushmer (1961) concurs in this. They also found a 14 % increase in peripheral resistance and a 45 % reduction in cardiac output. These changes could not be important in the present experiments because venous return was severely restricted and cardiac output held to predetermined levels.

Effects of Ventilation with Oxygen at Atmospheric Pressure

Kety & Schmidt (1948) in young male volunteers showed that breathing 85 to 100 % oxygen caused a 13 % reduction in cerebral blood flow, while Eckenhoff, Hafkenschiel & Landmesser (1947) noted a 11 % reduction in coronary blood flow in the dog breathing pure oxygen. It would appear from this that oxygen has a vasoconstrictor effect. However, it has now been shown that if the hypocapnia accompanying the inhalation of pure oxygen is prevented no cerebral vasoconstrictor effect of oxygen is seen (Turner, Lambertsen, Owen, Wendel & Chiodi, 1957), suggesting that constriction from oxygen actually results from the hypocapnia, which is known to cause cerebral vascular constriction (Kety & Schmidt, 1946). This information is relevant because hypocapnia was present in all experiments and there was evidence of vasoconstriction - especially in Group III experiments (see also discussion of arterial pressure rise in Group III experiments).

Significance of the Venous Return Preparation

In the experiments reported here the dogs were anesthetized with sodium pentobarbital, the levels of venous return to the heart were very low in comparison with normal cardiac output values reported for the dog (Howell, Horvath & Farrand, 1959; Rothe, Love & Selkurt, 1963), ventilation was with 100 % oxygen under positive pressure, and venous return was collected by means of a gravity feed system.

Important aspects of the preparation in this work were: 1. It utilized the animal's own heart to circulate the blood admitted to it, and thus, the arterial vasculature was still subjected to pulsatile flow, which is considered to be of value in the maintenance of normal vasomotor tone (Wilkens, Regelson & Hoffmeister, 1962; Mandelbaum, Berry, Silbert, Burns & Rothe, 1965). 2. It avoided possible adverse effects of artificial systems by maintaining autogenous

pulmonary circulation and oxygenation. Such effects from artificial systems might be complications from micro-bubbles (Friedman, Gelman, Lowenfels, Landew & Lord, 1962) or denatured protein (Dimililer & Trout, 1964). 3. It utilized the animal's own blood thus avoiding the deletrious effects that arise from incompatibility. These are manifest as the 'homologous blood syndrone', which is characterized by mild or severe hyptension, portal venous hypertension, hepatic engorgement, splanchnic sequestration of blood, and fall of the buffer base (Dow, Dickson, Hamer & Gadboys, 1960; Gadboys, Slonim & Litwak, 1962; Hegarty & Stahl, 1967). 4. Surgical procedures were kept to a minimum as follows. The chest incision was small, no large muscle masses were transected and within the right chest cavity the maneuver of ligating the azygos vein and placing circumferential ligatures about the cavae required very little dissection. Furthermore, with the caval drainage technique employed (Fig. III - 1), there was no surgical interference with the heart.

In summary then, the use of the heart and lungs instead of a pump-oxygenator, no donor blood and minimal surgery, were considered to be important contributory factors in the preservation of the physiological integrity of the preparation.

RESULTS AND INTERPRETATION

For purposes of discussion the results of the 42 experiments in Groups I, II and III are broadly referred to as 'low' and 'high' flow experiments. The low flow experiments are equivalent to Group I and the high flow ones to Group III. These terms are only relative because the venous return in the high flow experiments was only 6 to 20 % of the normal value. In a 12 kg dog, setting the venous return at 40 ml/kg/min, which is in the upper range of Group III experiments, would provide a blood flow of only 480 ml/min. This is 20 % of the normal 2.36 L/min cardiac output reported by Howell, Horvath & Farrand (1959) - average of 245 dogs. In the case of the low flow experiments if the flow were set at 13 ml/kg/min in a 12 kg dog (i.e., at the lower range for Group I experiments) the venous return would be 156 ml/min or 6 % of normal.

Responses of Arterial Pressure and Reservoir Blood Volume in the Low Flow Experiments

The prominent feature in this group of experiments was the lack of arterial pressure response during the two hours of constant venous return. At no time did the pressure rise above 50 mmHg. This is especially evident in Figures V - 1 and V - 2. It is also evident from Figure V - 5 that with values of constant venous return rate below 17 ml/kg/min, arterial pressure remained low ('flat type' of response). However, above values of 17 ml/kg/min there was usually a pressure rise during the last 90 minutes of the constant venous return period, particularly when the rates reached levels of 27 ml/kg/min and above ('rise-type' of response). The former flat type response has also been observed to occur in the azygos flow experiment, but in this type of preparation when the venae cavae are occluded no control exists over the blood flow returning via the patent azygos vein.

In these experiments one would expect that with a drop in arterial pressure at the baroreceptors of the magnitude observed, a very strong constrictor

reflex would occur followed by a rise in the arterial pressure. The failure of the arterial pressure to rise in the early part of the constant venous return period might be explained in one or more of the following ways: 1. Failure of the vasomotor centers. 2. Loss of reactivity of the precapillary resistance vessels. 3. Underfilling of the system.

Evidence in the literature indicates that action potentials recorded from sympathetic nerves continue during periods of severe hemorrhagic hypotension (Gernandt, Liljestrand & Zotterman, 1946; Floyd & Neil, 1952; Beck & Dontas, 1955). The last authors remark that sympathetic activity in some animals can also decrease after prolonged hemorrhage. In the experiments of Group I the arterial pressure in several of the dogs was below 30 mmHg (Table X, Appendix) and Lundgren, Lundwall & Mellander (1964) by indirect means showed that depression of the sympathetic discharge could accompany severe bleeding particularly when the arterial pressure was below 30 to 40 mmHg. Rothe, Schwendenmann & Selkurt (1963) also thought that in some of their dogs there was likely central vasomotor failure. The last two groups of investigators report that small transfusions restored sympathetic discharge. It seems from the above unlikely that vasomotor failure would occur within the first few minutes of the constant venous return period, yet in many of the experiments of Group I the arterial pressure showed essentially no response at this time. Later in the period however vasomotor failure could have been a factor. Separate perfusion of the brain via the common carotid arteries with arterial blood might have been helpful in evaluating this aspect.

Loss of reactivity of the precapillary resistance vessels, due to accumulated metabolic products, could presumably account for the lack of arterial pressure response in the low flow experiments. There is no doubt that after reduction of the circulation to the extent that occurred in Group I experiments metabolic acidosis would develop. In the azygos flow preparation (Andreasen & Watson, 1952; Cohen & Lillehei, 1954) the venous return rates are comparable to those in Group

l experiments. Darby, Aldinger, Gadsden & Thrower (1960) carried out the 'azygos flow' experiment for intervals of 10 minutes and even in this short space of time found some evidence of metabolic acidosis; the pH fell, although not severely, and lactate rose two to four times above its normal level. When the venae cavae were occluded the arterial pressure fell to the 20 to 30 mmHg range and remained at this level. Correction of the pH in their experiments by 0.3 M THAM, judging from their figures, did not appear to affect the course of the arterial pressure. This lack of response at this early interval is not due to absence of catecholamines, because, Belisle, Woods, Nunn, Parker, Lee & Richardson (1960), using the same preparation, showed that both noradrenaline and adrenaline blood plasma levels rose, respectively, to + 20 and + 100 ug/liter. Such a catecholamine response suggests strong sympathetic activity. However, acidosis considerably reduces the vascular response to catecholamines (Nash & Heath, 1961) and so might be expected to reduce the effectiveness of vasomotor reflexes.

In experiment No. 608 (Table XXX, Appendix) it is observed that the arterial pH fell to 7.10 after 30 minutes of constant venous return (13.7 ml/kg/min). The fact, that the Pa_{CO_2} was 29 mmHg indicates that this was due to a metabolic acidosis with respiratory compensation. Stronger evidence that metabolic acidosis developed in these low flow experiments can be found in Table XXI (Appendix), because in these experiments the data for the Pv_{CO_2} are available, which showed an average value for the experiments of 57.4 mmHg. The elevated Pv_{CO_2}, taken together with the low pH (average = 7.216) and the low Pa_{CO_2} (average = 19.64 mmHg) would indicate the presence of metabolic acidosis. However, correction of the low pH by the administration of appropriate amounts of 0.3 M THAM had no effect at all on the course of the arterial pressure in three experiments with low constant venous return rates (Table XXX, Appendix).

Mellander & Lewis (1963), in their isolated hindlimb preparation

demonstrated that 20 minutes after holding the systemic arterial pressure at 40 mmHg the reactivity of the precapillary resistance vessels was still 60 % of control, and at one hour was less than 25 % of control. The authors assumed that the reduction in reactivity was due to accumulated metabolic products, as the isolated muscle in their preparation was denervated. It thus seems likely in the low flow experiments that at 20 minutes there was still reactivity present in the precapillary resistance vessels, yet the arterial pressure did not rise above the very low levels observed (e.g., average for Group I experiments was 28.7 mmHg, Table V - II).

In three experiments, summarized in Table XXIX (Appendix), reactivity was tested at the end of the experiment by observing whether or not the arterial pressure rose after the administration of a dose of noradrenaline. In two out of the three experiments, namely, Nos. 551 and 553, the values of constant venous return were comparable to those in Group I experiments. The doses of noradrenaline (levophed) were supramaximal - approximately five times the supramaximal dose of 12 ug/kg/min used by Mellander & Lewis (1963). Inspite of the fact that these doses were administered at the end of the experiment there was still approximately a 100 % increase in arterial pressure in each of these experiments after the noradrenaline administration. Mellander & Lewis also observed that constrictor responses could be obtained with supramaximal doses late in the period of hemorrhagic hypotension.

The experiments of Mellander & Lewis (1963) suggest that reactivity of the precapillary resistance vessels would be only partially lost at the 20 minute interval in the low flow experiments. In the Group I type of experiment there was evidence that metabolic acidosis developed early (Table XXX, Appendix), but correction of the pH by THAM was not followed by a rise in the arterial pressure. It can be assumed with a fair degree of certainty that there was present a strong reflex sympathetic activity, which apparently failed to raise the arterial pressure.

Central vasomotor failure could explain this flat type of response in the arterial pressure, but, assuming such failure did not occur, then it seems necessary to consider the possibility that gross underfilling of the arterial tree may have been the basic abnormality.

The most extreme case of underfilling occurs after complete arterial occlusion; however, under conditions of normal arterial pressure and cardiac output the body has the capability to compensate for obstruction of arterial inflow because of the presence of collateral circulation; the degree of collateral circulation that developes depends on the particular artery involved. In the case of the carotid and femoral arteries, for instance in the dog, it is abundant, while in the case of the coronary, collateral blood flow following obstruction is small (Eckstein, Gregg & Pritchard, 1941). Following arterial occlusion the pressure distally falls drastically but will rise towards normal if the collateral flow is adequate, otherwise it will remain low. If an artery is incompletely occluded, thereby reducing the arterial inflow, the pressure distally will also fall, but again if the collateral flow is adequate it may partially compensate. However, in the venous return preparation, when there was sufficient reduction in the cardiac output, and this was so in the low flow experiments, then the blood flow to the various organs was drastically reduced. Despite the reduction, which in magnitude is comparable to almost total occlusion of the femoral artery, there was no collateral blood flow because the pressure in the collateral arteries was also low. In this situation constriction of the precapillary vessels may well have taken place, but the reduction in blood flow was so severe it was of no avail.

This would be in agreement with Simeone's thesis (1963):

> "Students of shock are now agreed that the abnormality which gives rise to the clinical signs and symptoms is a relative or absolute deficit of blood within the arterial side of the circulation, and that this can be brought about in a number of different ways: . . . . . ."

On the supposition that the arterial side of the circulation was underfilled, it is of interest to examine Figure V - 20 with this thought in mind. The figure shows the set of pressure curves calculated for various levels of constant venous return. It can be observed that the curve representing the response at a venous return rate of 30 ml/kg/min shows the rising type of pressure curve. The difference between this rate and that for the flat type of pressure curve at the level of 15 ml/kg/min is 15 ml/kg/min. In a 12 kg dog (approximate average weight of dogs used in experiments) this difference represents 180 ml per minute of blood flow. This value might approximate the degree of underfilling of the arterial tree in the low flow experiments. If this is so, it suggests that there has to be a certain degree of distention of the arterial tree before the precapillary resistance vessels can operate effectively.

Response of Arterial Pressure in the High Flow Experiments

The arterial pressure in the high flow experiments, in contrast to the low flow experiments, exhibited a biphasic course. The pressure increments undoubtedly are a reflection of compensatory mechanisms, which may not be unique to this type of preparation. For instance, Chien (1967) in his review on the role of the sympathetic nervous system in hemorrhage mentions that there appears to be a biphasic characteristic to the compensatory response in hemorrhagic shock. As can be seen from Figures V - 3 and V - 4 and the upper 3 to 4 curves of Figure V - 20 there was a hump in the curves which usually occurred 5 to 15 minutes after the pump was started, then the pressure slowly rose furing the remainder of the two-hour interval. This was the same type of response noted in the preliminary experiments of Elliot (1961b) - the curves for the nine experiments being reproduced here in Figure VI - 1. The curves referred to in Figure VI - 1 are especially those marked by numbers 24, 30 and 37 in brackets in the lower graph of the figure. The experiments of Group III (high flow experiments) in general confirmed this rise-type of pressure response that seemed to occur when the venous return to the heart was held constant at values

between 25 and 40 ml/kg/min.

The gradual rise in arterial pressure indicates an increase in resistance to the pump-controlled constant cardiac output. This could not be due to intravasation of fluids, because this would occur in the low pressure or venous side of the circulation which was open to the reservoir. It must have therefore been due to a progressive constriction of the precapillary resistance vessels, which are primarily arterioles. This phenomenon could have been due to a generalized constriction or limited to specific vascular beds.

There must have been a noradrenergic sympathetic component in the pressure rise as blocking the alpha receptors in Group VI experiments eliminated the pressure rise (compare Figs. V - 5 and V - 18). The arteriolar response may also have been potentiated by cortical steroids. The cortical steroids are known to increase following hemorrhage (Hume, 1961). Halpern, Benacerraf & Briot (1952) showed that the effect of adrenaline could be potentiated by cortisone. Fritz & Levine (1951) with the Chambers-Zweifach rat mesoappendix preparation observed in the adrenalectomized rat that responsiveness to noradrenaline could be restored by topical application of aqueous adrenal cortical extracts. Some authors have disagreed with this viewpoint (Small, Weitzner & Nahas, 1959; Sambhi, Weil & Udhoji, 1962; Nagy, Tárnoky & Petri, 1965). The presence of hypocapnia may also have been a potentiating factor, in view of the report by Turner, Lambertsen, Owen, Wendel & Chiodi (1950) that cerebral vasoconstriction accompanying oxygen inhalation would not occur if hypocapnia were prevented.

The renin-angiotensin system has been implicated in the poor response to hemorrhage that nephrectomized dogs and rats show, compared to non-nephrectomized (Bahnson, 1943-44; Collins & Hamilton, 1943-44; Mikasa & Masson, 1961). In high flow experiments performed with the venous return preparation on six dogs in which the renal arteries were either clamped or the kidneys removed, the arterial pressure response was less at the 60, 70, 80 and 90 minute times when compared

with six dogs similarly treated except for sham laparotomies ($P < 0.05$; Elliot, 1962b). This suggests that angiotensin may have been present in the Group III experiments and influencing the arterial pressure. It may be argued that the arterial pressure was not particularly low in this group; however, it must be recalled that Hodge, Lowe & Vane (1966) presented evidence to show that the stimulus for renin release may be a low central venous pressure, which was very likely present in Group III experiments. In Group VI experiments, however, if angiotensin were present it did not overcome the effects of the phenoxybenzamine blockade, which it is capable of doing (Douglas, 1965).

With regard to the Group VI high flow experiments (phenoxybenzamine blockade) a further consideration is necessary in view of the inference that phenoxybenzamine acts directly on arteriolar smooth muscle distal to the endings of the sympathetic nerves or causes release of some systemic vasodilator substance (Duff, 1956). Diana & Masden (1966) imply that this substance is histamine and show that the responses after separate intra-arterial injections of phenoxybenzamine and histamine - under conditions of constant arterial inflow in the dog hindlimb preparation - are similar, namely, arteriolar dilatation, peripheral digital vein constriction and reduction in peripheral venous pressure. These findings, in the case of histamine, confirmed Haddy's previous observations in 1960. If histamine were released in Group VI experiments causing arteriolar dilatation, which would be superimposed on the alpha blockade, it could serve to explain the presence of the very low levels of arterial pressure observed in this group (for additonal speculation, see below, under - Changes in Adrenaline and Noradrenaline . . . .).

Hemodilution and Hematocrit Determinations

It was mentioned above that intravasation of fluid would not likely contribute to the arterial pressure rise because the venous system was open to the reservoir. Hemodilution was nevertheless shown to occur (Group VII experiments, Table XXVII, Appendix). It is of interest that in the non-splenectomized dogs, the hematocrit values remained essentially constant in the presence of hemodilution.

Presumably this was due to the addition of red cells from the contracting spleen (Table XXVII, Appendix). In the splenectomized dogs, on the other hand, there was a progressive reduction in hematocrit values during the constant venous return period (Group IX experiments, Table XXVIII, Appendix).

Reservoir Blood Volume Changes in the Low and High Flow Experiments

In order to evaluate the reservoir blood volume changes it is worthwhile to consider the following aspects. Because the venous return was syphoned into the reservoir bottle, the central venous pressure in the venae cavae in all experiments would be atmospheric. There would therefore always be a gradient between the capillary bed and the juxtacardiac caval vessels. The amount of blood entering the systemic arterial system was held constant in these experiments. However, the quantity of blood entering the reservoir bottle exceeded this value during approximately the first hour of the constant venous return period, in both the low and high flow experiments. During the last hour the amounts entering and leaving the arterial and venous systems respectively were about equal. The extra blood came from both systems, the venous likely contributing the greater share. The important question is, however, how was this additional blood mobilized? Folkow, Lewis, Lundgren, Mellander & Wallentin (1964) have some helpful thoughts on this aspect:

> "If venous outflow pressure is kept very low, a decrease in mean capillary pressure along with a neurogenic increase of the pre- to postcapillary resistance ratio can so lower venous transmural pressure as to precipitate a collapse of the veins. A profound expulsion of blood would then occur, whether the venous smooth muscles were simultaneously activated or not. In this situation passive-elastic factors would overshadow, to a considerable extent, active venous contractions and in the venous collapse phase, the active component would hardly reveal itself at all."

It would seem that active constriction of the capacitance vessels was responsible for the drainage rate into the reservoir bottle being higher than the pump rate, but, passive-elastic factors may also have contributed. There is some

indirect evidence bearing on this aspect. In Group VI experiments, inspite of the fact the venous flow rates were equivalent to those in the high flow experiments of Group III, the adrenergic blockade was so effective that the arterial pressure levels were not different from Group I experiments (e.g., 30 mmHg). Assuming that the capacitance vessels were also blocked, one would expect pooling of blood to occur on the venous side of the circulation; instead, in Group VI experiments the same amount of blood collected in the reservoir as in Group I experiments. Therefore, in the absence of vasoconstriction, passive-elastic factors must have maintained the pressure gradient along the veins. Lundgren, Lundwall & Mellander (1964) felt that the reactivity in the capacitance vessels in cats could be blocked by phenoxybenzamine (1-3 mg/kg intra-arterially to the region studied), but, Thulesius & Johnson (1966) found that the venous resistance was attenuated but not abolished by phenoxybenzamine. There is the possibility then, that the capacitance vessels were not blocked. The confusion on this aspect is heightened by the thought that histamine, if liberated, possibly causes venous constriction (Haddy, 1960; Diana & Masden, 1966).

Table VI - I summarizes the reservoir blood volume changes. The difference between Groups I and III seems to be that at the higher flow rate arteriolar constriction likely traps more blood within the arterial tree, thus reducing the amount of blood collected in the reservoir. When phenoxybenzamine blockade (Group VI experiments) precedes the high flow experiment (Group III type of experiment) then the arteriolar or precapillary resistance trapping effect is eliminated and the extra blood passes into the venous system and then into the reservoir, possibly as described above. Thus, in Groups I and VI experiments the circulating blood volumes must have been about equal, but at twice the rate in Group I because of less blood flowing through the tissue (compare Groups IV & VI, Table V - V).

Changes in Adrenaline and Noradrenaline Blood Plasma Levels in Low & High Flow and Adrenergic Blockade Experiments

The plasma levels of both catecholamines in the low flow experiments (Group) IV became elevated (Table V - IV). Adrenaline levels reached average values of 96 and 116 ug/liter respectively at the one- and two-hour times. These values were approximately ten times higher than the noradrenaline values. The occurrence of higher adrenaline levels is characteristic of the picture seen in hemorrhagic shock in dogs (Lund, 1951; Millar & Benfey, 1958; Walker, Reutter, Shoemaker, Friend & Moore, 1959). The catecholamine levels observed in Group IV experiments were higher than those reported by Lund (1951) and Millar & Benfey (1958); the explanation might be that these authors used arterial blood for the determinations, whereas, in the venous return preparation the venous plasma samples were collected from the inferior vena cava from a catheter whose tip was close to the suprarenal veins.

In contrast to the low flow experiments, plasma catecholamine levels in the high flow experiments were much lower (Table V - IV). In fact the noradrenaline values in Group V experiments were in the normal range although the adrenaline levels were elevated. For example, the average levels of adrenaline at the one- and two-hour times were respectively, 15 and 13.5 ug/liter; these levels occurred despite arterial pressures between 60 and 90 mmHg (Table V - I). Other reports indicate that more severe degrees of hypotension are necessary before the adrenaline output increases (Lund, 1951). This may point to the importance of reduced blood flow as a stimulative factor. The arterial pressure was fairly well maintained in Group V experiments (Tables XII & XX, Appendix), but the cardiac output was still greatly below normal in these experiments; therefore, regionally reduced blood flows may have been important in the release of adrenaline in these experiments.

In Group VI experiments the phenoxybenzamine blockade eliminated the arterial pressure rise during the constant venous return period and caused extremely low levels of arterial pressure, similar to those seen in Group I experiments (compare Groups I & VI, Table V - I). Phenoxybenzamine blocks the alpha receptors of the effector organs but, does not interfere with the release of norepinephrine (Rosell, Kopin & Axelrod, 1963; Nickerson, 1965). As would be expected, the catecholamines were therefore elevated in this group. Harrison, Bartlett & Seaton (1967) found a similar experience with phenoxybenzamine administered prior to hemorrhagic shock. The catecholamine elevation in Group VI experiments was less than expected with arterial pressures as low as 30 mmHg (compare Tables V - IV; V - VI & V - VII). These results suggest, that not only were the low arterial pressures in Group I experiments important, but also, that the extremely low blood flows were likely contributory factors leading to the high levels of catecholamines in the blood plasma. The reduced blood flows could have had their effect via ischemia of the carotid chemoreceptors (Comroe, 1964). In group VI experiments, on the other hand, inspite of the low arterial pressure the blood flow was approximately twice that of the Group I experiments, and therefore, probably perfused the chemoreceptors more effectively.

It was noted above, under the discussion of the arterial pressure response in the high flow experiments, that release of histamine by phenoxybenzamine might have been a factor in producing the low levels of arterial pressure in Group VI experiments. There is still another possibility. Stimulation of the beta adrenergic receptors produces peripheral arterial vasodilation (Ahlquist, 1948). Thus, in the presence of alpha adrenergic blockade, only beta receptors would be stimulated by adrenaline and noradrenaline(Glick, Epstein, Wechsler & Braunwald, 1967). Since both these catecholamines were elevated in Group VI experiments this would be another mechanism that might have played a role in bringing about the severe hypotension that occurred in this group of experiments.

Relationship Between the Changes in Arterial Pressure and Reservoir Blood Volume

The set of curves depicted in Figure V - 24 serve to summarize the changes and interrelationship between these two variables in Groups I, II and III experiments. At the low levels of constant venous return rate the arterial pressure curve is observed to plateau earlier than the curve for the reservoir blood volume; this is especially noticeable at the 15 and 20 ml/kg/min levels of venous return. This could mean that the precapillary resistance vessels fail before the postcapillary ones, which would agree with the thesis of Mellander & Lewis (1963); but, as pointed out above, there is the possibility that underfilling of the arterial side of the circulation is the basic defect of the precapillary resistance vessels at these very low levels of venous return. It would seem that the capacitance vessels are capable of constricting even at the lowest levels of venous return, although, as mentioned active constriction could have been masked by passive collapse of the veins.

As the levels of venous return were increased the arterial pressures showed a steady rise in pressure, especially in the (30 to 120) minute interval, and accordingly the curves for the two variables tend to rise at the same rate (e.g., at 30 ml/kg/min level of constant venous return).

SUMMARY AND CONCLUSIONS

1.) When the venous return to the heart was experimentally reduced in anesthetized mongrel dogs there occurred a varying degree of hypotension depending on the severity of reduction in the cardiac output.

a) If the cardiac output was reduced sufficiently there was almost no pressure rise following the initial hypotension to 30 mmHg. The most probable explanation was gross underfilling of the arterial side of the circulation; however, the metabolic acidosis that developed could have been a contributory factor. The range of venous return responsible for this type of response was determined to be 13 to 17.5 ml/kg/min (called the 'low flow' experiments). The arterial pressure never rose above 50 mmHg during the two-hour experimental period, and the slight rise usually occurred within the first 15 to 20 minutes.

b) A lesser reduction in cardiac output caused greater filling of the arterial tree and this appeared to allow the precapillary resistance vessels to operate more effectively. This resulted in a rise in the arterial pressure above the initial low levels following fixation of the venous return to the heart, to approximately 70 to 100 mmHg. This type of pressure response occurred frequently with constant venous return rates above 27 ml/kg/min (called the 'high flow' experiments). The fact that this type of response was eliminated by the prior administration of the adrenergic blocking agent, phenoxybenzamine, implies that the arteriolar constriction was dependent on alpha receptor stimulation. Other mechanisms, however, may have been operative, and several possibilities were suggested and discussed.

2.) The outflow of blood into the reservoir bottle was mainly due to a reduction in the venous capacitance vessels of the vascular system. Active veno-constriction probably played a role in the movement of the blood, but passive-elastic factors could not be excluded. The fact that large quantities of blood collected in the reservoir in the adrenergic blockade experiments points to the latter possibility, based of course on the assumption that alpha receptors were present in the venous side of the circulation and were actually blocked.

3.) Adrenaline and noradrenaline plasma concentrations became elevated to approximately 100 and 10 ug/liter, respectively, in the low flow experiments. The occurrence of higher adrenaline than noradrenaline levels, is similar to what has been observed in hemorrhagic shock preparations. In the high flow experiments, inspite of the fact that arterial pressures were almost within the normal range, there still occurred elevations in the plasma adrenaline concentration. In the phenoxybenzamine experiments the adrenaline and noradrenaline concentrations were elevated even though the cardiac output was double that of the low flow experiments. This was an expected response in view of the severe hypotension in these experiments, together with the fact that the phenoxybenzamine does not block the release of catecholamines.

4.) The low cardiac outputs in the low flow experiments caused a metabolic acidosis, which was characterized by low arterial pH and low arterial P_{CO_2} and high venous P_{CO_2}.

5.) Hemodilution occurred in these experiments. If the spleen was not removed the hematocrit values stayed constant, probably because of the addition of red cells from the contracting spleen. In the experiments carried out in dogs after splenectomy, progressive reduction in hematocrit values occurred during the experimental period.

6.) It was evident from the curves developed to show the over-all changes in arterial pressure and reservoir blood volume, that the curves for the arterial pressure reached a plateau before the reservoir blood volume ones - particularly in the very low flow experiments. This would suggest that the precapillary resistance vessels failed to respond when the venous capacitance vessels were still contracting. However, with regard to the latter vessels, there is the added qualification that the progressive rise in reservoir blood volume, which was seemingly due to veno-constriction, might have in fact been in part or whole, due to passive-elastic collapse of the veins.

Table VI - I - Summary of Data for Groups I, III and VI Experiments, for the Average Values of Mean Arterial Pressure and Reservoir Blood Volume for the (30 to 120) Minute Intervals with the Corresponding Average Values of Constant Venous Return.

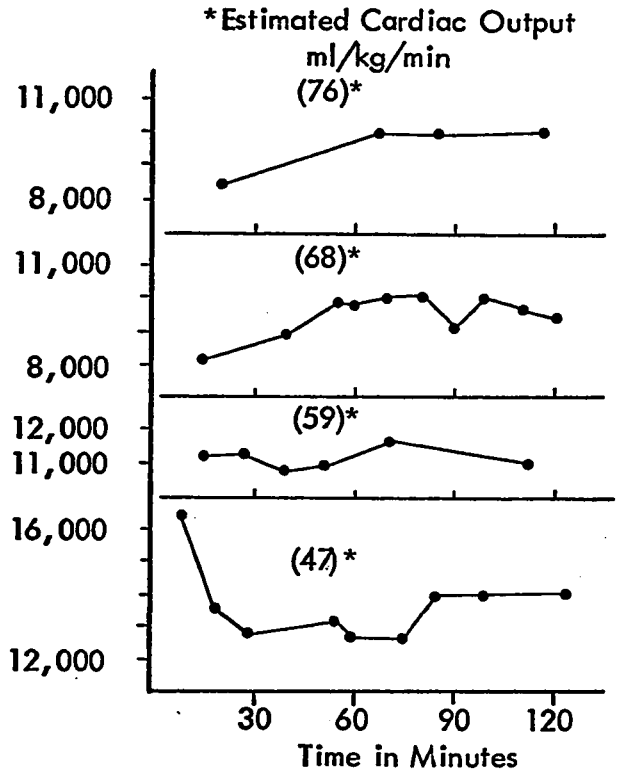
Experiment Groups	Average Value of Constant Venous Return	Average (30 to 120) Minute Mean Arterial Pressure	Average (30 to 120) Minute Reservoir Blood Volume
Group I			
N	18	16	16
$\bar{x}$ and S.E.	15.3 ± 0.5	32.9 ± 1.94	39.1 ± 2.08
Group III			
N	15	15	15
$\bar{x}$ and S.E.	32.6 ± 1.37	74.7 ± 2.93	27.3 ± 2.26
Group VI			
N	6	6	6
$\bar{x}$ and S.E.	30.8 ± 0.55	30.0 ± 1.51	41.5 ± 3.00

Figure VI - 1. Graph illustrates the values of total peripheral vascular resistance in a.u., which were calculated at intervals (black dots) throughout the two hours of "controlled caval return." The experiments are arranged in descending order of estimated cardiac outputs from the top of the graph to the bottom, the value for the estimated cardiac output appearing in brackets above each line joining the black dots. The period of 120 minutes along the abscissa corresponds to the period of "controlled caval return." The TPVR was expressed in absolute units (a.u.) =

$$\frac{\text{MABP} \times 1332}{\text{estimated cardiac output ml/sec}} = \frac{\text{dynes . sec}}{\text{cm}^5}$$

(from Elliot, 1961b).

Total Peripheral Vascular Resistance (Absolute Units)



Total Peripheral Vascular Resistance (Absolute Units)

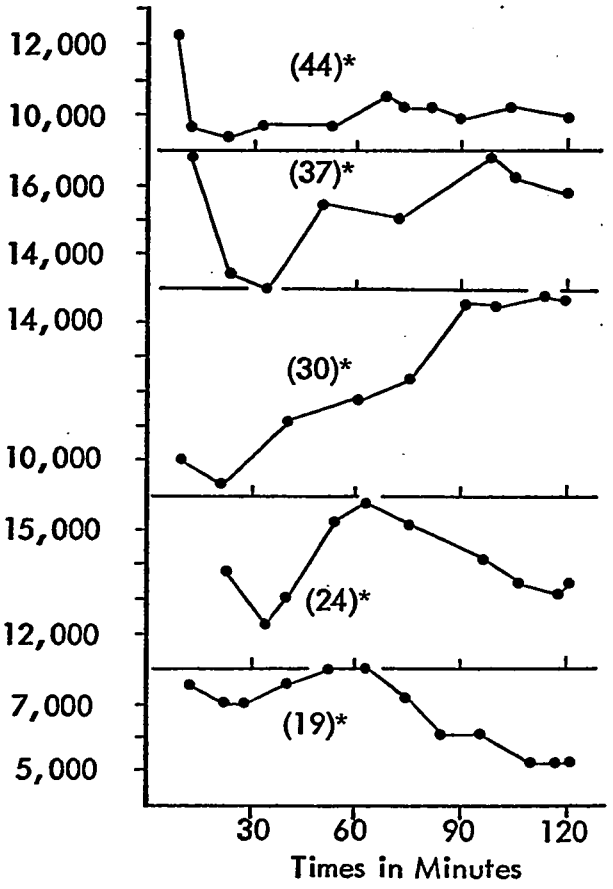


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TABLE I - Data for the Gross and Net Weights of Dogs for the II Groups of Experiments.

Experiment Number	Gross Weight of Dog in Kilograms	Net Weight of Dog in Kilograms	Weight of Hair in Grams
Group I Experiments			
614	9.580	9.470	110
618	17.390	17.070	320
595	12.820	12.690	130
605	11.370	11.260	110
615	11.490	11.320	170
616	14.800	14.690	110
596	15.850	15.500	350
579	10.800	10.530	270
590	11.480	11.270	210
592	16.340	15.970	370
581	13.500	13.240	260
594	12.650	12.260	390
576	11.900	11.480	420
543	11.560	11.260	300
540	13.460	13.240	220
577	11.160	10.970	190
575	10.330	10.100	230
536	10.760	10.470	290
Group II Experiments			
574	14.660	14.500	160
598	9.250	9.140	110
542	10.270	9.930	340
537	9.460	9.310	150
548	12.620	12.240	380
539	12.400	12.050	350
545	15.190	15.060	130
541	11.440	11.260	180
544	9.060	8.830	230
Groups III Experiments			
530	16.660	16.310	350
529	13.510	13.370	140
523	11.730	11.460	270
602	10.470	10.250	220
601	9.030	8.870	160
583	12.400	12.260	140
599	14.340	14.010	330
600	13.430	13.160	270
587	9.560	9.360	200
603	12.350	12.240	110
538	14.110	13.950	160
528	9.340	9.080	260

TABLE I - Continued.

Experiment Number	Gross Weight of Dog in Kilograms	Net Weight of Dog in Kilograms	Weight of Hair in Grams
Group III Experiments Continued			
527	12.210	12.010	200
531	12.940	12.680	260
535	13.020	12.720	300
Group IV Experiments (Included in Group I; see Table XIX)			
Group V Experiments (Included in Group III; see TableXX)			
Group VI Experiments			
610	11.770	11.560	210
613	12.160	11.900	260
612	12.070	11.950	120
619	12.540	12.320	220
617	10.250	10.140	110
611	11.230	10.980	250
Group VII Experiments			
554	12.180	12.120	60
555	12.300	12.080	220
556	15.380	15.160	220
557	11.220	11.030	190
558	12.020	11.830	190
Group VIII Experiments (Included in Groups I, II & III; see Table XXVI)			
Group IX Experiments			
591	10.970	10.740	230
593	14.900	14.650	250
597	13.860	13.700	160
Group X Experiments			
548			
551	12.770	12.580	190
553	11.700	11.580	120
Group XI Experiments			
607	16.840	16.680	160
608	16.620	16.400	220
609	12.500	12.260	240
N		61	61
$\bar{x}$		12.238	221
s^2		0.4157	6837.033
S.D.		0.645	82.69

TABLE II - Results of Experiment to Show the Degree of Error in the Method Used for Determining the Volume in the Reservoir Bottle.

Measured Volume - Reservoir Bottle Emptied into One Liter Graduated Cylinder and Volume Determined*	Estimated Volume - Amount In Reservoir Bottle Read to the Nearest 5 ml Amount at Eye Level	Difference Between Measured and Estimated Volumes
270	260	-10
155	165	+10
388	385	-3
699	700	+1
316	318	+2
470	465	-5
418	415	-3
826	825	-1
908	905	-3
626	620	-6
830	840	+10
772	760	-12
636	635	-1
585	585	0
445	450	+5
380	380	0
228	225	-3
187	180	-7
115	110	-5
840	830	-10
N		20
$\bar{x}$		-2.55
s^2		30.85
S.D.		5.56

* For each observation an arbitrary amount of water was placed in the reservoir bottle.

Table IIA - Values for the Partial Pressure of Oxygen (mmHg) of Arterial and Venous Blood Samples During the Constant Venous Return Period, for Several of the Experiments in Groups IV and VI.

	Experiment Number	Pa_{O_2}	Pv_{O_2}
Group IV	614	320	
		330	20
		360	20
	615	260	20
		350	15
		200	
	616	390	60
		390	50
	618	400	30
		330	15
		370	10
Group VI	611	440	
		380	
		390	
		380	
	612	460	
		520	
		440	22
		390	16
	613	360	14
		340	30
		280	20
	617	600	40
		400	35
		380	10
		330	10
	619	320	25
		380	10
N		28	20
$\bar{x}$		375	24
S. D.		74.8	13.4

TABLE III - Data of These Experiments Show the Per Cent Recovery of Known Amounts of Catecholamines Added to Aliquots of Blood Plasma Which Were Obtained before Start of Constant Venous Return Period.

	Noradrenaline Recovery Data			Adrenaline Recovery Data		
Experiment Number	Micrograms Added to 9-10 ml Aliquot of Plasma	Micrograms Recovered From Aliquot by Chemical Assay	Per Cent Recovery	Micrograms Added to 9-10 ml Aliquot of Plasma	Micrograms Recovered From Aliquot by Chemical Assay	Per Cent Recovery
594	0.05	0.035	70	0.05	0.02	40
595	0.05	0.034	68	0.05	0.047	94
605	0.05	0.06	128	0.1	0.083	83
606	0.05	0.04	80	1.0	0.8	80
613	0.05	0.032	63	1.0	0.77	77
*	0.05	0.31	62	0.2	0.153	76
*	0.10	0.73	73	0.5	0.38	77
*	0.08	0.069	74	1.0	0.65	65
N			8			8
$\bar{x}$			77.25			74
s^2			398.1			222
S.D.			19.95			14.9

* These aliquot samples obtained from one of the non-experimental dogs.

TABLE IV - Data Demonstrates the Difference Between the Galvanometric Readings of the Non-Decomposed and Decomposed Plasma Samples and the Readings for the Reagent Blanks - At the Wave Length Noted.

	Galvanometer Readings			
	385 to 485 mu			385 to 485 mu
Experiment Number	Decomposed Plasma Sample	Non-Decomposed Plasma Sample	Difference	Reagent Blank
594		14.5		9
595	17	14	+3	10
596	19	9.5	+9.5	6
598 *	12	18.5	-6.5	11
599 *	16	19.5	-3.5	13
600 *	7.5	8	-0.5	3.5
601 *	8	11	-3	3
602 *	9	12.5	-3.5	4
603 *	11	14.5	-3.5	3
604 *	14.5	17	-2.5	4.5
605 *	11.5			6
606 *	9	7	+2	3.2
607 *	16	12	+4	3
608	18.5	12.5	+6	4.5
609	12	9	+3	3
610		22		4.5
611		25.5		3
612		14		3
615		15		5
616		11		4.5
618		15		4.5
619		20		4
N		21	13	22
$\bar{x}$		14.38	+0.346	5.25
s^2		21.33	19.784	8.175
S.D.		4.618	4.448	2.86

* Reagents, alkaline sulfite and iodine given in inverse order to normal procedure, to obtain a blank.

TABLE V - Data Demonstrates the Difference Between the Galvanometric Readings of the Non-Decomposed and Decomposed Plasma Samples and the Readings for the Reagent Blanks - At the Wave Length Noted.

	Galvanometer Readings			
	440 to 510 mu			440 to 510 mu
Experiment Number	Decomposed Plasma Sample	Non-Decomposed Plasma Sample	Difference	Reagent Blank
594		5.5		4
595	6	5.5	+1.5	4.5
596	7	5	+2	4.5
598 *	5.5	6.5	-1	5.7
599 *	8	9	-1	7.5
600 *	3.5	3.5	0	2.5
601 *	4	3	+1	2
602 *	3	4	-1	2.5
603 *	4	5	-1	2.5
604 *	5.5	5.5	0	2.5
605 *	4.5			3.5
606 *	4.5	4	+0.5	3
607 *	6	5	+1	2.5
608	7	5.5	+1.5	3.5
609	5.5	4.5	+1	3
610		7.5		4
611		6.5		2.5
612		6		3
615		6		4
616		5.5		4
618		5.5		4
619		7		3.5
N		21	13	22
$\bar{x}$		5.5	+0.3077	3.58
s^2		1.78	0.116	1.513
S.D.		1.334	0.3405	1.23

* Reagents, alkaline sulfite and iodine given in inverse order to normal procedure, to obtain a blank.

TABLE VI - Data Presented to Determine if Using Lean Body Mass (LBM) Gives Better Parameter to Relate Venous Return to than Net Body Weight (kg). Also Venous Return Related to Surface Area and to Body Weight Raised to the 3/4 Power.

Experiment Number	Average Mean Arterial Pressure During (0 to 30)' Interval mmHg	ml/kg /min	ml/kg /min (LBM)	ml /kg$^{3/4}$ /min	ml /kg$^{3/4}$ /min (LBM)	L/M^2 /min (kg)	L/M^2 /min (LBM
	Y (1)	x (2)	x (3)	x (4)	x (5)	x (6)	x (7)
523	50	27.8	35.4	49.2	60.7	0.539	0.648
527	67	34.8	50.6	64.6	85.8	0.712	0.909
528	47	34.7	41.3	60.2	68.6	0.646	0.726
529	61	27.4	37.2	52.3	65.8	0.579	0.712
530	53	27.0	41.0	54.8	74.3	0.618	0.813
531	72	43.4	69.9	81.7	117.0	0.902	1.241
535	66	45.3	51.2	87.4	93.4	0.945	1.023
536	26	17.4	21.4	31.2	36.5	0.338	0.390
537	25	18.9	24.8	32.7	40.4	0.352	0.425
538	67	34.4	51.1	66.6	89.5	0.760	0.960
539	44	21.6	28.0	48.2	49.0	0.443	0.526
540	28	16.7	17.0	32.3	41.4	0.360	0.447
541	28	23.1	29.9	42.5	51.8	0.463	0.547
542	44	18.8	21.6	33.3	46.2	0.360	0.400
543	26	16.4	21.5	29.9	36.8	0.328	0.390
544	50	24.6	36.5	42.3	56.9	0.454	0.591
545	51	21.8	33.6	43.0	59.4	0.482	0.640
548	37	20.4	24.4	38.2	43.7	0.420	0.470

Plot of Average (0 to 30) minute Interval Mean Arterial Pressures of the First 18 Experiments in Column (1) - Versus - Variables in Columns (2) through (7)	Coefficient of Correlation 'r' For the Six Plots Above
(1) Versus (2)	0.84
(1) Versus (3)	0.88
(1) Versus (4)	0.86
(1) Versus (5)	0.91
(1) Versus (6)	0.87
(1) Versus (7)	0.89

TABLE VIA - Measurements and Calculation Involved in the Determination of Lean Body Mass.

Experiment No. 527

Volume of Extracorporeal Blood Removed from Dog.

Volume of blood in reservoir and lines	825 ml	
Volume of blood used in samples	23 ml	
Volume of blood lost in surgery (estimate)	15 ml	
Volume of blood in suctions	27 ml	
Total		890 ml (A)

Specific Gravity of Blood at End of Experiment (after two hours of constant venous return)

Blood in reservoir bottle 1.053

Weight of Extracorporeal Blood (B)

$\frac{\text{Weight of blood}}{\text{Volume of blood}}$ = Specific Gravity = $\frac{(B)}{(A)}$ = 937 g (B)

Calculation of Post-Constant Venous Return Period Weight in Air

Weight of dog in air + weight of endotracheal tube	10,900 g	
Weight of endotracheal tube	34 g	
Weight of dog in air	10,866 g	10,866 g (C)
Plus weight (B)	937 g	
Total weight of dog in air		11,803 g (D)

Calculation of Specific Gravity of Dog

Weight of dog in water = weight of water in can		394 g (E)
Volume of water displaced = (C) - (E)	10,472 ml	
But total amount of water displaced would include (A)	890 ml	
Total volume displaced		11,362 ml (F)

Dog Specific Gravity = $\frac{(D)}{(F)}$ = 1.039

Accordingly % Fat *

$= 100 \times \frac{(5.548 - 5.044)}{(1.039} = 30\ \%$

Lean Body Mass

= (100 - 30%) x (D) 8,262 g or 8.262 kg

* Rathbun & Pace (1945)

TABLE VII - Group I Experiments. Data for the Average Values of Mean Arterial Pressure, Reservoir Blood Volume and Heart Rate - During the (0 to 30) and (30 to 120) minute Intervals.

Experiment Number	Net Weight in Kilograms	Value of Constant Venous Return Rate ml/kg/min	Control Mean Arterial Pressure mmHg	Average Mean Arterial Pressure During (0 to 30)' Interval mmHg	Average Mean Arterial Pressure During (30 to 120)' Interval mmHg	Difference Between Average (30 to 120)' - (0 to 30)' Mean Arterial Pressure mmHg
	(1)	(2)	(3)	(4)	(5)	(6)
614	9.470	13.2	70			
618	17.070	13.5	102	29	31	+2
595	12.690	13.8	80			
605	11.370	13.8	118	31	32	+1
615	11.320	14.0	82	28	26	-2
616	14.690	14.3	125	51	46	-5
596	15.500	14.5	147	49	38	-11
579	10.530	14.7	105	40	32	-8
590	11.270	15.1	132	37	31	-6
592	15.970	15.3	95	33	40	+7
581	13.240	15.9	115	30	23	-7
594	12.260	15.9	81	27	30	+3
576	11.480	16.1	100	36	45	+9
543	11.260	16.4	134	26	25	-1
540	13.240	16.7	120	28	23	-5
577	10.970	16.9	105	35	33	-2
575	10.100	17.3	95	40	46	+6
536	10.470	17.4	148	26	25	-1
N	18	18	18	16	16	16
$\bar{x}$	12.38	15.3	108	34.1	32.9	-1.25
s^2	4.4306	1.74	502.13	56.24	59.49	9.0
S.D.	2.11	1.319	22.4	7.5	7.75	3.0

TABLE VII - Continued.

Experiment Number	Average Reservoir Blood Volume During (0 to 30)' Interval ml/kg	Average Reservoir Blood Volume During (30 to 120)' Interval ml/kg	Difference Between Average (30 to 120)' - (0 to 30)' Reservoir Blood Volume ml/kg	Control Heart Rate Beats/min	Average Heart Rate During (0 to 30)' Interval Beats/min	Average Heart Rate During (30 to 120)' Interval Beats/min	Difference Between Average (30 to 120)' - (0 to 30)' Heart Rate Beats/min
	(7)	(8)	(9)	(10)	(11)	(12)	(13)
614							
618	24.5	37.8	+13.3	132	99	119	+20
595				120	102	90	-12
605	26.8	41.6	+14.8	192	144	175	+31
615	26.7	37.8	+11.1	120	86	105	+19
616	20.0	18.2	-1.8	132	116	138	+22
596	28.7	40.0	+11.3	156	146	147	+1
579	28.6	36.5	+7.9	120	138	122	-16
590	32.6	49.3	+16.7	180	122	131	+11
592	17.6	33.0	+15.4	132	108	125	+17
581	18.1	23.4	+5.3	144	129	151	+22
594	34.6	51.1	+16.5	144	89	106	+17
576	29.1	46.9	+17.8				
543	32.7	44.6	+11.9	168	126	167	+41
540	27.8	44.6	+16.8	156	135	141	+6
577	25.6	41.2	+15.6	108	118	110	-8
575	28.5	40.5	+12.0	96	112	139	+17
536	21.7	40.0	+18.3	156	132	163	+31
N	16	16	16	16	16	16	16
$\bar{x}$	26.5	39.1	+12.7	141	119	133	+13.68
s^2	23.93	69.64	26.18	639	322	546	239
S.D.	4.89	8.34	5.11	25.3	17.9	23.4	15.5

TABLE VIII - Group II Experiments. Data for the Average Values of Mean Arterial Pressure, Reservoir Blood Volume and Heart Rate - During the (0 to 30) and (30 to 120) minute Intervals.

Experiments Number	Net Weight in Kilograms	Value of Constant Venous Return Rate ml/kg/min	Control Mean Arterial Pressure mmHg	Average Mean Arterial Pressure During (0 to 30)' Interval mmHg	Average Mean Arterial Pressure During (30 to 120)' Interval mmHg	Difference Between Average (30 to 120)' - (0 to 30)' Mean Arterial Pressure mmHg
	(1)	(2)	(3)	(4)	(5)	(6)
574	14.500	17.9	120	48	60	+12
598	9.140	18.6	112	41	54	+13
542	9.930	18.8	84	44	38	-4
537	9.310	18.9	132	25	21	-4
548	12.240	20.4	150	37	31	-6
539	10.050	21.6	135	44	87	+43
545	15.060	21.8	131	51	57	+6
541	11.260	23.1	87	28	35	-5
544	8.830	24.6	110	50	38	-12
N	9	9	9	9	9	9
$\bar{x}$	11.15	20.63	117.9	40.89	46.77	+4.78
s^2	4.802	4.6822	433.21	76.543	350.62	247.72
S.D.	2.912	2.16	20.8	8.75	18.72	15.73

TABLE VIII - Continued

Experiment Number	Average Reservoir Blood Volume During (0 to 30)' Interval ml/kg	Average Reservoir Blood Volume During (30 to 120)' Interval ml/kg	Difference Between Average (30 to 120)' - (0 to 30)' Reservoir Blood Volume ml/kg	Control Heart Rate Beats/min	Average Heart Rate During (0 to 30)' Interval Beats/min	Average Heart Rate During (30 to 120)' Interval Beats/min	Difference Between Average (30 to 120)' - (0 to 30)' Heart Rate Beats/min
	(7)	(8)	(9)	(10)	(11)	(12)	(13)
574	23.0	38.0	+15.0	156	129	167	+38
598	36.4	40.7	+4.3	156	132	146	+14
542	22.9	25.6	+2.7	120	127	130	+3
537	26.4	44.2	+17.8	144	128	145	+17
548	10.7	39.8	+29.1	180	145	165	+20
539	18.4	28.0	+9.6	144	133	165	+32
545	15.6	28.2	+12.6	132	115	124	+9
541	15.1	20.2	+5.1	132	110	126	+16
544	12.6	32.5	+19.9	120	107	123	+16
N	9	9	9	9	9	9	9
$\bar{x}$	20.12	33.02	+12.9	143	125	143	+18.3
s^2	57.153	58.095	65.52	334	132	308	93.3
S.D.	7.56	7.62	8.09	18.3	11.5	17.5	9.65

TABLE IX - Group III Experiments. Data for the Average Values of Mean Arterial Pressure, Reservoir Blood Volume and Heart Rate - During the (0 to 30) and (30 to 120) minute Intervals.

Experiment Number	Net Weight in Kilograms (1)	Value of Constant Venous Return Rate ml/kg/min (2)	Control Mean Arterial Pressure mmHg (3)	Average Mean Arterial Pressure During (0 to 30)' Interval mmHg (4)	Average Mean Arterial Pressure During (30 to 120)' Interval mmHg (5)	Difference Between Average (30 to 120)' - (0 to 30)' Mean Arterial Pressure mmHg (6)
530	16.310	27.0	112	53	82	+29
529	13.370	27.4	125	61	93	+32
523	11.460	27.8	129	50	78	+38
602	10.250	27.8	125	61	63	+2
601	8.870	29.3	124	82	82	0
583	12.260	29.8	127	70	73	+3
599	14.010	31.0	114	56	77	+21
600	13.160	30.0	106	70	80	+10
587	9.360	32.6	105	43	48	+5
603	12.240	33.5	120	69	67	-2
538	13.950	34.4	120	67	71	+4
528	9.080	34.7	99	47	62	+15
527	12.010	34.8	140	67	77	+11
531	12.680	43.4	118	72	94	+22
535	12.720	45.3	145	66	74	+8
N	15	15	15	15	15	15
$\bar{x}$	12.11	32.6	120.6	62.3	74.7	+13.2
s^2	3.9463	28.4529	145.364	106.06	130.062	145.893
S.D.	1.986	5.332	12.05	10.3	11.4	12.08

TABLE IX - Continued.

Experiment Number	Average Reservoir Blood Volume During (0 to 30)' Interval ml/kg	Average Reservoir Blood Volume During (30 to 120)' Interval ml/kg	Difference Between Average (30 to 120)' - (0 to 30)' Reservoir Blood Volume ml/kg	Control Heart Rate Beats/min	Average Heart Rate During (0 to 30)' Interval Beats/min	Average Heart Rate During (30 to 120)' Interval Beats/min	Difference Between Average (30 to 120)' - (0 to 30)' Heart Rate Beats/min
	(7)	(8)	(9)	(10)	(11)	(12)	(13)
530	22.1	30.7	+8.6	168	158	176	+18
529	17.8	30.0	+12.2	132	106	120	+14
523	32.9	44.3	+11.4	144	156	188	+32
602	16.5	26.4	+9.9	144	124	125	+1
601	9.5	10.8	+1.3	156	143	139	-4
583	24.2	34.0	+9.8	156	114	149	+35
599	13.7	26.5	+12.8	132	112	136	+24
600	16.9	18.5	+1.6	144	137	137	00
587	25.2	32.5	+7.3	132	122	122	00
603	16.1	24.4	+8.3	132	112	114	+2
538	9.4	16.9	+7.5	132	139	166	+27
528	10.5	27.2	+16.7	192	152	174	+22
527	26.5	39.6	+13.1	204	177	207	+30
531	9.1	18.3	+9.2	144	138	152	+14
535	14.2	30.8	+16.6	144	160	180	+20
N	15	15	15	15	15	15	15
$\bar{x}$	17.64	27.27	+9.6	150	137	152	+15.6
s^2	48.0744	76.9292	20.6778	458	422	741	160
S.D.	6.93	8.77	4.547	21.4	20.5	27.2	12.6

TABLE X - Group I Experiments. Data for the Interpolated Values of Mean Arterial Pressure at the five and 10 minute Times During the Constant Venous Return Period (see Chapter III).

Minutes	Control	2-3	5	10	15	20	25	30	40	50	60	70	80	90	100	110	120
Experiment Number																	
614	70	20	20	20	20	19	19	19	18	19	19						
618	102	25	25	25	25	25	26	30	37	37	35	33	31	30	29	27	25
595	80																
605	118	20	25	32	24	25	30	35	35	30	35	35	33	30	30	29	30
615	82	25	26	26	26	25	25	24	22	21	22	24	25	25	25	25	25
616	125	34	36	41	47	52	56	60	60	60	56	50	41	31	35	34	30
596	147	25	36	54	50	42	42	52	40	44	39	32	34	36	32	35	35
579	105	17	40	41	36	34	33	32	31	31	33	33	33	33	33	32	30
590	132	25	28	33	34	30	39	40	39	34	33	34	29	28	27	25	25
592	95	25	28	32	28	29	30	39	40	40	40	40	42	40	40	37	39
581	115	25	26	24	24	22	24	25	30	26	26	24	23	21	20	17	17
594	81	21	21	23	26	26	26	28	30	30	30	29	30	29	30	30	30
576	100	32	34	28	30	30	31	38	43	49	50	45	49	47	45	45	45
543	134	19	25	25	21	20	23	20	23	27	29	29	28	26	25	23	23
540	120	20	20	24	21	20	20	22	21	21	23	25	25	23	24	22	20
577	105	30	35	35	32	30	30	30	30	31	32	32	34	36	36	34	33
575	95	30	34	42	41	35	38	43	49	53	51	47	45	45	45	45	45
536	148	27	27	21	21	24	26	24	23	22	25	27	30	30	27	23	22

TABLE XI - Group II Experiments. Data for the Interpolated Values of Mean Arterial Pressure at the five and 10 minute Times During the Constant Venous Return Period (see Chapter III).

Minutes	Control	2-3	5	10	15	20	25	30	40	50	60	70	80	90	100	110	120
Experiment Number																	
574	120	32	38	44	40	45	52	60	65	65	60	67	70	65	60	50	42
598	112	24	25	38	42	42	42	46	55	55	58	61	58	55	55	52	47
542	84	18	33	47	51	47	45	43	40	39	38	37	36	36	36	36	36
537	132	24	21	24	21	19	19	19	20	20	20	20	21	20	20	20	23
548	150	32	40	35	34	33	30	31	35	41	38	34	30	28	27	25	25
539	135	30	33	35	38	44	49	55	77	80	88	94	100	96	95	93	90
545	131	52	59	58	43	37	37	45	63	67	69	65	59	52	53	52	48
541	87	25	34	34	31	29	31	34	34	34	34	35	36	36	35	36	38
544	110	35	44	61	54	44	42	42	42	42	41	38	36	35	35	36	35

TABLE XII - Group III Experiments. Data for the Interpolated Values of Mean Arterial Pressure at the five and 10 minute Times During the Constant Venous Return Period (see Chapter III).

Minutes	Control	2-3		5	10	20	25	30	40	50	60	70	80	90	100	110	120
Experiment Number																	
530	112	32	62	56	47	46	55	62	71	75	77	81	83	85	90	95	97
529	125	40	50	52	64	64	66	77	82	92	98	98	100	95	98	98	96
523	129	37	47	46	47	55	50	55	62	71	75	75	77	85	89	92	95
602	125	25	53	60	62	66	63	59	70	62	65	66	67	64	60	56	59
601	124	50	65	90	83	81	83	82	81	81	80	80	78	76	79	87	95
583	127	43	60	70	73	74	70	59	58	66	72	73	74	77	81	84	81
599	114	30	61	50	50	52	55	59	60	63	65	70	82	85	95	95	100
600	106	40	54	75	75	70	75	76	75	80	85	86	85	80	80	75	75
587	105	25	30	39	42	40	40	40	41	42	46	49	51	52	51	53	55
603	120	35	55	76	67	67	72	79	76	75	69	64	65	57	60	60	59
538	120	56	64	73	66	63	65	65	75	74	76	71	71	70	70	69	73
528	99	36	58	36	42	48	52	55	57	63	65	65	65	65	63	62	63
527	140	57	73	65	60	62	65	69	73	74	74	77	82	82	80	80	77
531	118	42	82	66	66	70	75	85	89	91	96	98	100	100	98	94	92
535	145	42	55	72	65	60	60	60	62	70	76	77	78	81	81	77	75

TABLE XIII - Group I Experiments. Data for Interpolated Values of Reservoir Blood Volume at the five and 10 minute Times During the Constant Venous Return Period (see Chapter III).

Minutes	0	5	10	15	20	25	30	40	50	60	70	80	90	100	110	120
Experiment Number																
614																
618	0	23.0	24.5	25.5	27.0	29.5	34.0	35.0	38.0	37.5	36.5	37.0	39.5	39.5	40.0	41.6
595																
605	0	22.0	24.0	26.0	30.5	35.5	36.5	39.0	40.5	41.7	43.0	43.0	43.0	44.0	43.0	42.0
615	0	25.0	26.5	29.0	31.0	36.0	34.0	36.0	36.7	37.5	38.0	39.0	39.5	40.2	40.5	37.0
616	0	23.0	25.0	24.0	21.5	17.5	14.1	12.5	13.5	13.0	11.5	13.5	17.5	17.5	31.0	33.5
596	0	20.0	28.5	31.0	28.5	37.0	40.0	40.5	41.0	41.5	41.5	40.5	40.0	39.0	37.5	38.0
579	0	33.2	32.8	32.3	33.2	33.7	35.1	36.1	37.0	38.0	38.0	37.0	37.0	37.0	36.1	34.2
590	0	26.6	32.8	37.3	41.7	44.4	45.2	47.9	49.7	51.0	50.6	49.7	49.7	49.7	49.7	49.7
592	0	16.6	17.5	17.8	20.0	24.4	26.9	30.3	31.9	33.2	33.8	33.8	33.8	35.1	35.7	35.1
581	0	15.9	18.1	19.2	22.6	24.5	26.4	28.7	27.2	24.9	26.0	23.4	22.6	21.9	16.6	15.9
594	0	23.0	35.0	38.5	40.0	48.5	45.0	47.0	49.5	51.0	53.5	53.0	53.0	53.0	53.0	53.0
576	0	27.0	29.6	33.1	35.7	38.3	40.0	43.5	44.4	45.7	47.9	48.7	48.7	48.7	50.5	50.5
543	0	30.2	33.7	38.2	40.0	42.6	44.4	47.9	50.6	50.6	47.8	45.3	43.5	41.7	39.1	35.5
540	0	27.9	30.2	29.4	32.5	34.7	40.0	44.2	45.3	46.4	47.6	48.3	47.6	43.8	42.3	40.8
577	0	25.5	27.3	29.2	31.0	32.8	33.7	36.5	39.2	41.5	42.8	43.7	43.7	43.7	43.7	43.7
575	0	24.7	31.2	34.6	34.6	37.1	37.1	40.6	40.6	39.6	40.6	40.6	41.6	41.6	41.6	41.6
536	0	19.1	20.5	22.9	26.7	30.5	32.5	35.3	37.2	39.1	41.0	43.0	43.0	43.0	43.0	43.0

TABLE XIV - Group II Experiments. Data for Interpolated Values of Reservoir Blood Volume at the five and 10 minute Times During the Constant Venous Return Period (see Chapter III).

Minutes	0	5	10	15	20	25	30	40	50	60	70	80	90	100	110	120
Experiment Number																
574	0	21.4	24.8	26.2	28.3	29.6	30.7	33.1	35.2	37.2	37.9	39.3	40.7	41.4	41.4	43.4
598	0	23.0	30.0	24.5	37.0	37.5	37.0	36.5	38.0	39.5	41.0	41.5	42.0	42.5	44.0	45.0
542	0	20.1	25.2	27.2	28.2	29.2	30.2	30.2	30.2	29.2	27.2	25.2	23.1	21.1	20.1	19.1
537	0	8.6	17.2	34.4	37.6	41.9	45.1	48.3	49.4	48.8	48.3	48.3	40.8	37.6	37.6	37.6
548	0	6.5	12.2	11.7	13.1	13.9	17.6	26.1	35.5	42.3	44.9	47.2	46.1	45.7	46.5	46.5
539	0	17.4	20.3	24.1	24.9	21.6	20.7	24.9	24.9	26.5	24.9	25.7	31.5	34.7	33.2	33.2
545	0	10.3	16.6	19.0	19.6	21.1	22.6	25.9	27.8	28.7	29.5	29.9	29.9	29.5	29.2	29.2
541	0	13.3	16.0	17.7	17.7	18.6	22.2	24.9	24.9	23.1	22.2	21.3	19.1	16.9	14.6	12.4
544	0	10.7	10.7	11.3	14.7	18.9	22.0	25.7	30.6	30.0	32.3	35.1	36.2	36.2	38.5	38.5

TABLE XV - Group III Experiments. Data for Interpolated Values of Reservoir Blood Volume at the five and 10 minute Times During the Constant Venous Return Period (see Chapter III).

Minutes	0	5	10	15	20	25	30	40	50	60	70	80	90	100	110	120
Experiment Number																
530	0	21.4	23.3	25.7	27.6	27.9	28.8	29.4	29.4	30.3	31.3	31.3	31.3	31.6	31.9	31.9
529	0	14.9	17.2	18.7	22.4	25.4	26.2	27.3	28.4	28.4	29.9	29.9	30.6	32.1	33.6	33.6
523	0	27.9	37.5	41.0	41.0	41.0	41.9	44.0	44.5	44.9	46.2	46.2	44.5	43.6	43.6	43.6
602	0	12.5	17.5	18.5	19.5	19.5	20.0	20.0	22.0	24.5	27.0	28.0	30.0	31.0	31.0	31.0
601	0	11.0	10.0	9.5	10.0	10.5	13.5	13.0	10.6	10.0	7.8	7.8	7.8	7.5	5.0	7.2
583	0	22.4	26.1	28.5	30.2	31.0	31.0	32.6	33.8	34.2	34.2	34.2	34.7	35.1	35.1	35.1
599	0	11.0	12.5	14.0	16.0	17.5	19.3	21.4	23.5	24.0	25.0	26.5	28.0	28.7	29.3	29.3
600	0	17.5	17.0	17.5	18.0	19.0	20.5	21.0	19.5	18.5	18.5	18.5	20.0	20.0	16.5	14.5
587	0	24.6	25.6	28.8	31.5	33.1	33.1	37.4	39.5	34.2	33.1	33.1	31.0	28.3	27.8	27.8
603	0	14.5	15.0	16.0	17.5	20.0	22.0	23.0	23.5	24.5	25.0	26.0	25.0	25.0	25.0	25.0
538	0	4.3	9.3	12.1	12.1	13.6	14.3	15.8	16.8	15.8	16.5	17.2	17.9	17.9	18.6	17.9
528	0	8.8	8.8	8.8	12.1	16.5	18.7	22.1	25.3	27.5	27.5	27.5	29.7	30.3	31.9	31.9
527	0	25.8	28.3	30.0	31.6	34.1	35.8	38.3	38.3	39.1	39.9	40.8	41.6	41.6	40.8	39.9
531	0	6.3	7.9	7.9	11.8	14.2	15.8	17.3	18.1	18.9	19.3	19.7	19.7	18.9	18.1	17.3
535	0	14.1	14.9	16.5	20.4	23.6	26.7	29.9	31.4	31.4	31.4	31.4	31.4	31.4	31.4	31.4

TABLE XVI - Regression Equations and Coefficients of Correlation Tabulated to Show the Correlation Between the Interpolated Values of Mean Arterial Pressure (y) at the Five and Ten Minute Times Observed During the Constant Venous Return Periods of Groups I, II and III Experiments and the Values of Constant Venous Return (x).

Times Minutes	Regression Equation	N	$\bar{x}$	$\bar{y}$	'r'	S.D. of y	S.E. of b
2-3	Y = 12.9736 + 0.8018x	41	22.817	31.268	0.67	7.67	±0.142
5	Y = 5.0830 + 1.5752x	41	22.817	41.0243	0.82	9.34	±0.173
10	Y = 8.8037 + 1.5682x	41	22.817	44.5853	0.73	12.59	±0.233
15	Y = 8.4263 + 1.5214x	41	22.817	43.14	0.75	11.67	±0.216
20	Y = 6.6896 + 1.5732x	41	22.817	42.585	0.77	11.39	±0.21
25	Y = 7.7845 + 1.5947x	41	22.817	44.171	0.76	11.80	±0.22
30	Y = 10.3554 + 1.5964x	41	22.817	46.780	0.72	13.10	±0.24
40	Y = 11.0855 + 1.6884x	41	22.817	49.610	0.71	14.58	±0.27
50	Y = 9.1248 + 1.8414x	41	22.817	51.140	0.72	15.20	±0.28
60	Y = 6.9925 + 1.9843x	41	22.817	52.268	0.74	15.40	±0.28
70	Y = 6.6752 + 2.0091x	40	23.057	53.000	0.74	15.90	±0.29
80	Y = 4.2599 + 2.1312x	40	23.057	53.400	0.74	16.50	±0.30
90	Y = 0.2209 + 2.2424x	40	23.057	51.925	0.77	16.10	±0.30
100	Y = -0.0481 + 2.2725x	40	23.057	52.350	0.76	16.90	±0.32
110	Y = -1.6636 + 2.3057x	40	23.057	51.500	0.75	17.40	±0.33
120	Y = -3.3201 + 2.3667x	40	23.057	51.250	0.76	17.7	±0.33

TABLE XVII - Regression Equations and Coefficients of Correlation Tabulated to Show the Correlation Between the Interpolated Values of Mean Arterial Pressure (y) at the Five and Ten Minute Times Observed During the Constant Venous Return Periods of Group III Experiments and the Values of Constant Venous Return (x).

Times Minutes	Regression Equation	N	$\bar{x}$	$\bar{y}$	'r'	S.D. of y	S.E. of b
2-3	Y = 23.4963 + 0.4860x	15	32.59	39.33	0.27	9.8	±0.47
5	Y = 32.1668 + 0.7907x	15	32.59	57.93	0.37	11.36	±0.55
10	Y = 46.5738 + 0.4652x	15	32.59	61.73	0.17	15.5	±0.75
15	Y = 54.6628 + 0.1800x	15	32.59	60.60	0.08	12.9	±0.63
20	Y = 58.8766 + 0.0713x	15	32.59	61.20	0.03	11.62	±0.56
25	Y = 57.5237 + 0.1701x	15	32.59	63.01	0.08	11.70	±0.57
30	Y = 55.7900 + 0.2970x	15	32.59	65.47	0.13	12.70	±0.62
40	Y = 63.5895 + 0.0721x	15	32.59	68.80	0.07	12.60	±0.61
50	Y = 65.4519 + 0.1989x	15	32.59	71.93	0.09	12.80	±0.62
60	Y = 66.0100 + 0.2636x	15	32.59	74.60	0.11	13.20	±0.64
70	Y = 67.7469 + 0.2328x	15	32.59	75.33	0.10	13.10	±0.64
80	Y = 69.7866 + 0.2275x	15	32.59	77.20	0.10	13.30	±0.65
90	Y = 67.4995 + 0.2895x	15	32.59	76.90	0.12	13.70	±0.66
100	Y = 77.1990 + 0.0348x	15	32.59	78.30	0.01	15.30	±0.74
110	Y = 88.3175 - 0.3023x	15	32.59	78.47	-0.11	15.90	±0.77
120	Y = 97.0535 - 0.5397x	15	32.59	79.47	-0.12	16.00	±0.78

TABLE XVIII - Regression Equations and Coefficients of Correlation Tabulated to Show the Correlation Between the Interpolated Values of Reservoir Blood Volume (y) at the Five and Ten Minute Times Observed During the Constant Venous Return Periods of Groups I, II and III and the Values of Constant Venous Return (x).

Times Minutes	Regression Equation	N	$\bar{x}$	$\bar{y}$	'r'	S.D. of y	S.E. of b
5	Y = 28.6920 - 0.4301x	40	23.06	18.77	-0.50	6.4	±0.12
10	Y = 34.1672 - 0.5265x	40	23.06	22.03	-0.55	6.8	±0.13
15	Y = 36.8913 - 0.5617x	40	23.06	23.94	-0.54	7.6	±0.14
20	Y = 38.6502 - 0.5494x	40	23.06	25.98	-0.55	7.8	±0.15
25	Y = 41.6757 - 0.5865x	40	23.06	28.15	-0.51	8.5	±0.16
30	Y = 42.4341 - 0.5603x	40	23.06	29.51	-0.50	8.3	±0.15
40	Y = 44.4287 - 0.5682x	40	23.06	31.33	-0.49	8.7	±0.16
50	Y = 46.7119 - 0.5910x	40	23.06	33.08	-0.49	9.0	±0.17
60	Y = 47.9665 - 0.6234x	40	23.06	33.59	-0.50	9.3	±0.17
70	Y = 49.0661 - 0.6416x	40	23.06	34.27	-0.50	9.6	±0.18
80	Y = 48.2826 - 0.6074x	40	23.06	34.28	-0.47	9.8	±0.18
90	Y = 48.1935 - 0.5979x	40	23.06	34.41	-0.48	9.3	±0.17
100	Y = 47.8546 - 0.5923x	40	23.06	34.20	-0.48	9.3	±0.17
110	Y = 48.4933 - 0.6199x	40	23.06	34.20	-0.49	9.6	±0.18
120	Y = 48.0969 - 0.6142x	40	23.06	33.93	-0.48	9.7	±0.18

TABLE XIX - Group IV Experiments. Data for the Average Values of Mean Arterial Pressure, Reservoir Blood Volume and Heart Rate - During the (0 to 30) and (30 to 120) minute Intervals.

Experiment Number	Net Weight in Kilograms	Value of Constant Venous Return Rate ml/kg/min	Control Mean Arterial Pressure mmHg	Average Mean Arterial Pressure During (0 to 30)' Interval mmHg	Average Mean Arterial Pressure During (30 to 120)' Interval mmHg	Difference Between Average (30 to 120)' - (0 to 30)' Mean Arterial Pressure mmHg
	(1)	(2)	(3)	(4)	(5)	(6)
614	9.470	13.2	70			
618	17.070	13.5	102	29	31	+2
605	11.370	13.8	118	31	32	+1
595	12.690	13.8	80			
615	11.320	14.0	82	28	26	-2
616	14.690	14.3	125	51	46	-5
596	15.500	14.5	147	49	38	-11
594	12.260	15.9	81	27	30	+3
598	9.140	18.6	112	41	54	+13
N	9	9	9	7	7	7
$\bar{x}$	12.61	14.62	101.9	36.6	36.7	+0.14
s^2	6.45	2.51	584.3	90.82	85.44	47.55
S.D.	2.54	1.58	24.18	9.53	9.24	6.9

TABLE XIX - Continued.

Experiment Number	Average Reservoir Blood Volume During (0 to 30)' Interval ml/kg (7)	Average Reservoir Blood Volume During (30 to 120)' Interval ml/kg (8)	Difference Between Average (30 to 120)' - (0 to 30)' Reservoir Blood Volume ml/kg (9)
614			
618	24.5	37.8	+13.3
605	26.8	41.6	+14.8
595			
615	26.7	37.8	+11.1
616	20.0	18.2	-1.8
596	28.7	40.0	+11.3
594	34.6	51.1	+16.5
598	36.4	40.7	+4.3
N	7	7	7
$\bar{x}$	28.24	38.17	+9.93
s^2	28.65	83.96	35.82
S.D.	5.35	9.16	5.98

TABLE XX - Group V Experiments. Data for the Avererage Values of Mean Arterial Pressure, Reservoir Blood Volume and Heart Rate - During the (0 to 30) and (30 to 120) minute Intervals.

Experiment Number	Net Weight in Kilograms	Value of Constant Venous Return Rate ml/kg/min	Control Mean Arterial Pressure mmHg	Average Mean Arterial Pressure During (0 to 30)' Interval mmHg	Average Mean Arterial Pressure During (30 to 120)' Interval mmHg	Difference Between Average (30 to 120)' - (0 to 30)' Mean Arterial Pressure mmHg
	(1)	(2)	(3)	(4)	(5)	(6)
602	10.250	27.8	125	61	63	+2
601	8.870	29.3	124	82	82	0
600	13.160	30.0	106	70	80	+10
599	14.010	31.0	114	56	77	+21
603	12.240	33.5	120	69	67	-2
N	5	5	5	5	5	5
$\bar{x}$	11.7	30.3	117.8	67.6	73.8	+6.2
s^2	3.57	3.614	49.8	78.6	55.8	71.4
S.D.	1.89	1.9	7.06	8.86	7.47	8.45

TABLE XX - Continued

Experiment Number	Average Reservoir Blood Volume During (0 to 30)' Interval ml/kg	Average Reservoir Blood Volume During (30 to 120)' Interval ml/kg	Difference Between Average (30 to 120)' - (0 to 30)' Reservoir Blood Volume ml/kg
	(7)	(8)	(9)
602	16.5	26.4	+9.9
601	9.5	10.8	+1.3
600	16.9	18.5	+1.6
599	13.7	26.5	+12.8
603	16.1	24.4	+8.3
N	5	5	5
$\bar{x}$	14.54	21.32	+6.78
s^2	7.59	36.15	21.02
S.D.	2.753	6.01	4.585

TABLE XXI - Group IV Experiments. Data for Values of, Arterial & Venous Blood pH & P_{CO_2} Determinations and Venous Noradrenaline & Adrenaline Blood Plasma Determinations - At One and Two Hours After Start of the Constant Venous Return Period.

Experiment Number	pH		P_{CO_2}		Catecholamines		pH		P_{CO_2}		Catecholamines	
	Art	Ven	Art	Ven	NA	A	Art	Ven	Art	Ven	NA	A
614	7.26	7.05	12.5	65	13.3	135.0						
618	7.18	7.06	19.0	36	3.2	47.4	7.18	7.08	18	57	2.9	39.7
595					4.2	44.9					9.9	94.0
605	7.22		16.0		12.5	101.0	7.08		16		19.2	203.0
615	7.35	7.18	12.0	37	2.1	38.0	7.07	6.96	12.5	57	6.2	57.0
616	7.20	7.02	17.5	88	14.2	103.0	7.04	6.8	24	122	13.7	172.8
596	7.04	6.99	49.0	61	18.8	222.5	6.96	6.92	34	68	9.7	150.5
594					5.5	92.0						
598	7.26		11.5		5.0	76.5	7.04	6.97	16.5	59	8.4	96.0
N	7	5	7	5	9	9	6	5	6	5	7	7
$\bar{x}$	7.216	7.06	19.64	57.4	8.8	95.6	7.06	6.94	20.17	72.6	10.00	116.1
s^2	0.00775	0.0042	150.84	376.3	31.6	2925.46	0.00428	0.0081	50.05	626.6	23.69	3185.23
S.D.	0.088	0.0648	12.28	19.40	5.62	54.1	0.0648	0.09	7.07	25.02	4.86	56.44

TABLE XXII - Group V Experiments. Data for Values of, Arterial Blood pH & P_{CO_2} Determinations and Venous Noradrenaline & Adrenaline Blood Plasma Determinations - At One and Two Hours After the Start of the Constant Venous Return Period.

Experiment Number	pH		P_{CO_2}		Catecholamines		pH		P_{CO_2}		Catecholamines	
	Art	Ven	Art	Ven	NA	A	Art	Ven	Art	Ven	NA	A
602	7.41		14		0.56	13.5	7.34		13.5		0.67	13.87
601	7.23		23		1.77	24.89	7.16		38		0.73	9.27
600	7.20		21		0.6	6.0	7.36		17.5		0.6	7.4
599					0.3	18.6	7.34		14		0.68	17.97
603	7.36		29		0.4	12.0	7.44		26		0,6	18.8
N	4		4		5	5	5		5		5	5
$\bar{x}$	7.3		21.75		0.73	15.0	7.328		21.8		0.65	13.5
s^2	0.00765		28.69		0.2842	42.6	0.008416		85.66		0.0025	20.661
S.D.	0.0874		5.36		0.533	6.53	0.0917		9.25		0.05	4.55

TABLE XXIII- Group VI Experiments. Data for the Average Values of Mean Arterial Pressure, Reservoir Blood Volume and Heart Rate - During the (0 to 30) and (30 to 120) minute Intervals.

Experiment Number	Net Weight in Kilograms	Value of Constant Venous Return Rate ml/kg/min	Control Mean Arterial Pressure mmHg	Average Mean Arterial Pressure During (0 to 30)' Interval mmHg	Average Mean Arterial Pressure During (30 to 120)' Interval mmHg	Difference Between Average (30 to 120)' - (0 to 30)' Mean Arterial Pressure mmHg
	(1)	(2)	(3)	(4)	(5)	(6)
610	11.560	29.0	84	37	32	-5
613	11.900	29.4	75	40	37	-3
612	11.950	30.6	50	29	30	+1
619	12.320	30.8	87	42	26	-16
617	10.140	32.1	102	32	27	-5
611	10.980	32.8	83	35	28	-7
N	6	6	6	6	6	6
$\bar{x}$	11.47	30.8	80.2	35.8	30	-5.8
s^2	0.53	1.8	24.7	19.8	13.67	26.8
S.D.	0.73	1.34	4.97	4.45	3.69	5.18

TABLE XXIII - Continued.

Experiment Number	Average Reservoir Blood Volume During (0 to 30)' Interval ml/kg	Average Reservoir Blood Volume During (30 to 120)' Interval ml/kg	Difference Between Average (30 to 120)' - (0 to 30)' Reservoir Blood Volume ml/kg	Control Heart Rate Beats/min	Average Heart Rate During (0 to 30)' Interval Beats/min	Average Heart Rate During (30 to 120)' Interval Beats/min	Difference Between Average (30 to 120)' - (0 to 30)' Heart Rate Beats/min
	(7)	(8)	(9)	(10)	(11)	(12)	(13)
610	30.7	47.8	+17.1	192	163	179	+16
613	16.0	29.5	+13.5		149	158	+9
612	24.4	34.5	+10.1	144	180	180	00
619	33.7	50.1	+16.4	180	171	184	+13
617	34.6	45.6	+11.0		129	144	+15
611	24.6	41.8	+15.2	192	167	152	-15
N	6	6	6	4	6	6	6
$\bar{x}$	27.3	41.5	+13.88	177	160	166	+6.3
s^2	41.53	53.92	6.86	393	276	239	119.2
S.D.	6.44	7.34	2.62	19.8	16.6	15.5	10.9

TABLE XXIV - Group VI Experiments. Data for the Interpolated Values of Mean Arterial Pressure (upper part of Table) and Reservoir Blood Volume (lower part of Table) at the five and 10 minute Times During the Constant Venous Return Period (see Chapter III).

Minutes	Control	2-3	5	10	15	20	25	30	40	50	60	70	80	90	100	110	120
Experiment Number																	
610	84	30	34	36	34	33	33	34	35	35	30	33	35	32	30	29	25
613	75	37	37	35	36	37	38	38	37	37	37	36	36	37	38	39	40
612	50	29	26	27	29	28	27	28	29	29	29	30	30	31	31	30	30
619	87	30	34	44	42	40	39	38	36	32	29	26	25	24	20	18	17
617	102	25	25	25	25	25	25	25	27	28	29	28	27	27	25	26	25
611	83	30	30	32	31	31	30	29	28	30	29	27	29	30	25	25	26

Minutes	0	5	10	15	20	25	30	40	50	60	70	80	90	100	110	120
610	0	27.0	30.0	32.0	33.5	35.0	36.5	40.0	43.5	45.5	47.5	49.5	51.5	54.0	55.0	55.0
613	0	12.5	15.0	17.5	19.0	20.5	21.0	26.0	25.5	26.5	28.0	29.0	31.5	33.5	36.0	38.0
612	0	19.5	24.0	26.5	28.0	29.5	31.0	33.0	32.0	34.0	35.0	35.0	35.0	35.5	37.0	38.0
619	0	24.0	35.5	38.0	39.5	40.5	42.0	44.5	48.0	49.0	50.0	51.5	53.5	54.0	55.0	53.5
617	0	30.0	34.0	37.0	38.5	41.5	43.5	44.0	45.5	46.0	47.5	47.5	47.5	45.5	44.0	45.0
611	0	21.5	23.5	25.0	27.5	29.5	31.5	35.0	37.5	39.5	42.5	44.0	46.0	46.5	47.0	49.0

TABLE XXV - Group VI Experiments. Data for Values of, Arterial & Venous Blood pH & P_{CO_2} Determinations and Venous Noradrenaline and Adrenaline Blood Plasma Determinations - At One and Two Hours After Start of the Constant Venous Return Period.

Experiment Number	pH		P_{CO_2}		Catecholamines		pH		P_{CO_2}		Catecholamines	
	Art	Ven	Art	Ven	NA	A	Art	Ven	Art	Ven	NA	A
610	7.41		19		2.3	18.2	7.35		20		6.8	30.2
613	7.38	7.19	33	49	2.5	19.4	7.27	7.25	35	51	3.8	22.6
612	7.22	7.19	18	44	0.5	26.2	7.20	7.11	20	47	0.5	32.8
619	7.25	7.18	27	49	14.6	53.3	7.11	7.03	23	54	9.8	54.2
617	7.26	7.18	14	28	3.9	18.3	7.18	7.06	13	26	4.9	17.1
611	7.28		20	40	0.0	13.9	7.22		11	43	0.0	4.6
N	6	4	6	5	6	6	6	4	6	5	6	6
$\bar{x}$	7.30	7.185	21.8	42	3.96	24.9	7.22	7.11	20.33	44.2	4.3	26.9
s^2	0.005	0.00003	38.81	60	24.2922	174.66	0.0055	0.0071	60.56	96.56	11.673	233.801
S.D.	0.07	0.0054	6.23	7.74	4.93	13.22	0.0742	0.0842	7.78	9.83	3.42	15.28

TABLE XXVI - Group VII Experiments. Summary of Salient Data to Show the Effect of Phenoxybenzamine in the Dosage of One mg/kg.

Experiment Number	Value of Constant Venous Return Rate ml/kg/min (1)	Minimum Mean Arterial Pressure During (0 to 30)' Interval mmHg (2)	Maximum Mean Arterial Pressure During (30 to 120)' Interval mmHg (3)	Maximum Reservoir Blood Volume During (0 to 120)' Interval ml/kg (4)	Time During (0 to 120)' Interval When Maximum Reservoir Blood Volume Reached (5)	Reservoir Blood Volume at the End of (0 to 120)' Interval ml/kg (6)
554	23.4	35	50	29.3	50 to 60 min	26.0
555	28.1	32	55	29.4	90 to 100 min	28.5
556	15.7	17	20	38.9	20 to 30 min	31.3
557	21.5	28	30	58.5	70 to 80 min	51.2
558	32.1	30	60	37.2	120 min	37.2

TABLE XXVII - Group VIII Experiments. Data Presented to Show the Values of Blood Plasma Volume Determinations and Venous Hematocrit Determinations.

Experiment Group and Experiment Number	Value of Constant Venous Return Rate ml/kg/min	Control Plasma Volume ml	Point 'A' - Number of Minutes After Start of Constant Venous Return Period Plasma Volume Re-determined	Plasma Volume at Point 'A' ml	Mean Arterial Pressure at Point 'A' mmHg	Plasma Volume Gain Between Control and Point 'A' ml	Plasma Volume Gain Between Control and Point 'A' ml/kg	Plasma Volume Gain Expressed as a Percentage of Control Plasma Volume
II - 574	17.9	675	47	785	65	110	7.6	16.2
I - 575	17.3	475	41	675	50	150	14.8	31.6
I - 576	16.1	750	50	910	48	160	13.9	21.3
I - 577	16.9	540	40	670	30	130	11.8	24.0
I - 579	14.7	565	50	720	32	155	12.8	27.4
III - 583	29.8	580	45	660	64	80	6.5	13.8
III - 587	32.6	555	41	660	42	105	11.2	18.9
$\bar{x}$	20.7	591	44.8	726	47.3	127	11.2	21.9
s^2	45.06	7212	1.6	7403	166	771	8.32	33.75
S.D.	6.71	84.9	1.26	86	12.9	27.8	2.88	5.85

46.0(C), 48.0(C)	44.0(7)	48.0(30)	46.0(60)	45.0(90)		
45.3(C)	50.0(30)	51.0(72)	51.5(132)			
39.8(C), 36.9(C)	37.2(32)	35.3(48)	36.6(79)	34.4(95)	32.4(131)	
48.0(C), 49.5(C)	47.6(39)	40.0(110)				
44.6(C)	43.3(45)	44.6(61)	43.6(119)			
42.3(C)	43.1(55)	42.7(76)	44.8(114)			

TABLE XXVIII - Group IX Experiments. Data of Hematocrit Values and Blood Plasma Volume Values Determined Before and During the Period of Constant Venous Return. The Three Dogs in this Group Were Splenectomized Several Days Prior to the Experiment (see Chapter III).

Experiment Number - 591. Value of Constant Venous Return in this Experiment was 14.4 ml/kg/min. Average Mean Arterial Pressure During the (30 to 60) minute Interval was 21 mmHg.

Minutes	Control	4	7	10	15	20	25	30	40	60
Hematocrit	44.5	40.5	40.5	41.0	40.9	39.0	38.0	38.3	37.2	36.1
Plasma Volume	625	736		721	721	783	817	807	846	887

Experiment Number - 593. Value of Constant Venous Return in this Experiment was 16.0 ml/kg/min. Average Mean Arterial Pressure During the (30 to 100) minute Interval was 53 mmHg.

Minutes	Control	3	6	9	12	15	20	25	30	40	50	60	70	80	90
Hematocrit	55.0	54.8	55.3	53.5	54.4	54.8	54.2	53.5	52.7	52.1	52.0	51.5	51.7	50.5	51.6
Plasma Volume	650		642	690		655	671	690	713	730	747			778	

Experiment Number - 597. Value of Constant Venous Return in this Experiment was 13.5 ml/kg/min; Average Mean Arterial Pressure During the (30 to 120) minute Interval was 19.2 mmHg.

Minutes	Control	2	17	27	37	47	72	102	117
Hematocrit	49.0	48.5	47.5	46.7	46.1	45.0	44.1	43.1	43.2
Plasma Volume	650	662	690	712	729	763	791	824	820

Table XXIX - Data Presented to Show the Effect of Noradrenaline Administration at the End of the Period of Constant Venous Return on, Mean Arterial Pressure, Reservoir Blood Volume and Heart Rate.

Experiment Number	Value of Constant Venous Return Rate ml/min	Average Mean Arterial Pressure During (30 to 120)' Interval mmHg	Value of Mean Arterial Pressure at the End of Constant Venous Return Period mmHg	Reservoir Blood Volume at the End of Constant Venous Return Period ml	Heart Rate at End of Constant Venous Return Period Beats/min
548	250	31	25	570	172
551	220	40	35	560	185
553	185	19	17	625	147

Maximum Values Reached After the Addition of 2000 Micrograms of Noradrenaline to the Reservoir Bottle at the End of the Constant Venous Return Period.

Experiment Number	Mean Arterial Pressure mmHg	Heart Rate Beats/min	Reservoir Blood Volume ml	Time of Maximum Changes After NA Added to Reservoir Bottle	Value of Constant Venous Return Rate In Each Experiment ml/kg/min
548	140	220	700	2 min	20.4
551	90	230	590	2 min	17.5
553	40	193		2 min	16.0

TABLE XXX - Group XI Experiments. The Data of Three Dogs are Presented to Illustrate the Effect of Raising the pH by Means of Administering 0.3 Molar THAM solution into the Reservoir Bottle.

Experiment No. 607. Net Dog Weight - 16.680 kg. Pump Rate Pre-set at 245 ml/min. Pump Rate was Slowed Several Times During this Experiment. Final Rate was 120 ml/min or 7.2 ml/kg/min.

Procedure	Time Minutes	Mean Arterial Pressure mmHg	Heart Rate Beats /min	Reservoir Blood Volume ml	Venous NA	Venous A	Arterial pH	Arterial P_{CO_2}
Control	-1	125	140	0			7.36	28
Pump On	0							
	32	38	140	460	5.0	77.9	7.33	18
	69	32	168	525			7.29	
	81	37	171	540			7.12	
	92	38	170	517	25.9	226	7.10	18
THAM 5 ml	100							
THAM 5 ml	102							
	105	33	157	490			7.20	12
THAM 5 ml	106							
THAM 5 ml	109	26	144	490			7.22	
THAM 2 ml	114							
THAM 2 ml	121							
	126	25	140	510	16.3	209	7.43	10.5
THAM 2 ml	129							
	135	33	128	500			7.49	10.5
	138	33	130	500	20.3	218		

Experiment No. 608. Net Dog Weight - 16,400 kg. Pump Rate Pre-set at 245 ml/min. Final Pump Rate 225 ml/min or 13.7 ml/kg/min.

Control	-1	112	130	0			7.30	30
Pump On	0							
	8	25	122	510				
	30	30	144	760	16.5	78.7	7.10	29
	45	29	147	790				
	55	27	152	810	24.8	105	7.05	28.5
	58	30	153	800				
THAM 5 ml	59							
THAM 5 ml	63							
	66						7.20	
THAM 10 ml	67							
THAM 4 ml	70							
THAM 4 ml	74						7.30	20
THAM 4 ml	78	19						
THAM 4 ml	80	19						
	81	19	120	945				
	84						7.29	21
	86				12.6	57		
THAM 53 ml	to							
	109	17						
	111				7.2	33.8	7.38	18
	114	17	83	950				

TABLE XXX - Continued.

Experiment No. 609. Net Dog Weight - 12.260 kg. Final Pump Rate was 13.8 ml/kg/min.

Procedure	Time Minutes	Mean Arterial Pressure mmHg	Heart Rate Beats /min	Reservoir Blood Volume ml	Venous NA	Venous A	Arterial pH	Arterial P_{CO_2}
Control	-1	125	170	0			7.29	40
Pump On	0							
	5	25	102	175				
	30	25	108	225				
	33				0.83	6.5		
	45	24	107	200				
	60	25	99	200	0.8	5.8		
	63						7.1	19
	70	25	92	160				
	90	25	88	160				
	101	27	85	160			7.04	20
	118	27	82	160	1.1	3.5	7.04	22
	122							
THAM 55 ml	to							
	134							
	123						7.30	
	128							
	134	20					7.53	13.5

TABLE XXXI - Data from Experiment No. 580. These Data were used for the Standard Curve of Figure III - 2, which was used for the Calculation of the Blood Plasma Volume Determinations.

Divisions of Micrometer* Syringe per 25 ml Aliquot of Pooled Plasma	Dilution of Dye in Plasma	Concentration of Dye in Plasma Ratio of Dilution Divided by 100 x	Optical Density Measured by Beckman Model - B Spectrophotometer y
104	1:1200	0.083	0.318
125	1:1000	0.100	0.345
139	1:900	0.111	0.410
156	1:800	0.125	0.465
178	1:700	0.140	0.521
208	1:600	0.166	0.610
250	1:500	0.200	0.727
312	1:400	0.250	0.911
417	1:300	0.330	1.170
625	1:200	0.500	1.740

* The Micrometer syringe was filled with the 5 % Stock solution of T - 1824 blue dye. One ml in syringe equalled 5000 divisions.

Regression equation for the plot of Optical Density versus Concentration of Dye in Plasma, that is the last two columns of the above table for values of concentration from 0.111 through 0.250, was $Y = 0.018 + 3.569x$ and the coefficient of correlation was $r = 0.99985$.

Outline of Chemical Assay Method for the Determination of Noradrenaline and Adrenaline Plasma Concentrations

1.) Isolation of Catecholamines

a) The dog was heparinized by the time the blood samples for the catecholamines were taken. Twenty ml of blood was taken in a glass syringe from the inferior vena cava catheter and placed in a 50 ml polyethylene centrifuge tube to which has been added one ml of sodium metabisulfite solution (0.5 mg/ml of blood). The centrifuge tube was placed in a beaker of ice and immediately spun down in a cold room at four degrees C. The plasma was poured off and kept at four degrees C until treated further.

b) The plasma was removed to the laboratory and 10 ml added to a 50 ml beaker containing 0.5 ml of 0.2 M EDTA (ethylenediaminetetraacetic acid).

c) The beaker was swirled constantly while adjusting the pH to 8.4 with one N sodium hydroxide and 0.1 N sodium hydroxide. This was done as quickly as possible and step (d) immediately performed.

d) The adjusted plasma + EDTA solution was transferred to a 12 ml test tube containing 250 - 300 mg of alumina (Woelm - Activity grade I for chromatography) which had been previously wetted with cold boiled deionized water (CBDW). If the test tube was not completely filled it was filled to the top with CBDW and the top covered with parafilm. The tube was inverted up and down by hand for 4 minutes. The tube was centrifuged for a minute in a clinical centrifuge machine to pack the alumina and the supernatant sucked off with a long needle taking care not to suck off any of the alumina. The tube was filled again to the top with CBDW rotated for a few seconds, centrifuged and the aqueous layer aspirated. The alumina was washed in this manner at least twice. If the alumina had been contaminated

by some red cells when the plasma was originally poured off, the procedure was repeated more than twice. After the last wash the centrifuging was more prolonged and the aqueous layer sucked off as completely as possible.

e) Elution was carried out with 4.9 ml of 0.01 N hydrochloric acid. A parafilm was placed over the top and the tube gently rotated for 3 minutes. The tube was stored in the cold room until all samples had been treated. All test tubes were then centrifuged in the cold room in a clinical centrifuge. The acid supernatant layer was then assayed by the iodine oxidation method.

2.) Oxidation of Catecholamines*

a) Two ml aliquot of the sample to be assayed was pipetted into a test tube containing 1.0 ml of 4 % Versene (pH 6.3 - 6.5).

b) Then 0.2 ml of 0.1 M iodine was added and mixed.

c) After exactly 2 minutes 0.5 ml of alkaline sulfite solution was added and mixed.

d) After exactly 2 minutes 0.6 ml of 5 M acetic acid was added and mixed.

e) The test tube was heated in boiling water for 5 minutes after which the contents were rapidly cooled in cold water. The cooling time was not critical.

f) The fluorescence was then read in an Aminco Bowman Spectrophotofluorometer. The sample for determination of adrenaline concentration was activated at a wave length of 385 mu and fluorescence read at 485 mu, and that for noradrenaline activated at 440 mu and fluorescence read at 510 mu.

The above procedure could be carried out on a maximum of eight samples at a time.

* This method was brought back from the National Institutes of Health, Bethesda, Maryland, U.S.A., by Dr. C. W. Nash of the Dept. of Pharmacology, University of Alberta. Dr. Nash evidently obtained the method from Miss Alice Hogans, who was working at the time at NIH.

3.) Reagents

a) 4 % Versene (disodium salt of EDTA). The pH of this solution had to be between pH and 6.5 and was adjusted by addition of NaOH.

b) 0.1 M Iodine --- 0.25 g I_2
4.80 g KI
q.s. ad 100 ml H_2O

c) Alkaline sulfite solution --- 0.63 g anhydrous Na_2SO_3 dissolved in 5 ml H_2O. Add 20 ml of 5 N NaOH.

d) Alumina (Woelm) was washed with HCl and H_2O as described by Crout(1961).

e) NA and A were stored as stock solutions (100 ug/ml in 0.01 N HCl). Standards were made up each day from these (NA standard = 0.05 ug; A standard = 0.5 ug). Photomultiplier was adjusted to 100 on the A standard.

f) Quinine sulfate standard was used to check Instrument each day (1 ug quinine sulfate per ml in 0.1 N H_2SO_4).