"MYOCARDIAL FUNCTION IN HEMORRHAGIC SHOCK"

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"A Study of Myocardial Function in Hemorrhagic Shock"

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Thesis submitted to the Faculty of Graduate Studies and Research at McGill University, in partial fulfillment of the requirements for the Degree Master of Science.

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PREFACE

The experimental work presented in this thesis was carried out in the Mc Gill University Surgical Research Clinic in The Montreal General Hospital while the candidate was the holder of the John Mc Crae Fellowship in Experimental Surgery at Mc Gill University. Financial support was also received from the Medical Research Council of Canada.

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Dr. A. Hope Mc Ardle modified the biochemical assays for use in this study. She also spent considerable time in editing the manuscript for this thesis.

Miss Louise Carpentier carried out the tedious biochemical assays required in this study.

Mr. David Hodges B.Sc., did all the histology and was responsible for taking all the photomicrographs presented. Mr. H. Artinian reproduced the graphs used in this thesis.

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INTRODUCTION

The concept of impaired myocardial function in shock has been suspect and a matter of debate for many years.

A French surgeon, LeDran[1] as early as 1743, described a severe gunshot wound, postulating that "spasmodic contraction of the fibers of the heart," may play a role in the observed syncope, or "interception of the stream of Animal Spirits."

Jordan[2] made the dogmatic statement in 1881: "Without impaired cardiac action, shock is impossible." He attributed death to extreme contraction of the heart. He advocated external heat, transfusions and cardiac puncture. One appreciates some of the frustrations he must have experienced in treating such patients, from his statement: "to watch and assist nature is our chief duty."

Henderson[3] in 1908 spoke of "cardiac tetanus" in hemorrhagic or traumatic shock. He described a slowly developing acapnia in shock with a resulting hypertonicity of the heart. The hypertonicity of ventricular action prevented diastolic relaxation, which was in turn aggravated by a decreased venous return due to a failing venopressor mechanism.

A vast amount of research has been carried out in the field of shock since the turn of the century. This work was greatly stimulated by the two great wars. Early in this century following the work of Groenigen, and Crile[4] and others, considerable attention was given to the role that peripheral circulatory failure played in both hemorrhagic and traumatic shock.

Cannon's classic treatise[5], following the First World War,

contained several theories explaining the pathogenesis of traumatic shock. Some of these included: excessive vasoconstriction, metabolic disturbances, fat embolism, traumatic toxemia and heart failure."

The most significant developments in the period between the two World Wars was the work of Parsons, Phemister[6] and Blalock[7]. They challenged Cannon's hypothesis that muscle contusion produced only minor local fluid loss. They were the first to point out the importance of a decreased effective circulating blood volume in shock of any etiology. It was this work which established without a doubt, the value of homologous blood transfusions in the treatment of shock.

The work of Lamson[8], Fine[9] and Wiggers[10], during the same period served to standardize the methods of studying hemorrhagic shock in the dog.

It soon became apparent, both in the experimental laboratory, and on the hospital wards, that after a critical period of hypotension, the use of massive transfusion therapy failed to resuscitate all cases of shock. The term irreversible shock appeared to describe this group, which failed to respond to restoration of blood volume alone.

Many authors[11] have criticized the use of the work "shock" as being ill-defined and lacking in precision. Simeone[12] has defended the use of this word with certain reservations. He points out that clear definition and precision may not always be possible in describing a complex phenomenon as shock, in which many of the underlying mechanisms are poorly understood. Simeone has insisted that the word "shock" can be useful only if all agree that it describes a syndrome with many and varied etiological agents, which ultimately results in an inadequate perfusion of tissues and

organs. Moore has emphasized that the term "irreversible shock" must be reserved to describe the terminal circulatory decline which leads to a fatal outcome, following a critical period of controlled hypotension in a laboratory animal. He suggests that "refractory hypotension" better describes the complex phenomena seen in hypotensive patients who fail to respond to replacement of blood volume alone.

The basis of almost all investigations in the field of shock has been concentrated on attempts to elucidate the pathogenesis of this failure to respond to transfusions and of the ultimate fatal outcome in this refractory group of patients. Every physiological system in the body has been studied both at the organ and cellular level during varying degrees of hypotension. Almost every organ system has been incriminated as a contributor of irreversibility in hemorrhagic shock. Only the literature directly pertaining to myocardial function in hemorrhagic shock will be discussed in this introductory review.

Adequate circulation is the result of a delicate interplay between the heart, the circulating blood volume and the status of the peripheral vascular bed. Circulatory homeostasis is further integrated by the wide ranging activities of the neuro-endocrine system which transmits humoral influences from all parts of the body.

Wiggers[14] in 1946 suggested that a primary depression in myocardial function may be a factor in irreversible hemorrhagic shock. He based this observation on extensive experimental studies on a large number of dogs, using a standardized hemorrhagic shock model. He monitored central venous pressure, mean arterial blood pressure, intraventricular pressures, cardiac

output, and inferior vena caval flow during the various phases of shock induced by bleeding. The animals were bled over a short period to a mean arterial blood pressure of 50 mm of Hg. This blood pressure was maintained for ninety minutes and then the blood pressure was lowered to 30 mm of Hg., for an additional period of forty-five minutes. This critical period of hypotension was referred to as "oligemic shock" and up to a certain limit was readily reversible by restoration of blood volume. The hypotension which developed in the period following re-infusion of blood was termed "normovolemic shock". The syndrome consisting of the progressive circulatory decline which supervenes after an effective period of hypotension was referred to as "irreversible hemorrhagic shock."

The period of oligemic shock was characterized by low systolic and diastolic pressures, a small pulse pressure due to a low systolic discharge, which, in turn, is secondary to a decreased venous return. The vena caval flow was noted to be less than 50% of normal, with a corresponding depression of central venous pressure. These changes could all be attributed to a decreased blood volume.

It was noted, shortly following infusion of all shed blood that vena caval flows had returned to normal levels, but that central venous pressures remained above control values in most cases. Heart size was noted to be greater than control at this point. The stroke volume and cardiac output were below control levels in spite of an elevated effective filling pressures. It was upon these findings that Wiggers and his colleagues (15,16) postulated that myocardial depression may play an important role in the

final circulatory decline seen in irreversible hemorrhagic shock. This view was contrary to that of his contemporaries who felt that the predominant lesion was a generalized increase in capillary permeability resulting in a continuing loss of fluids and colloids from the circulation. The theories proposed (17) to explain the capillary lesions included excessive vasoconstriction, hypotension, anoxemia and toxemia.

Kohlstaedt and Page (18) combined cardio-oncometric and roentgenologic measurements of heart size in hemorrhagic shock in dogs. They demonstrated a definite reduction in heart size during the initial hypotensive phase, but as the hypotension persisted, venous pressure rose sharply. This was followed by a progressive increase in heart size despite further bleeding. Stroke volume decreased as dilatation of the heart progressed. In the terminal phases of hypotension, administration of plasma frequently precipitated circulatory collapse and death. This experimental study certainly suggested that a primary decrease in myocardial contractility may follow hemorrhagic hypotension.

Sarnoff et al (19) while comparing the relative effects of intra-arterial and intra-venous infusion on coronary flow made incidental observations which suggested that an insufficient coronary flow may complicate terminal hemorrhagic shock. Case et al (20) had previously described a progressive rise in left auricular pressures, late in hemorrhagic shock, denoting a failing myocardium. They postulated an insufficient coronary flow as the etiological agent. Sarnoff augmented left coronary flow in late hemorrhagic shock, by means of the Dale-Schuster pump. This resulted in a prompt decline in left auricular pressures to normal levels. Attempts were made to

prevent any increase in blood volume during the periods of augmented coronary perfusion. The data presented in this paper strongly suggested that left coronary flow is deficient in late hemorrhagic shock. The deficient coronary flow was accompanied by a rise in left atrial pressures secondary to a decline in myocardial contractility. Sarnoff also pointed out that an augmentation of coronary flow and reduction of left auricular pressures in late hemorrhagic shock may be accomplished by one of the sympathomimetic amines (Aramine).

Gomez and Hamilton[21] recently studied the response of both a normal heart, and a heart subjected to varying periods of hypotension, to a massive infusion of blood via the left atrium. The hearts which had sustained a period of hypotension(mean arterial blood pressure of 30mm Hg.) for ninety minutes responded to the massive infusion load of an inability to increase cardiac work in spite of large increases in left atrial pressures. This incapacity was not evident immediately following the period of hypotension. The damage became more severe one or two hours following the hypotensive episode, despite the fact that the mean arterial blood pressure was maintained at 100 mm of Hg. The control animals subjected to similar operative proceedures did not show evidence of cardiac deterioration. They were always able to increase the rate of cardiac work throughout the infusion in the face of a relatively small rise in left atrial pressures. Gomez and Hamilton presented this work as further evidence that myocardial damage occurred over a ninety-minute period of hypotension. They also pointed out the fact that in the early stages these alterations in myocardial contractility were masked. They presented

the massive infusion test via the left atrium as a method of evaluating the functional capacity of the heart.

Crowell and Guyton [22] have carried out extensive studies on myocardial function in irreversible hemorrhagic shock. They have centred their attention on the transition period between reversible and irreversible shock. Many investigations [24] have shown that there is a critical point, before which restoration of blood volume to the hypotensive animal will lead to complete recovery; and after which restoration of blood volume leads to temporary restoration of blood pressure, followed by a progressive circulatory decline leading to death. The point at which an animal becomes irreversible is largely dependent upon the duration and severity of hypotension. Age, sex, species, and nutritional status of the animal have also been shown to influence the time of onset of irreversibility. The point at which an animal becomes irreversible is characterized by loss of reflexes, failure to require further anesthesia for operative procedures and the spontaneous reinfusion of blood from the bleeding reservoir to maintain the hypotensive arterial blood pressure (30 mm Hg). Crowell and Guyton [22] studied oxygen consumption, cardiac output, arterial blood pressure, right and left atrial pressures during the transition period from reversible to irreversible shock. Previous studies [25] in their laboratory had shown that the low arterial blood pressures associated with hemorrhagic hypotension were not sufficient to transport adequate amounts of oxygen to the tissues. Thus at low blood pressures, the oxygen supply becomes flow limited, and an increase or decrease in blood flow is reflected by corresponding changes in oxygen consumption. Crowell noted

that at the point of irreversibility the oxygen consumption remained constant indicating that the nutritive flow to the tissues did not become altered at this stage through some failure of the vasomotor or peripheral vascular system. They further demonstrated that with a constant blood viscosity, the cardiac output and the peripheral resistance also remained constant, suggesting that no significant changes have occurred in the peripheral circulation during the transition from reversible to irreversible shock. In studies of heart function, however, he noted a slight rise in left atrial pressures during this transition phase.

Crowell (23) using the same experimental model in a further group of experiments attempted to quantitate myocardial contractility by the use of "cardiac output curves" during the course of hemorrhagic hypotension. A cardiac output curve was obtained by plotting cardiac output on the ordinate, and left atrial pressure on the abscissa of an x-y recorder. He demonstrated that dogs bled to a mean arterial blood pressure of 30 mm of Hg., and held at this level, showed a slight rise in left atrial pressure after 72 minutes of hypotension. The rise in atrial pressure was associated with an uptake of blood from the arterial reservoir to maintain arterial pressure at 30 mm of Hg. As hypotension progressed, left atrial pressure increased and further blood was taken back from the bleeding reservoir until terminally the heart could not maintain this relatively low blood pressure in spite of high atrial pressures. In the next group of animals, all shed blood was reinfused after a period of 80 minutes of hypotension. He then transfused blood continuously in

order to maintain the pre-shock cardiac output. The left atrial pressures were steadily increased above control values in order to maintain a sub-normal cardiac output. Crowell had thus demonstrated myocardial hypo-function, as, at a given atrial pressure the heart subjected to hemorr-hagic hypotension pumped less blood than a normal heart. The findings suggested cardiac damage, along with no significant change in oxygen consumption or peripheral circulation at the point of irreversibility which prompted Crowell to make the statement that "progressive cardiac failure is the cause of the declining arterial pressure in irreversible hemorrhagic shock.

Rothe and Selkurt (26) using a closed chest model evaluated myocardial function in hemorrhagic shock, by the use of ventricular function curves. They concluded that there was a range of severity of hemorrhagic hypo-tension accompanied by moderate, reversible cardiac depression, and peri-pheral vascular damage, which, if not compensated for by extra transfusions, led to death from hypotension secondary to an inadequate venous return. They suggested that the decrease in cardiac filling, in the majority of cases is more important than primary myocardial failure in the decline of cardiac output leading to death.

Weidner, Roth and Simeone (27) studied the myocardial response to prolonged hemorrhagic hypotension, by the use of the Walton-Brodie strain gauge arch to measure alterations in the force of myocardial contraction. They observed that the contractile force of the myocardium remained normal in the terminal phases of irreversible hemorrhagic shock, despite a pro-gressive decrease in arterial pressure as the animal dies. From these

findings, they concluded that failure of a previously normal myocardium does not play a role in the deterioration of the circulation and death following periods of hypotension.

There is considerable indirect evidence suggesting myocardial damage in hemorrhagic and other forms of shock which have been obtained from studies of E.C.G., myocardial pathology, myocardial blood flow and myocardial metabolism in hemorrhagic shock.

Numerous studies of the electrocardiographic changes have been carried out both during and following various shock producing injuries. In a study of electrocardiographs from casualties in shock on the Italian front, Burnett, Bland and Beecher [28] observed that diagnostic changes were rare. These were all previously healthy young men. Izquieta and Pasternack [29] carried out a methodical series of electrocardiograms during the course of experiments on irreversible hemorrhagic and ischemic compression shock in dogs. In hemorrhagic shock there was an early depression of the S-T segment of all leads of the electrocardiogram. The electrocardiogram in the majority of cases returned to normal upon the replacement of the withdrawn blood. However, before arterial blood pressures began to fall suggesting irreversibility, the S-T displacement redeveloped and changes appeared in the T waves. They concluded that the electrocardiographic changes supported the concept that myocardial changes develop in hemorrhagic shock. Master et al [30] documented a large series of electrocardiograms on patients who had suffered varying degrees of hemorrhage from many and varied causes. He was impressed by the frequency with which hemorrhage caused and precipitated electrocardio-

graphic changes suggestive of coronary insufficiency. These changes assumed more importance in those patients with antecedent heart disease. The most common changes seen were flat or inverted T waves, RS-T depression and rarely combined RS-T and T wave changes. Hackel and Catchpole[31] observed electrocardiographic evidence indicative of myocardial ischemia and injury in 48 of 74 dogs in hemorrhagic shock. They also noted that these changes were not improved by l-norepinephrine infusions.

There have been many gross and microscopic studies done on the myocardium in both humans and animals following a shock-producing injury. Mylon[32] first described heart lesions in dogs surviving tourniquet shock. Huleper and Ichniowski[33] noted similar changes in animals sacrificed after recovery from histamine induced shock. Mallory[34] noted a fat vacuolization of the myocardium in humans who had suffered a shock-producing injury prior to death. Melcher and Walcott[35] in 1950 correlated the above findings with a detailed pathological study of myocardial lesions in dogs surviving shock produced by a variety of methods. They described a characteristic pathological picture in the myocardium. The most consistent early findings in the myocardium of dogs which died following hemorrhagic shock, were subendocardial hemorrhages involving predominately the papillary muscles of the left ventricle. The gross changes were most prominent in the left anterior and posterior papillary muscles and in the mid-portion of the interventricular septum. Similar changes were observed in the right ventricle, but to a lesser degree. Scattered para-coronary sub-epicardial hemorrhages have also been observed.

Hackel[31] has described minute petechial involving the mitral valve. Microscopic examination showed the areas of hemorrhage lie immediately below the endocardium and frequently involved adjacent conducting fibres. The involved cardiac muscle showed a loss of striations, a more deeply eosinophilic cytoplasm and more darkly staining nuclei than surrounding cells.

Gross examination of animals surviving three to ten days after shock, revealed widely scattered yellowish-grey areas with a similar subendocardial distribution in the myocardium. A cut section of the involved areas showed a greasy surface which tended to bulge above the surrounding cardiac tissue. Microscopic examination of these areas using both hematoxylin-eosin and Sudan III stains revealed large amounts of lipoid staining within individual muscle cells. The maximal amounts of lipoid staining material were seen between the third and fifth day following shock. Hematoxylin-eosin stain of these areas revealed myocardial fibres in various phases of necrosis. This change was associated with an inflammatory exudate consisting of large histiocytes, lymphocytes, plasma cells and rare polymorphonuclear leucocytes. Animals studied fifteen to thirty days following shock revealed minimal fibrosis or scarring.

Further evidence of cardiac impairment during hemorrhagic hypotension comes from detailed studies of myocardial carbohydrate metabolism. Edwards et al[81], Hackel and Goodale[82] have shown that the myocardial extraction of dextrose from coronary arterial blood is impaired following a period of hypotension. They have also demonstrated changes in myocardial lactate and pyruvate utilization during and following periods of hypotension.

It is even more interesting that the metabolic changes which develop during hypotension are not corrected by the restoration of myocardial circulation to normal or above, by the use of vasopressor drugs. It is still difficult to interpret metabolic alterations of the myocardium and to relate them to the concurrent functional status of the heart.

There have been several recent detailed hemodynamic studies of patients in shock, who failed to respond to adequate replacement of blood volume alone. Moore[13], Ponka[36] have used the term refractory hypotension to describe a small group of patients with hypotension who do not respond to the more commonly employed rescusitative measures. From all the clinical shock studies, there emerges a group of patients with hypotension who are normovolemic with a high central venous pressure and a low cardiac output suggesting myocardial failure. In the series reported by MacLean et al[37], more than 50% of the patients studied were classified as having a cardiac deficiency. This group of patients were usually elderly and the myocardial deficit was frequently masked. Stahl[38] and Lillehei[39] have suggested that a cardiac deficit is so common in the hypotensive patient that they have advocated the routine use of a cardiac glycoside in the elderly patient in shock.

There is therefore considerable evidence both in experimental animals and in man, that alterations in myocardial contractility may contribute to irreversible or refractory shock.

If heart failure played a role in irreversible hemorrhagic shock, it is conceivable that either pharmacological or mechanical support of the myocardium might play a role in the treatment of refractory hypotension.

McPherson and Haller[75] concluded that the use of ouabain did not correct, prevent or significantly alter irreversible shock in the dog. Keyl and North[76] however, demonstrated a decreased mortality rate using cardiac glycosides in hemorrhagic shock. Crowell and Guyton[22] showed that the use of ouabain did not influence the final fatal outcome of hemorrhagic shock in the dog, but significantly delayed the onset of irreversibility.

The possibility of supporting the heart in failure by mechanical means has been proposed for several years. The development of total heart by-pass as a useful surgical technique[77] has permitted the cardiovascular surgeon to repair a wide range of congenital and acquired heart lesions. The recent development of closed left heart bypass[78,79] has opened a new field in assisted circulation. Left heart bypass has been shown to effectively support a failing myocardium both clinically and in the experimental laboratory. A period of mechanical support to the myocardium following hemorrhagic shock could conceivably support systemic and coronary circulation, and put the myocardium at rest while it recovered from its injury.

OBJECTIVES

An attempt was thus made to study myocardial function in hemorrhagic shock, with the following objectives in mind:

(1) The study of myocardial function during the various phases of hemorrhagic shock, using a model which would allow a quantitative analysis of myocardial contractility.

(2) An attempt to elucidate the role of the myocardium in the determination of irreversibility following prolonged hemorrhagic hypotension.

(3) The study of changes in myocardial metabolism during hemorrhagic shock and attempt to correlate these changes with alterations in myocardial contractility.

(4) An evaluation of the use of left heart bypass as a method of supporting the myocardium in dogs subjected to prolonged hemorrhagic hypotension, with particular emphasis on the effect it may have on myocardial metabolism and contractility.

METHOD

Large adult mongrel dogs fasted overnight and anesthetized with 25 to 30 mgm/Kg. of sodium pentobarbital (Siegried S.A. Veterinary) were used in all experiments. Supplementary anesthetic was not required after the induction of hypotension. The dogs were placed left side down on an operating table equipped with a heating element which was used periodically to maintain body temperature between 37° and 40°C. Heparin sodium (Organon Inc) was used as an anticoagulant in the dosage of 2.5 mgm/Kg.

Each animal was intubated with a cuffed endotracheal tube and a positive pressure ventilator was used throughout the duration of the experiment. A polyethylene catheter (PE 330) was placed in each femoral artery. The catheter in the right femoral artery was used to continuously record mean arterial blood pressure. The catheter in the left femoral artery was introduced 10 to 12 cms, and used both to bleed the animal, and to measure cardiac output. A polyethylene catheter (PE 280) was placed in the right femoral vein, passed to the junction of the superior vena cava and right atrium and used to measure central venous pressure. The position of this catheter was verified at autopsy in each case. A similar sized catheter was placed in the identical position via the left femoral vein and used as an injection site for the cardio-green dye.

Statham model P23AC and P23BC strain gauge transducers were used to monitor all pressures. The zero pressure responses of the transducers were checked periodically by opening 3-way stopcocks to the atmosphere.

The hydrostatic zero reference levels were maintained constant during an experiment.

An electro-cardiogram, lead II was recorded continuously via subcutaneous electrodes. This was used to calculate pulse rate and to record electrocardiographic changes during the experiment.

A small right, antero-lateral thoracotomy was performed on each animal maintaining strict hemostasis at all times. The pericardium was opened parallel to the right phrenic nerve and a polyethylene catheter (PE 280) was placed in the left atrium via the atrial appendage to continuously monitor left atrial pressure. The thoracic organs were maintained warm and moist throughout the experiment by the use of warm saline soaked towels.

A four channeled, ink writing Grass recorder was used to continuously monitor all indices throughout each experiment.

Cardiac output was measured by the indicator dilution technique using indocyanine green (Hynson, Westcott and Dunning, Cardiogreen) and a cuvette densitometer (Gilford, model 103-1R). A constant amount of dye was used for each determination and injected via a catheter placed in the region of the right atrium and superior vena cava. Blood sampling was made from the left femoral artery. Blood was withdrawn at 25 ml/min with a constant-rate withdrawal syringe. Immediately after each determination, the blood was returned to the dog and the system flushed with 5 cc of normal saline. The linearity of the densitometer was checked periodically throughout the course of these experiments. Calibration solutions were made by diluting a 1 ml. sample of 2.5 mgm/ml. dye with

4 ml. of saline. This solution was further diluted 1 to 1. Then by adding .4 ml of saline or diluted dye to 9.6 ml. of dogs blood calibration solutions were obtained, containing 0, 10, and 20 mgm/liter of dye. The cardiac output curves were recorded on a Texas ink writing recorder. The individual cardiac outputs were calculated using the Stewart-Hamilton formula:

$$\text{Cardiac Output} = \frac{60I}{CT} \quad \text{(liters per minute)}$$

I = quantity of dye injected in milligrams

T = duration of curve in seconds

C = average concentration of dye in mg/liter during time T.

The aminals in the first section of this experiment were subdivided into three groups:

Group I (10 dogs), after placement of above mentioned catheters and electrodes, had control values of all indices recorded. Thoracotomy with placement of left atrial catheter was then performed, and fifteen to twenty minutes allowed for the animals to assume a "steady state". Post thoracotomy controls were then obtained. The mean arterial blood pressure was then lowered to 30 mm of Hg by controlled hemorrhage using a Lamson[8] reservoir. The mean arterial blood pressure was then maintained at 30 mm of Hg., by raising or lowering the reservoir, until 30% of the maximum bled volume was spontaneously returned to the animal. This is a modification of Fine's[9] standard method for producing irreversible hemorrhagic shock. Most authors[22,24,26] agree that this model uniformly leads to irreversible hemorrhagic shock. When 30% of the maximum bled volume was spontaneously reinfused, the animal had the remainder of the bled volume infused over a

fifteen to twenty minute period. At this point, the heparin effect was neutralized using protamine in a mgm per mgm dose of heparin. The animals were then monitored until death or severe circulatory depression had occurred. Throughout bleeding and reinfusion, a continuous recording of central venous pressure, left atrial pressure, mean arterial blood pressure, E.C.G. and pulse rate was made. Cardiac output was measured at regular intervals during each experiment. A micro-hematocrit was performed at 1 hour intervals during the course of each experiment.

Group II (6 dogs), underwent exactly the same operative procedures as in Group I. Identical pre and post thoracotomy values were documented and the animals were bled to a mean arterial blood pressure of 30 mm of Hg. using the Lamson reservoir. After one hour of hypotension the animals were reinfused and then re-bled to 30 mm of Hg over a period of twenty minutes. This procedure was repeated at approximately one hour intervals until the animal had spontaneously reinfused 30% of its initial maximal bled volume. All shed blood was then returned to the animal and the heparin neutralized. Regular measurement of cardiovascular variables were recorded as in Group I. The animals were then monitored until severe circulatory depression had supervened.

Group III (5 dogs) underwent the same preparation as in Group I and II. The mean arterial blood pressure was lowered to 30 mm of Hg., by bleeding using the Lamson reservoir. It was held at this level for five minutes and then the shed blood was completely infused. Heparin was neutralized as above. The animals were then maintained in the normotensive state for a period of five hours. These dogs required further pentobarbital

anesthesia at regular intervals. The animals were then bled again to 30 mm of Hg, held at this level for five minutes and then completely re-infused. The animals were then sacrificed. This group of animals served as a type of double control on the operative procedures.

An autopsy consisting of detailed gross examination of the thoracic and abdominal cavities was carried out at the conclusion of each experiment. Microscopic examination of the myocardium and lungs was done routinely. Selective microscopic examination of other organs were performed if indicated by gross pathological observations.

The usual difficulties encountered in the attempts to evaluate myocardial function in the intact animal are compounded by the rapid series of changes which occur during this investigation. Nearly 50 years ago in his Linacre lecture (40) on "the law of the heart" Starling presented the concept that the ultimate test of myocardial function was the relation of myocardial work to effective filling pressures at any point in time. However, Starling's studies were all carried out using a heart lung model which would not be applicable to this investigation using an intact animal.

Sarnoff and Berglund (41,42) in 1953 studied Starling's law of the heart in animals with an intact circulation and described a ventricular function curve for each ventricle. They suggested that a ventricular function curve could provide a good method to quantitate myocardial contractility, as well as to evaluate various physiological and pharmacological interventions. The relationship of the external work produced by a ventricle, to a range of effective filling pressures is termed a ventricular function curve. Many modifications of Sarnoff's original method have appeared (21,43).

Crowell used a cardiac output curve (a plot of cardiac output against changes in right atrial pressure) in all his recent investigations of myocardial function.

Ventricular function curves can be used in the hemorrhagic shock model, as the graded hemorrhage and retransfusion provide step-wise alterations in effective filling pressures. Therefore a modification of Sarnoff's ventricular curves was employed, wherein left ventricular stroke work per minute (left ventricular minute work) was plotted against left atrial pressure at any given time.

The left ventricular stroke work in gram-meters per stroke was calculated using the formula:

$$\text{L.V.S.W. (gm meters/stroke)} = \frac{\text{M.A.B.P.} - \text{L.A.P.}}{100} \times \text{S.V.}$$

where:

L.V.S.W. = left ventricular stroke work

M.A.B.P. = mean arterial blood pressure

L.A.P. = left atrial pressure

S.V. = stroke volume.

Stroke volume was obtained from the equation:

$$\text{S.V. (ml.)} = \frac{\text{C.O.}}{\text{P.R.}}$$

where:

S.V. = stroke volume

C.O. = cardiac output (liters/min)

P.R. = pulse rate.

Total peripheral resistance (T.P.R.), expressed as mm Hg per liter/min was calculated from the mean arterial blood pressure and from the cardiac

output.

$$T.P.R. = \frac{M.A.B.P.}{C.O.}$$

No correction was made for central venous pressure in this measurement.

There is a considerable individual variation in canine cardiac outputs [44] and arterial blood pressures. In order to compensate for this and to allow comparison of a group of dogs, all results have been expressed as percentage change from control values.

RESULTS

The mean control values which were calculated at the outset of each experiment are listed in table I.

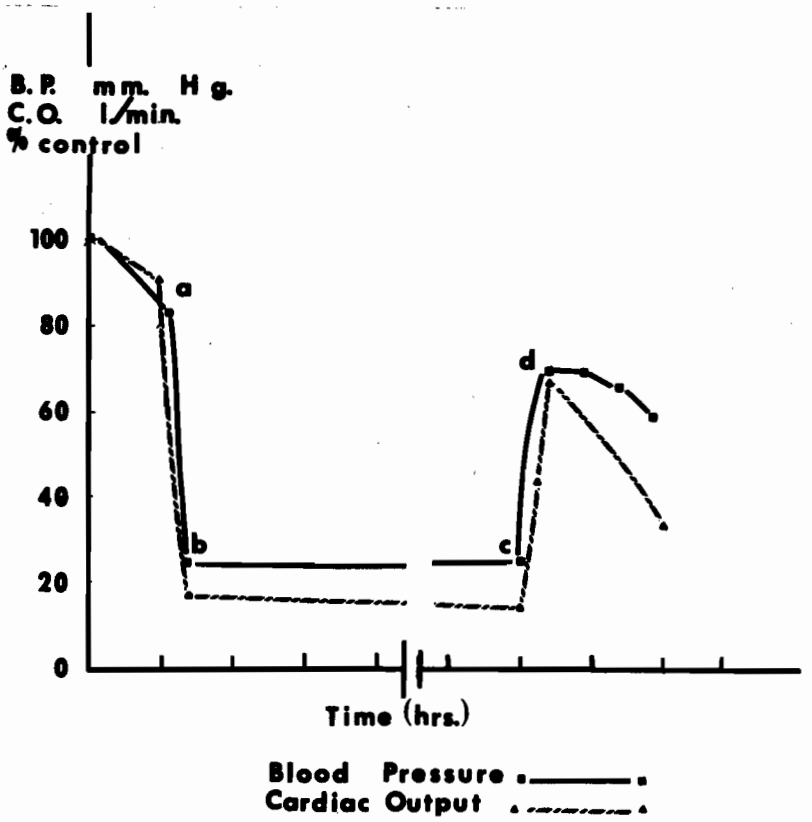
Table I

Body weight	22 kg.
Cardiac output	4.01 liters/min.
Mean arterial blood pressure	137 mm.Hg.
Central venous pressure (chest closed)	1.3 mm Hg.
Left atrial pressure (chest open)	5.1 mm Hg.
Pulse rate	136 per min.
Hematocrit	43 mgm%

Group I (10 dogs)

The average duration of hypotension in this group of animals was 296 minutes. An average initial blood loss of 56 ml/kg was required to lower blood pressure to 30 mm of Hg. The animals continued to bleed into the Lamson reservoir over the next 40 minutes, despite a constant blood pressure of 30 mm of Hg. The maximum bled volume averaged 62 ml/kg and was usually reached within 45 minutes of induction of hypotension.

The animals in this group survived from 2 to 18 hours following reinfusion of shed blood. The majority of animals died within 4 hours of reinfusion.



* Figure 1 - point "a" indicates the post thoracotomy control values and the starting point for controlled stepwise bleeding.

It can be seen in figure 1 that the blood pressure dropped to 82% of control values post thoracotomy. The blood pressure then dropped to 23% of the control value and was maintained at this level with the Lamson reservoir until 30% of the maximum bled volume had spontaneously returned to the animal. The mean arterial blood pressure reached 68% of control

* The broken lines along the abscissa of this graph and those to follow, are used to illustrate the fact that the duration of hypotension prior to reinfusion varied from animal to animal.

values following reinfusion of the remainder of the shed blood. Blood pressure remained at this level for 15 to 30 minutes, and then declined progressively until death ensued.

Cardiac output dropped to 89% of control values following thoracotomy and then followed a pattern similar to that of mean arterial blood pressure, falling to 14% of control during the early phases of hypotension. This stage was followed by an apparent decline in cardiac output as hypotension progressed. Cardiac output was 12% of the control value immediately prior to reinfusion of shed blood. This decline cannot be considered significant in view of the experienced difficulties in accurately measuring cardiac output at very low flow rates. The cardiac output was restored to 66% of control after reinfusion whereupon it soon declined rapidly and progressively.

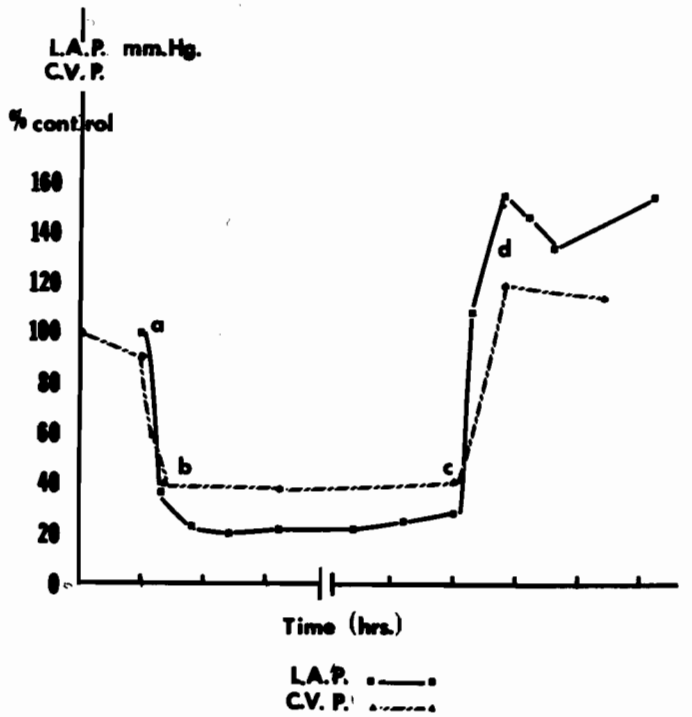


Figure 2 - illustrates left atrial pressure and central venous pressure.

The changes in left atrial pressure during hemorrhagic shock are seen in figure 2. It fell during hypovolemia to 20% of control values, remaining at this level until the animal began to take back blood spontaneously from the Lamson reservoir in order to maintain this low arterial blood pressure. Coincident with the onset of spontaneous reinfusion of blood, there was a small but definite rise in left atrial pressure in most dogs. Just prior to reinfusion, when 30% spontaneous reinfusion had taken place, left atrial pressures had reached 29% of control values. With reinfusion of shed blood, left atrial pressures rose considerably above control values, reaching an average of 154% of

control. In the period 30 to 90 minutes following reinfusion, the left atrial pressure declined gradually, but in only 2 of the 10 dogs did it drop below pre-hemorrhage controls. Terminally, the left atrial pressure reached extremely high values (184% of control). In some animals, left atrial pressures reached higher values than systemic arterial pressures terminally.

The central venous pressure, as seen in figure 2, fell with bleeding to 39% of control. This level was maintained until reinfusion, when central venous pressure rose to a higher value than that of the control, reaching 114%, with complete reinfusion the central venous pressure was maintained at or slightly above control values although a sharp rise occurred terminally. The alterations in central venous pressure appeared to lag behind similar changes in left atrial pressures.

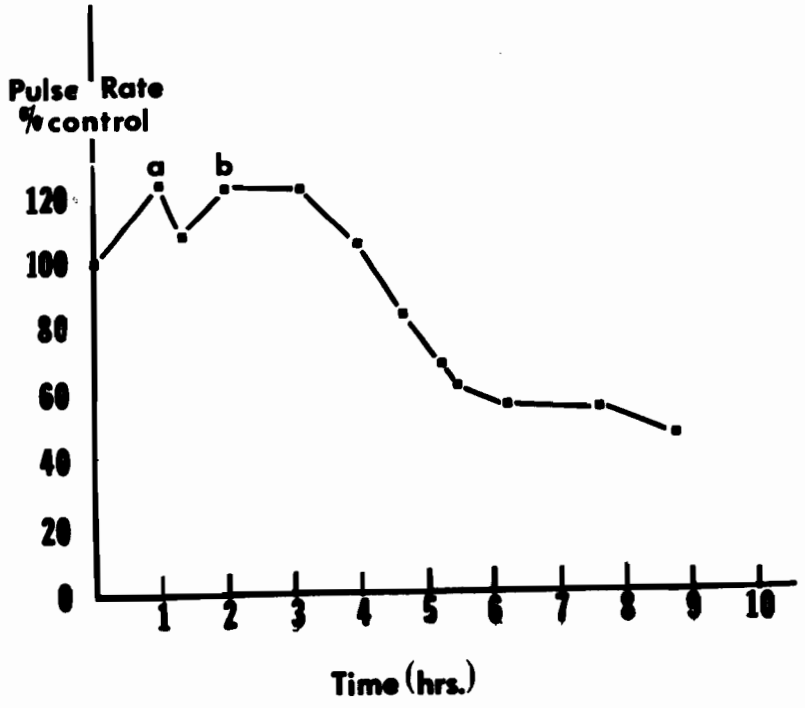


Figure 3

The heart rate increased rapidly to 120% of control (Figure 3) following the induction of hemorrhagic shock. It began to decline just prior to reinfusion. When all shed blood had been returned to the animal, the pulse rate averaged 70% of control. As the circulatory depression following reinfusion progressed, a further slowing of heart rate occurred. Terminally there was a marked bradycardia which was frequently associated with bizarre arrhythmias, including complete atrio-ventricular dissociation.

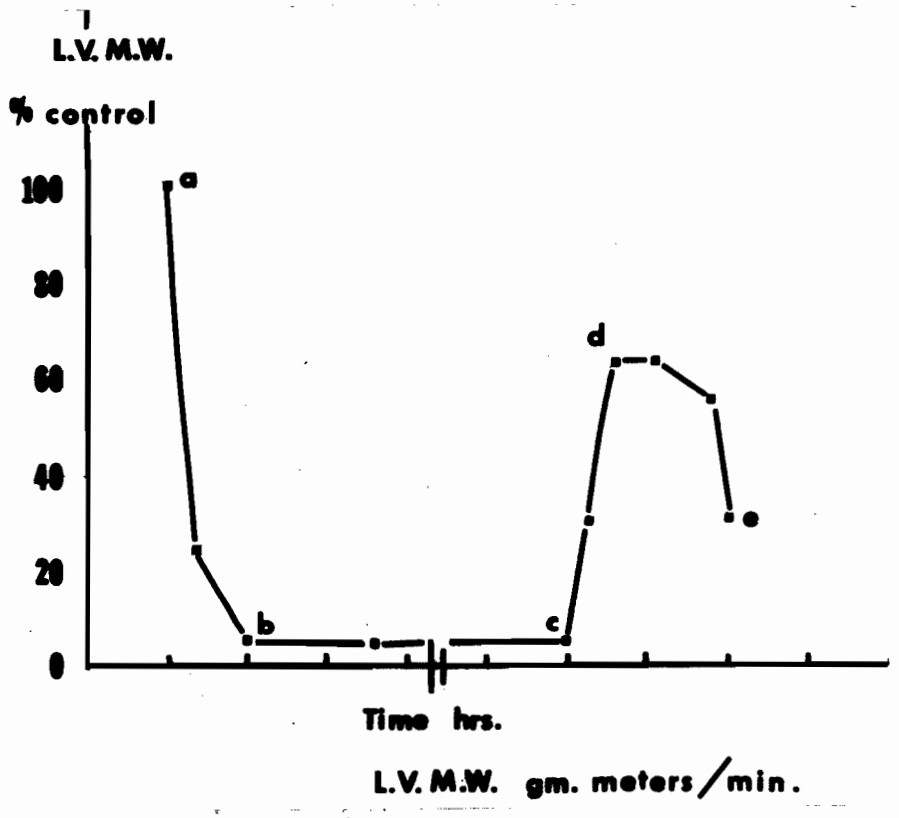


Figure 4

Left ventricular minute work (L.V.M.W.) as illustrated in figure 4, fell to very low levels with bleeding and when the point of maximum bled volume was reached, it was only 7% of the control value. Immediately prior

to reinfusion, it was 5.6% of control. The L.V.M.W. increased to only 64% of control following reinfusion, in spite of markedly elevated left atrial pressures. L.V.M.W. then began a precipitous decline as the animal deteriorated.

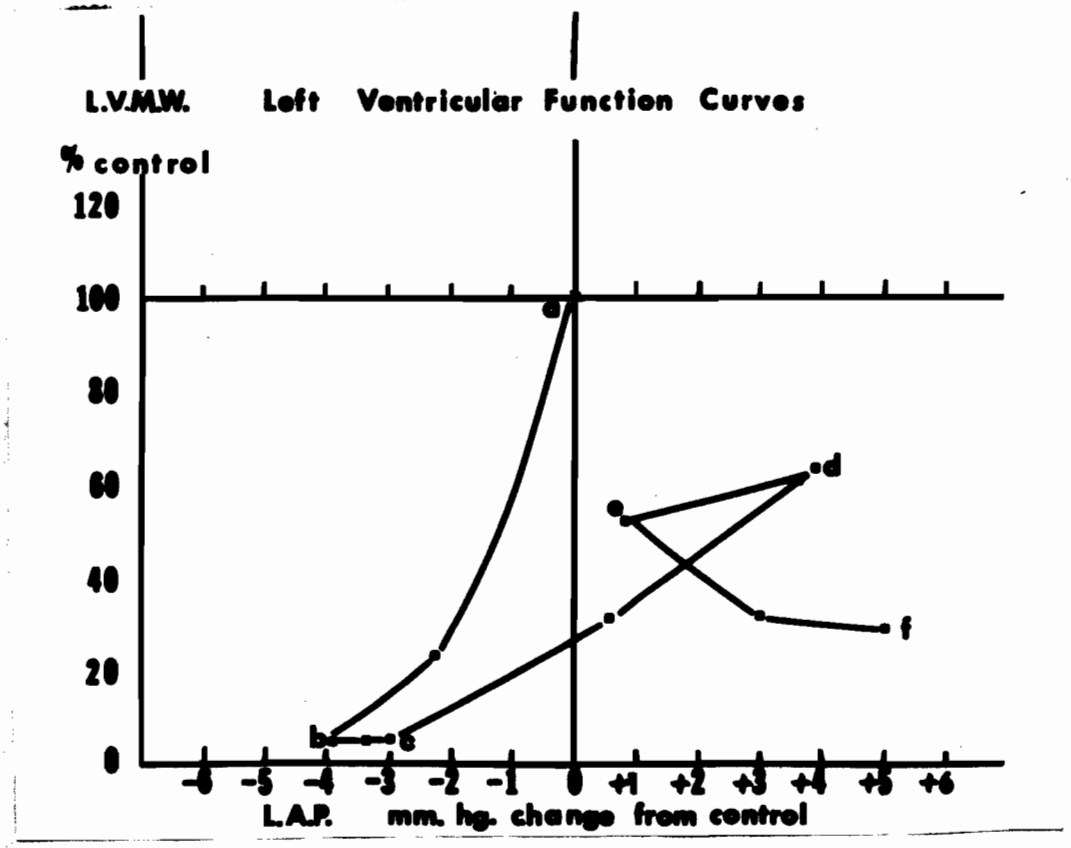


Figure 5

The left ventricular minute work (L.V.M.W.) was plotted against the changes in left atrial pressure at regular intervals during bleeding and reinfusion. The initial curve (a-b) is shown in figure 5 and was obtained during the stepwise bleeding, permitting it to serve as a type of control. The curve obtained following reinfusion (c-d) has shifted considerably to the right compared with the control curve. A "descending limb" also appears as the animals' circulatory system declines terminally.

The dimension of time is lost on this graph, but it can be seen that in order to maintain the low L.V.M.W. during the hypotensive period, there has been a continuous rise in left atrial pressure. This observation, along with the marked shift to the right of the reinfusion curve, suggests a decreased ability of the myocardium to perform external work at equivalent atrial pressures following prolonged hypotension. By definition, this is myocardial failure. The post reinfusion decline in L.V.M.W. was associated with the concurrent decline in left atrial pressure. The left atrial pressure increased again terminally, but L.V.M.W. had declined to extremely low levels.

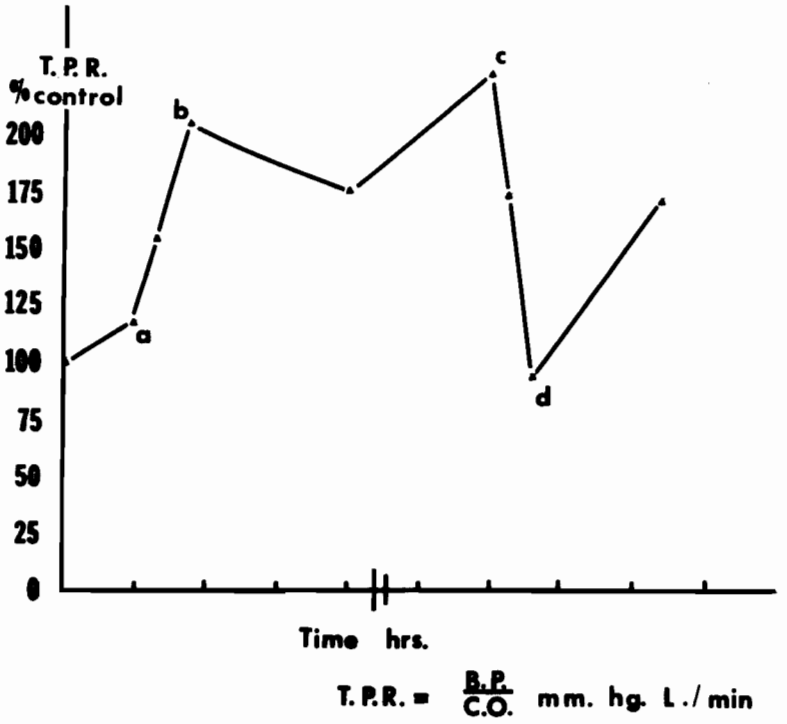


Figure 6

Total peripheral resistance (T.P.R.) increased steadily with bleeding (figure 6). T.P.R. had risen to 200% of the control value by the time maximum bled volume was reached. T.P.R. fluctuated only slightly from this level, with a minimal decline as hypotension progressed. T.P.R. fell to near control values with reinfusion of shed blood. T.P.R. subsequently increased again as the blood pressure and cardiac output declined following reinfusion.

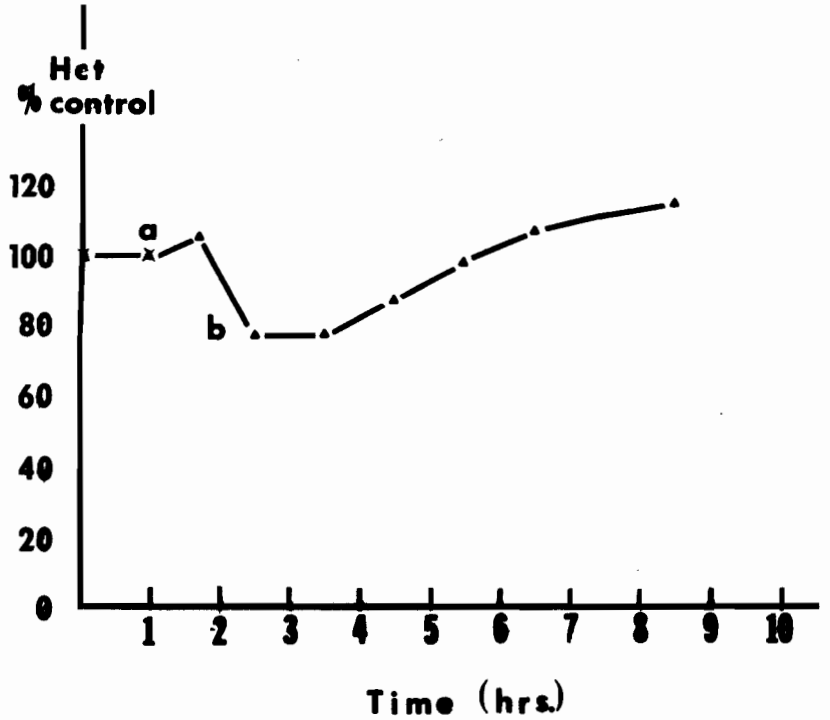
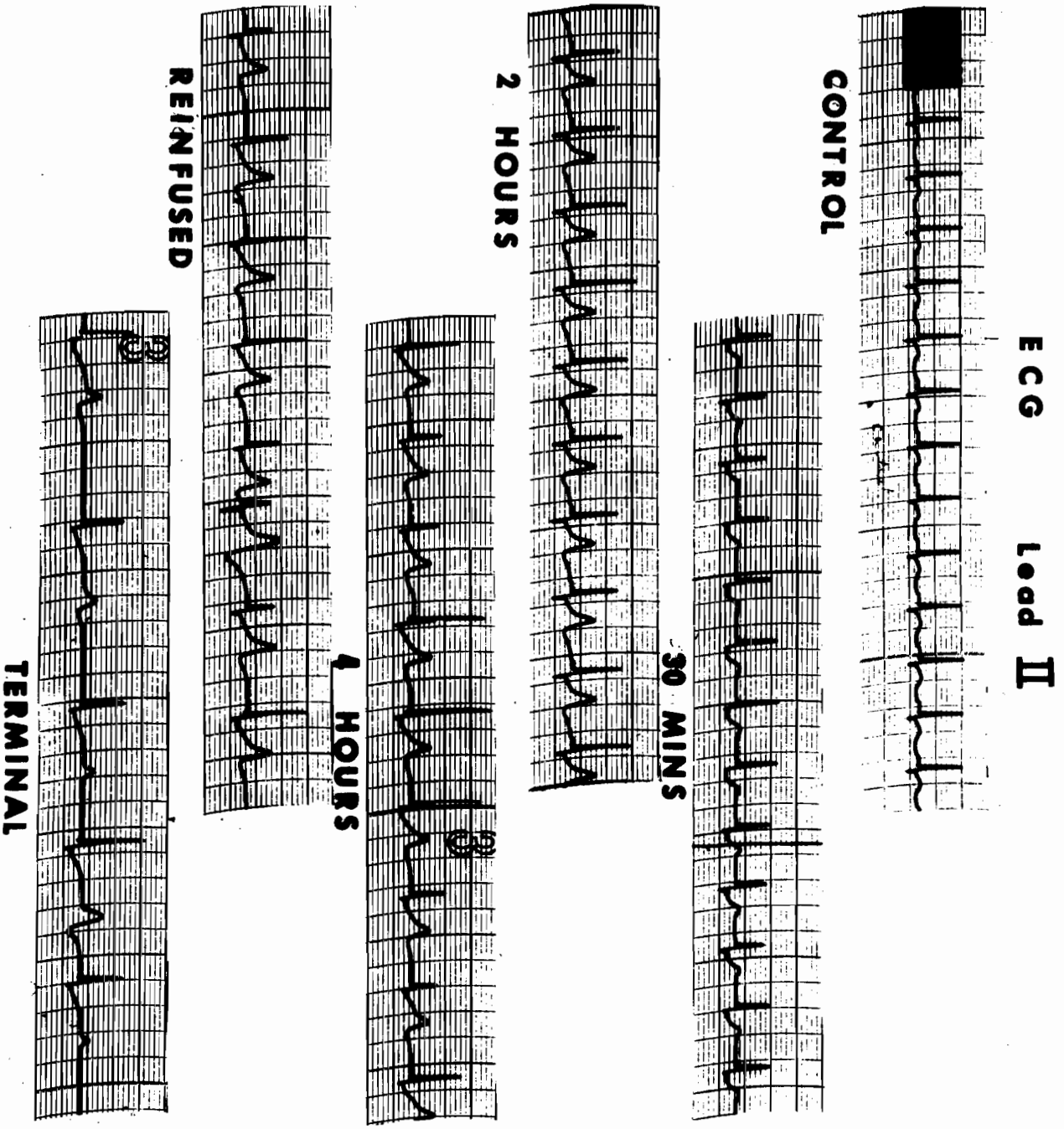


Figure 7

Figure 7 shows that the hematocrit fell to 80% of control values one hour following the induction of hypotension by bleeding. The hematocrit then rose slowly until, following reinfusion, it had returned to normal

Figure 8


ECG Lead II
CONTROL
30 MINS
2 HOURS
4 HOURS
REINFUSED
TERMINAL

values. It continued to rise until a value of 113% of control was reached terminally.

The control electrocardiograms in all dogs appeared normal. A varying degree of sinus tachycardia developed in all dogs during the first 30 minutes of oligemic hypotension. (Figure 8).

Alterations of the S-T segments early after induction of hypotension were seen in all dogs. S-T depression appeared early and progressed in severity during hypotension in 8 of the 10 dogs, as shown by serial electrocardiograms in figure 8. One dog showed complete inversion of the T wave prior to reinfusion of blood. All but 3 dogs showed definite improvement of these changes with reinfusion. The S-T segment depression reappeared shortly after reinfusion, prior to the decline of cardiac output and blood pressure. The S-T segment depression at this stage was frequently associated with T wave alterations. Tall, peaked and bizarre shaped T waves were commonly seen.

There was a progressive lenghtening of the QT interval, primarily due to prolongation of the S-T segments, as the animal reached the terminal phase. Arrhythmias, including one animal with a 2:1 heart block appeared terminally. Marked bradycardia associated with complete atrio-ventricular disassociation as well as wide, slurred, bizarre QRS configurations preceded death.

Ventricular fibrillation was a common terminal event.

Group II (6 dogs)

The operative procedures followed in this group were identical to those

of group I. The blood pressure in this group of animals was lowered to 30 mm of Hg by stepwise bleeding. It was maintained at this level for 1 hour, after which all blood was reinfused. All cardiovascular indices were recorded, and the animals were again bled to 30 mm of Hg. The animals were then reinfused at one hour intervals until 30% of the maximum bled volume had spontaneously returned to the animals. The animals were then reinfused and monitored until marked circulatory depression occurred. This produced a series of ventricular curves during the progression of hemorrhagic shock.

The average duration of hypotension in this group of animals was 330 minutes. The maximum bled volume was 58 cc/Kg. These animals also developed marked circulatory depression immediately following the final reinfusion of blood. Four of the six animals died within 4 hours following the final reinfusion. Two animals were sacrificed and autopsied 4 hours following final reinfusion.

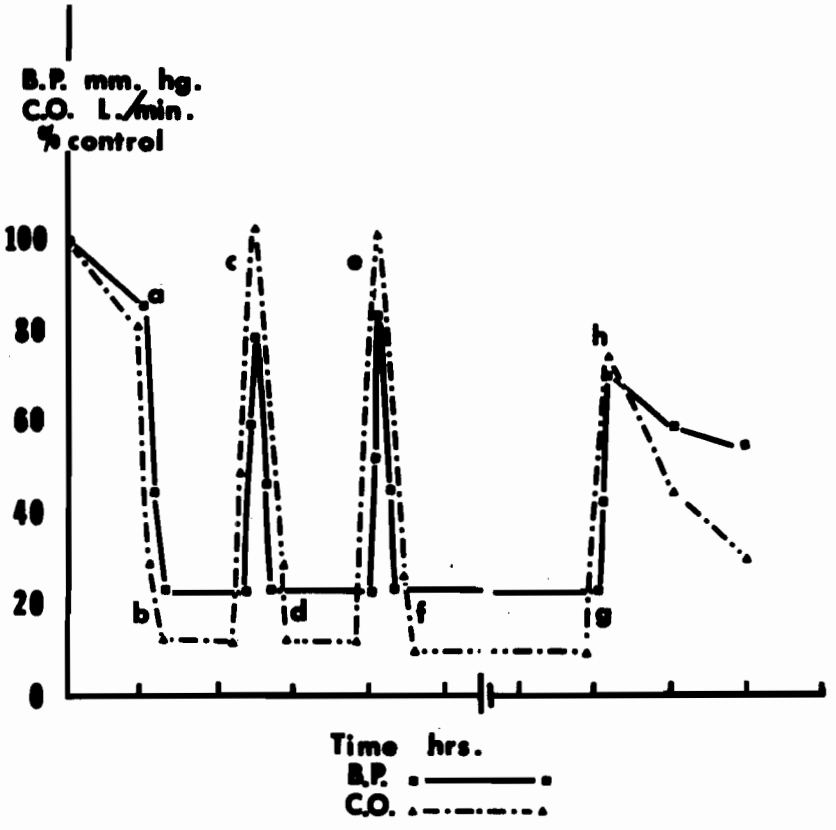


Figure 9

The blood pressure fell to 86% of control values following thoracotomy, and fell to 23% of control with initial step-wise bleeding. (Figure 9). Reinfusion of blood after one, and two hours of hypotension returned blood pressure to post-thoracotomy values or above. The blood pressure returned to 69% of pre-thoracotomy values with the final reinfusion of shed blood. Blood pressure began to decline within thirty minutes of reinfusion, and deteriorated progressively until death or sacrifice four hours later.

The cardiac output also shown in figure 9, followed a pattern similar to that of mean arterial blood pressure. Post-thoracotomy values were 92% of pre-thoracotomy controls. The cardiac output fell to 15% of control with bleeding, and returned to post-thoracotomy values or higher with the initial reinfusions following one and two hours of hypotension. Cardiac output returned to 74% of control with the final reinfusion and then began a progressive decline.

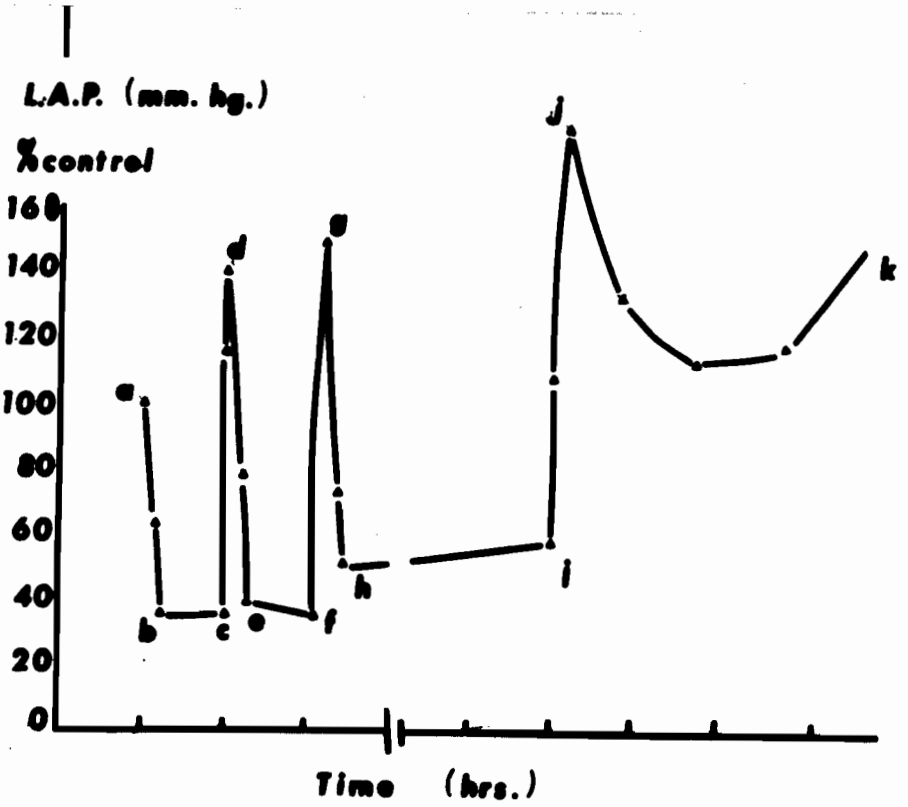


Figure 10

The left atrial pressure fell to 35% of control values with bleeding. Left atrial pressure rose to 140% of control, with reinfusion after one hour of hypotension, and to 148% of control after two hours of hypotension. The left atrial pressure prior to final reinfusion had slowly risen to 52% of control. The final reinfusion of shed blood resulted in grossly elevated left atrial pressures, reaching 174% of controls. The left atrial pressure then declined slowly along with arterial blood pressure and cardiac output. It never returned to less than 130% of control values. Terminally there was a sudden increase in left atrial pressure.

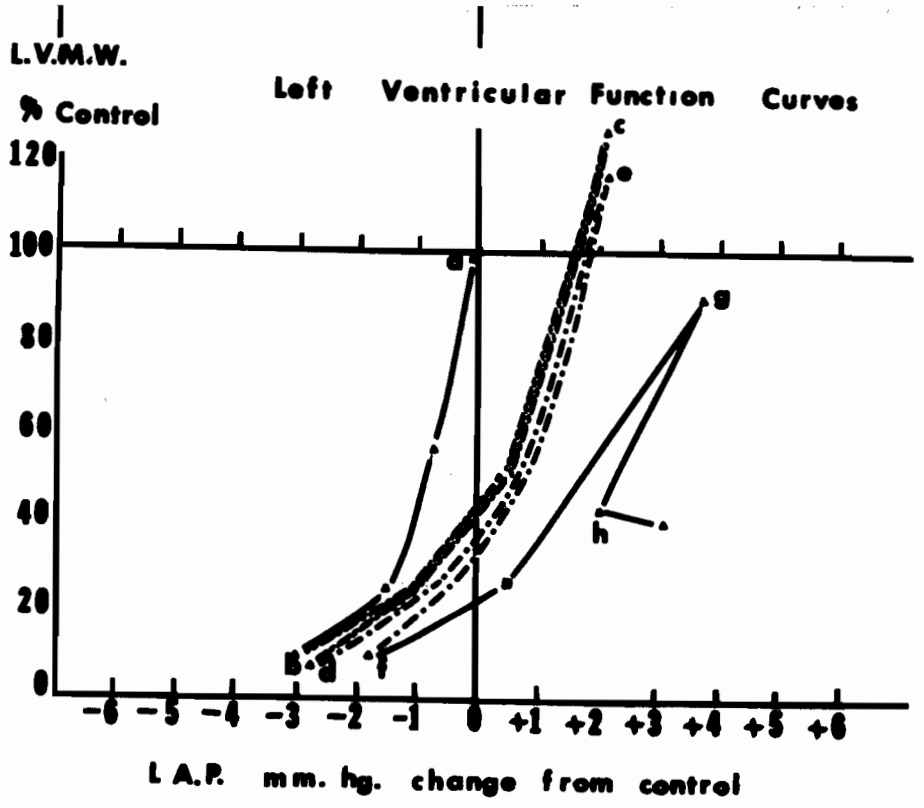


Figure 11

The changes in left ventricular minute work occurring during bleeding and reinfusion were plotted against the changes in left atrial pressure in order to obtain ventricular function curves in this group of dogs. They are illustrated in figure 11.

The curve recorded during the initial bleeding (a-b) served as a type of control. The curve obtained after one hour of hypotension (b-c-d-) demonstrates a shift to the right. The curve after two hours of hypotension (d-e-f) is almost superimposed on the curve after one hour of hypotension. The rise in left atrial pressure seen on these two curves is accompanied

in each case by an increase in values above the control (127% and 117%) for left ventricular minute work.

The curve obtained with the final reinfusion of blood was very markedly shifted to the right. The left ventricular minute work reached only 89% of control values, despite extreme elevation of left atrial pressure.

The pulse rate, total peripheral resistance and electrocardiograms demonstrated comparable responses to the dogs in Group I (see figures 3, 6 and 8).

Group III (5 dogs)

The animals of this group were subjected to identical operative procedures as described for groups I and II. The arterial blood pressure was then lowered to 30 mm of Hg., held at this level for 5 minutes and then reinfused. The animals were then maintained in this normotensive for 5 hours, following which they were bled to 30 mm of Hg and reinfused after a 5 minute period of hypotension. The animals were then sacrificed following the second reinfusion. This procedure served as a further control, permitting evaluation of the effect of the severe operative procedures on the ventricular function curve.

The animals in this group showed a decrease in cardiac output and blood pressure following thoracotomy, similar to the animals in groups I and II.

The variations in control indices during the 5 hour period between the initial and final bleeding and reinfusions were minimal. These animals all required further anesthetic during this 5 hour period.

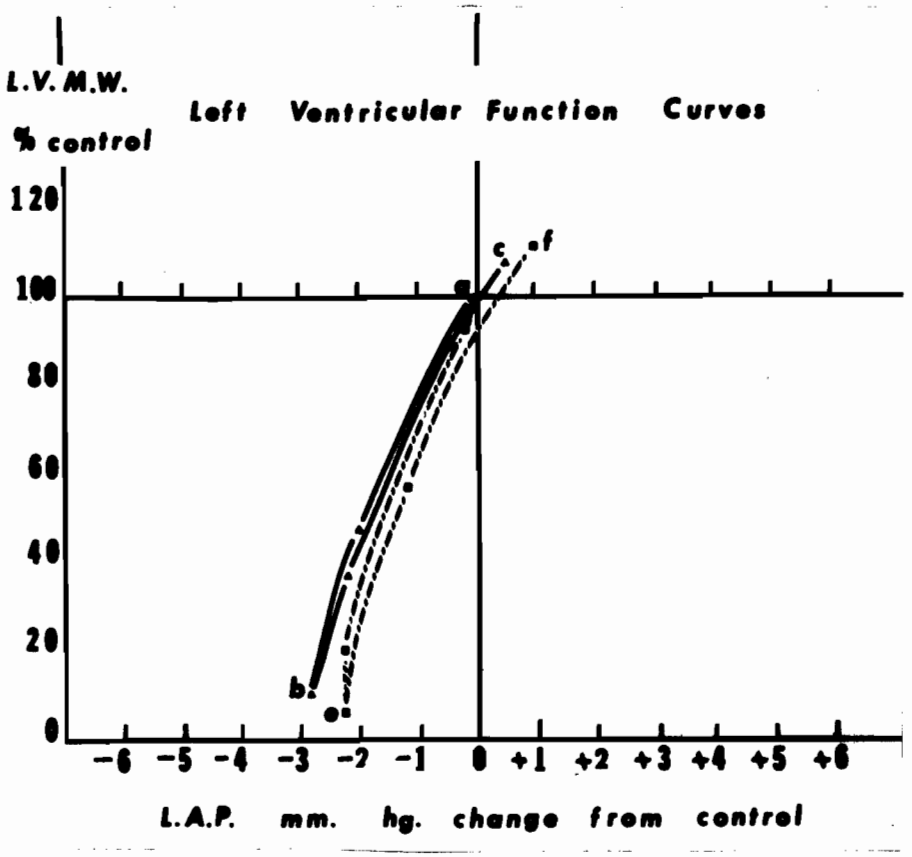


Figure 12

The left ventricular function curves obtained during the above procedure are shown in figure 12. The initial ventricular function curve (a-b-c) served as the control. The ventricular function curve after five hours on the operating table with a normal blood pressure (d-e-f) shows only a minimal shift to the right. The left ventricular minute work in both cases increased above control with the minimal elevations in left atrial pressure.

Other concurrent studies carried out during the course of these studies included gross observations of heart size. The heart appeared

smaller and collapsed after the induction of hypotension, and then appeared to increase in size as hypotension progressed. In groups I and II the heart appeared considerably larger than control after the final reinfusion. Heart size then appeared to decrease slightly until the terminal stage when heart size reached immense proportions, with gross dilatation of all chambers. These observations were the author's impressions and were not documented by accurate measurements of heart size.

The point at which the animal began to take back spontaneously its shed blood in order to maintain a blood pressure of 30 mm Hg was usually characterized by a generalized loss of reflexes in groups I and II. The eye reflexes were usually the first to disappear. Prior to reinfusion, relaxation of sphincter tone frequently occurred, with incontinence of feces and urine. The feces were usually liquid in consistency and contained both altered and fresh blood at this stage. A peculiar twitching at the corner of the animal's mouth, ressembling the primitive sucking reflex, often appeared during the circulatory decline following reinfusion of shed blood. Bounous (45) and others, have pointed out that the spontaneous reinfusion of blood, and the loss of reflexes, are pathognomonic signs of irreversible hemorrhagic shock in the dog.

The observation was made that manual compression of the dog's abdomen after the animal began to spontaneously take back its shed blood resulted in a precipitous temporary drop in mean arterial blood pressure (5 to 15 mm of Hg). Bradycardia became more pronounced, and arrhythmias frequently

occurred shortly after manual compression of the abdomen. This unexplained phenomenon appeared to be related to the severity of the hemorrhagic intestinal lesions in the animal, as described in the autopsy findings.

Thirteen dogs were used in this study and not included in the above results. Nine of these dogs died suddenly with cardiac asystole or ventricular fibrillation, immediately prior to or during reinfusion of shed blood. Two dogs developed massive bleeding from the thoracotomy wound during the course of the experiment, and thus were not included in this study. One dog developed a massive retroperitoneal hemorrhage, following a traumatic laceration of artery wall during catheterization. One dog bled extensively from the left atrium, following placement of the catheter. This dog was salvaged but not included in the above results.

The pathological findings in group I and II were similar. There were no significant pathological changes seen in group III.

The most striking feature on post-mortem examination of the abdominal viscera was the severe degree of tryptic hemorrhagic enteritis. All dogs showed this lesion to some degree. The lesions were usually most marked in the lower duodenum and upper jejunum, but also extended along the entire length of the small bowel. There were small patchy lesions seen in the colon and rectum. When examined in vivo during the terminal phases of shock, the intestinal mucosa grossly appeared almost black in color, was ulcerated, and in some areas actively bleeding. (Figure 13 demonstrates an example of the severe tryptic jejunitis). The small bowel in all of these animals was filled with varying amounts of altered and fresh blood. The microscopic examination of the small bowel lesions revealed almost

total destruction of intestinal villi with an associated hemorrhagic and inflammatory response. This lesion has been investigated in considerable detail by Bounous (45,46,47) and others. (39)

Six dogs in groups I and II demonstrated a gastric lesion ressembling hemorrhagic gastritis. This lesion was seen predominantly in the body of the stomach. Grossly this consisted of hemorrhage and superficial erosions, more marked in the folds between the gastric rugae. Microscopically there was local oedema polymorphonuclear cellular response, associated with the loss of superficial epithelium.

In eight dogs, varying degrees of hemorrhagic pancreatitis occurred. The pancreas was only minimally oedematous, but had diffuse areas of hemorrhage. One such case of pancreatitis is illustrated in figure 13. The hemorrhagic pancreatitis was usually associated with a sero-sanguinous peritoneal exudate. Microscopic examination of the pancreas revealed interlobular and intralobular hemorrhage and oedema. There was frank disruption of the ductal system, necrosis and dissolution of pancreatic parenchyma. No evidence of intra-vascular coagulation was found in the pancreas. The pathogenesis of this interesting lesion has been further investigated. (48)

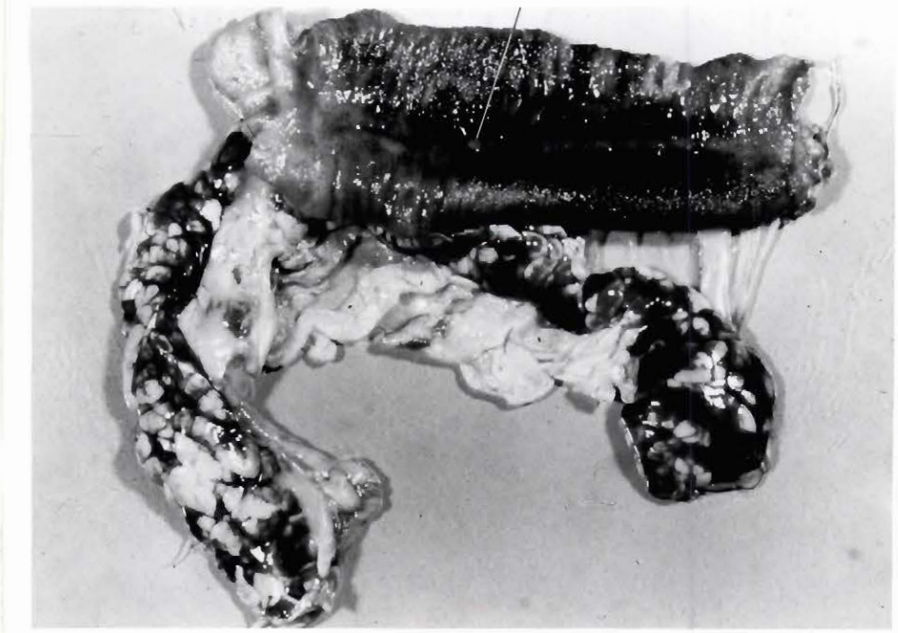


Figure 13 - duodenum and upper jejunum with pancreas attached. Probe is in main pancreatic duct.

The liver was examined grossly, and frequently revealed a turgid, bulging appearance terminally. No detailed microscopic studies were performed.

The kidneys appeared swollen, with pale cortices and dark, conjested medullary regions. Microscopic examination revealed medullary intra-capillary conjestion and stasis, with cloudy swelling of distal tubular cells.

Gross examination of the lungs revealed patchy areas of atelectasis, despite prolonged positive pressure ventilation throughout the experiment. Several animals appeared to die in pulmonary oedema with large amounts of reddish brown frothy material in the tracheo-bronchial tree. Microscopic examination of the lungs confirmed the patchy atelectasis. There

appeared to be a thickening of the alveolar-capillary membrane in these areas. The thickening was partially due to alveolar capillary conjestion and partially to an alveolar polymorphonuclear inflammatory response. The bronchioli were frequently filled with an amorphous eosinophilic staining material. Figure 14 shows bronchioli filled with this amorphous material. Figures 15 and 16 demonstrate areas of atelectasis and oedema.

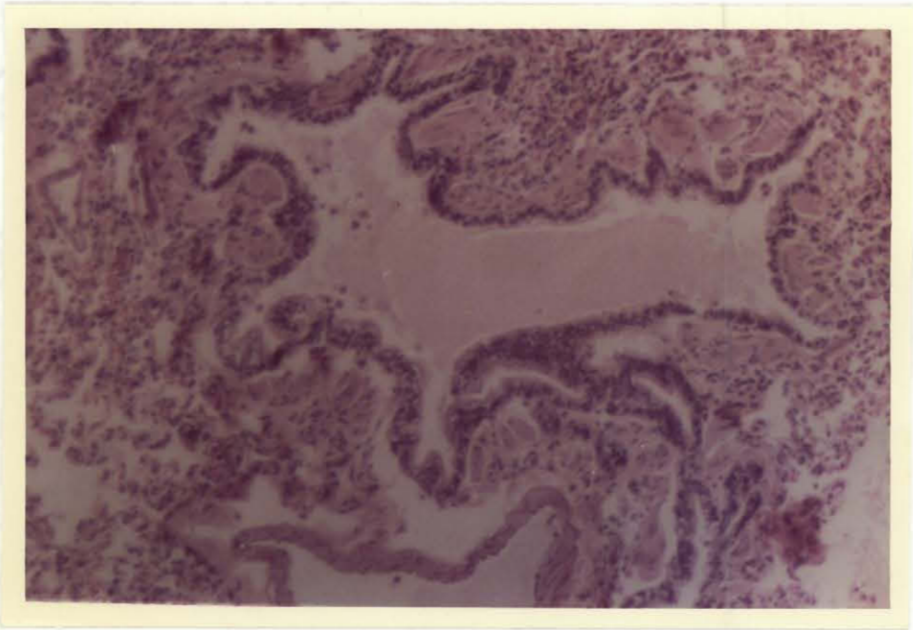


Figure 14 - Hematoxylin-eosin stained section of lung (x 100). This demonstrates a small bronchiole filled with an amorphous eosinophilic exudate.

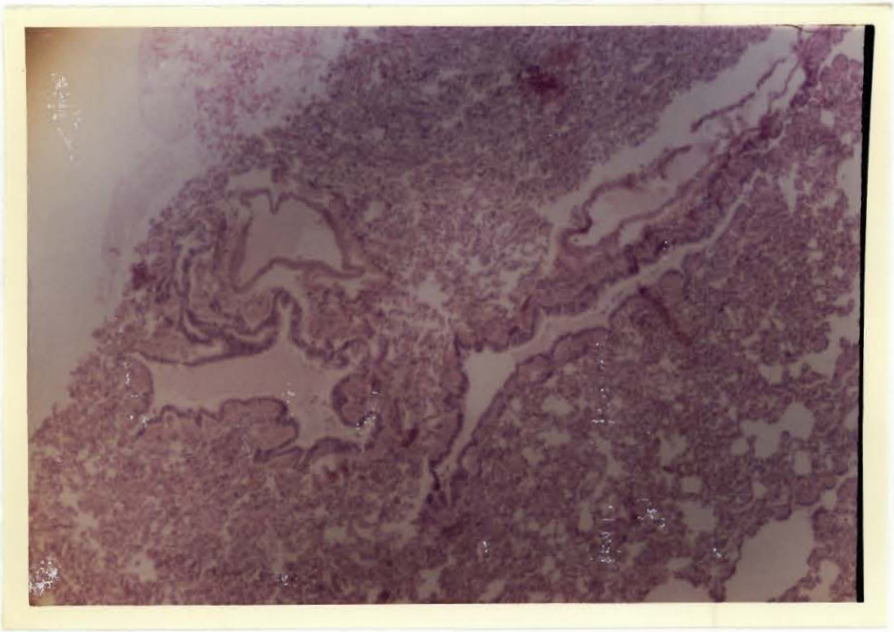


Figure 15 - Hematoxylin-eosin stained section of lung (x 40). This demonstrates an area of atelectasis

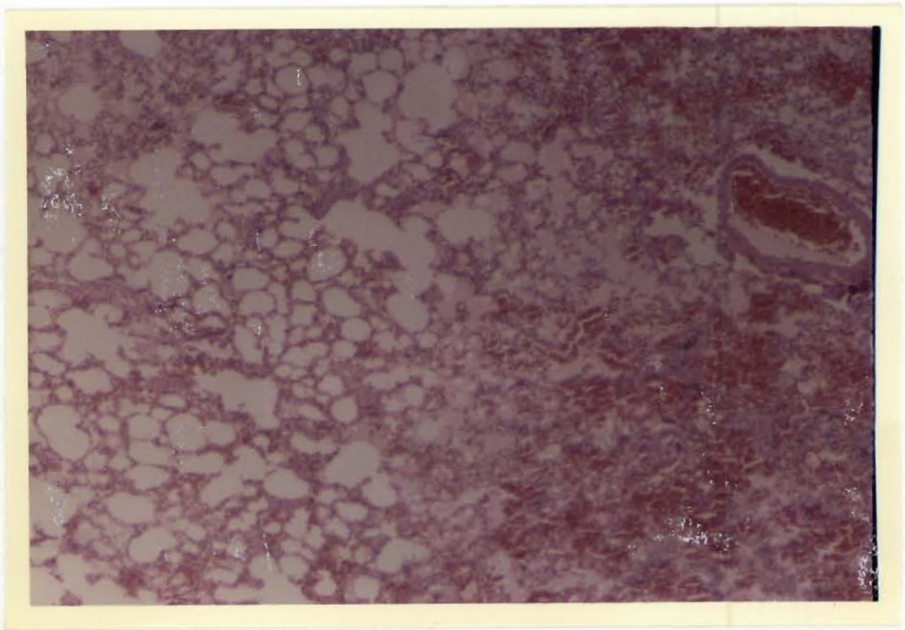


Figure 16 - Hematoxylin-eosin stained section of lung (x 40). On the right is an area of collapse, with a hemorrhagic inflammatory response. On the left is an area of lung tissue demonstrating a thickening of the alveolar-capillary membrane.

Gross examination of the heart revealed only occasional scattered para-coronary epicardial hemorrhages. The most consistent findings on opening the left ventricle were the subendocardial hemorrhages. These lesions varied greatly in severity and distribution. The most common pattern is illustrated in figures 17 and 18.

The subendocardial hemorrhages usually involved the opposing surfaces of the papillary muscles and the wall of the interventricular septum. Smaller lesions were frequently found at the base of the mitral valve cusps. The subendocardial lesions were present in 75% of the animals in groups I and II. Examination of the right ventricle revealed only minor, similarly located subendocardial hemorrhages.

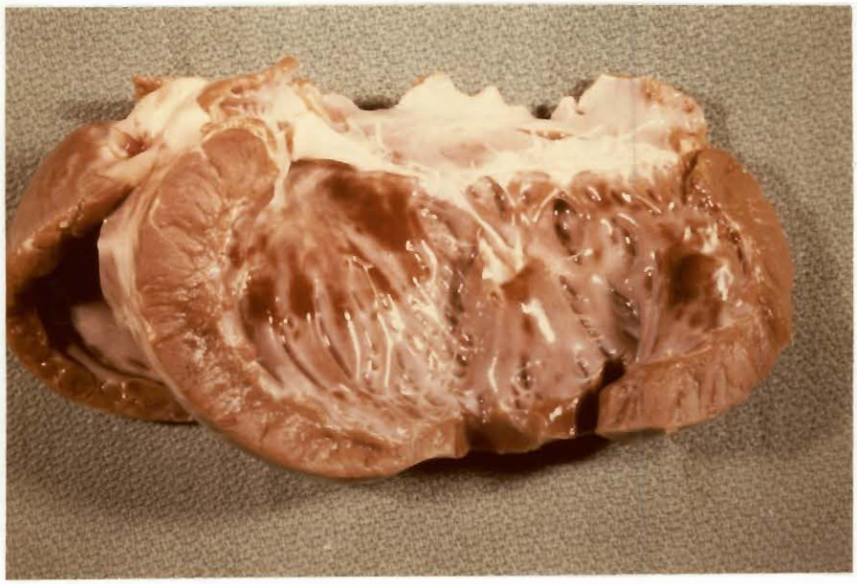


Figure 17 - The heart, with the left ventricle opened demonstrating subendocardial hemorrhages on the papillary muscles, and on the interventricular septum. The chordae tendineae have been cut.

Figure 18 - The heart showing the interior of the left ventricle. The subendocardial hemorrhages are more marked, particularly at the upper margin of the interventricular septum in the region of the bundle of His. This dog developed a right bundle branch block following re-infusion.

Microscopic examination of the myocardium confirmed the subendocardial hemorrhages described above. These lesions were usually very superficial and involved the adjacent conducting fibres as shown in figures 19 and 20. An epicardial hemorrhage of the left ventricle is demonstrated in figure 21.

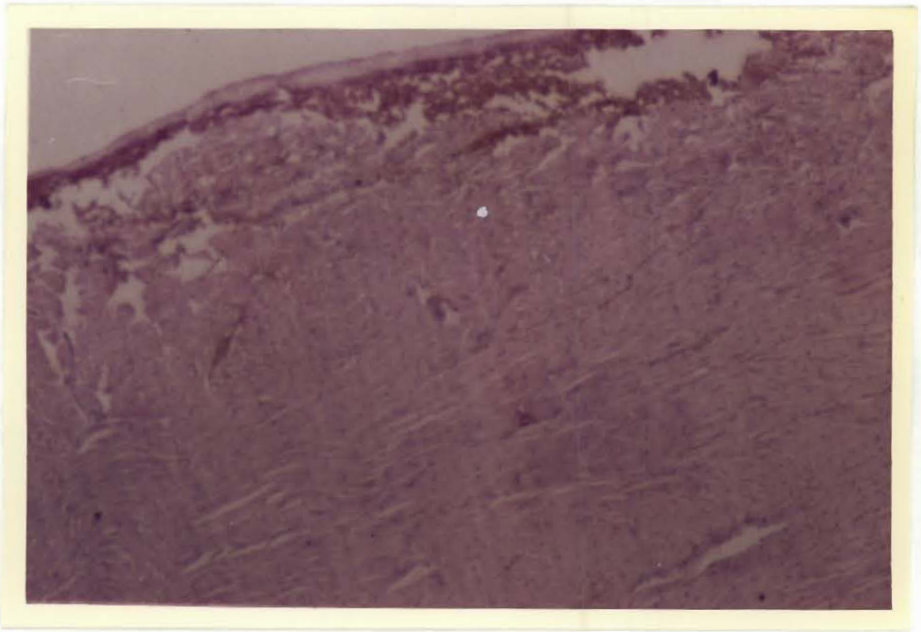


Figure 19 - Hematoxylin-eosin stained section of left anterior papillary muscle (x 40). This demonstrates the superficial nature of this lesion.

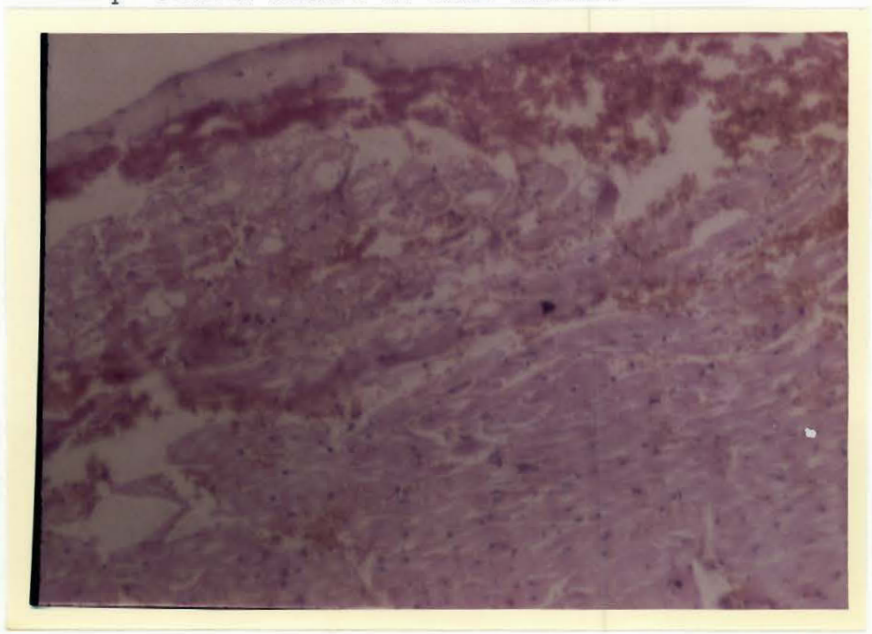


Figure 20 - Hematoxylin-eosin stained section of left anterior papillary muscle (x 100). The subendocardial hemorrhage is again demonstrated and appears to involve the adjacent conducting fibres. The area of myocardium immediately below the hemorrhagic lesion appears necrotic.

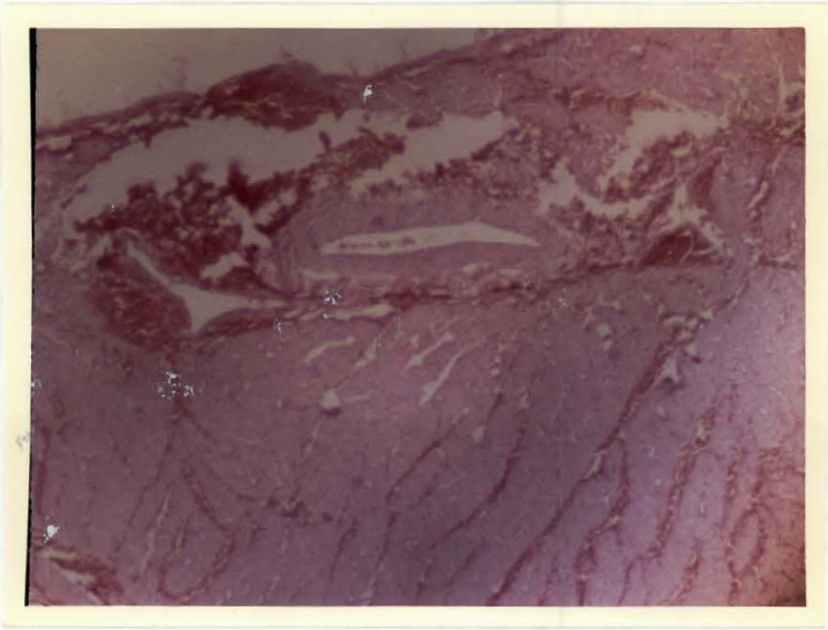


Figure 21 - Hematoxylin-eosin stained section of left ventricle (x 40). This demonstrates a subepicardial hemorrhage, adjacent to a small branch of the left coronary artery. There is some intra-myocardial extension of this lesion.

Closely associated with the hemorrhagic lesions were scattered areas of myocardium which stained more eosinophilic than normal. There was usually considerable capillary dilatation and congestion in these areas of myocardium. Occasionally the areas of myocardium which appeared more eosinophilic were surrounded by foci of polymorphonuclear cells. A high power examination of the damaged myocardium showed a loss of striations and a peculiar swelling of the myocardial fibre in the region of the intercalated disc as shown in figure 24. The myocardial changes were always more marked in the left ventricle.

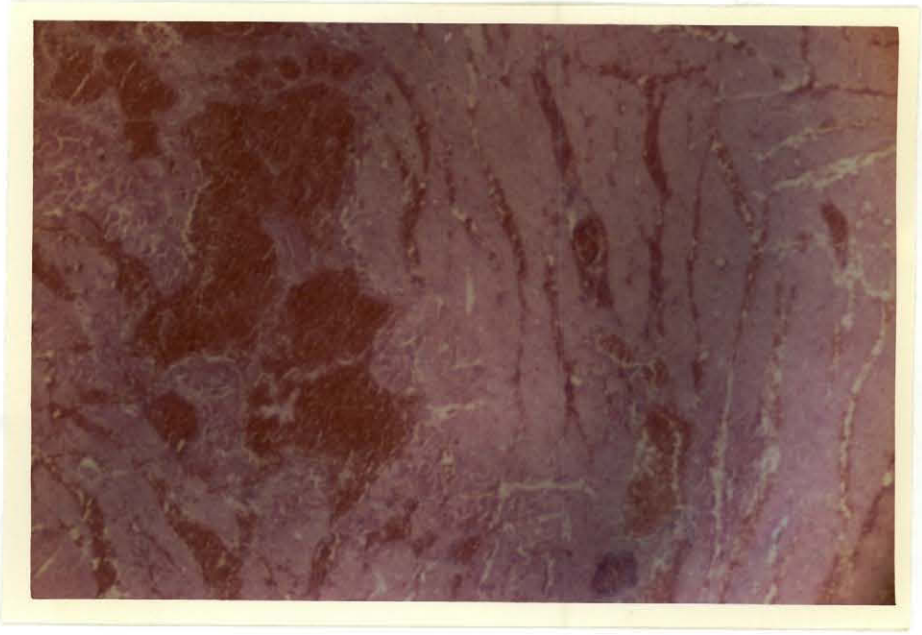


Figure 22 - Hematoxylin-eosin stained section of left ventricular wall (x 40). This demonstrates marked intramyocardial hemorrhage and conjestion. There are scattered areas of more deeply eosinophilic areas of myocardium.

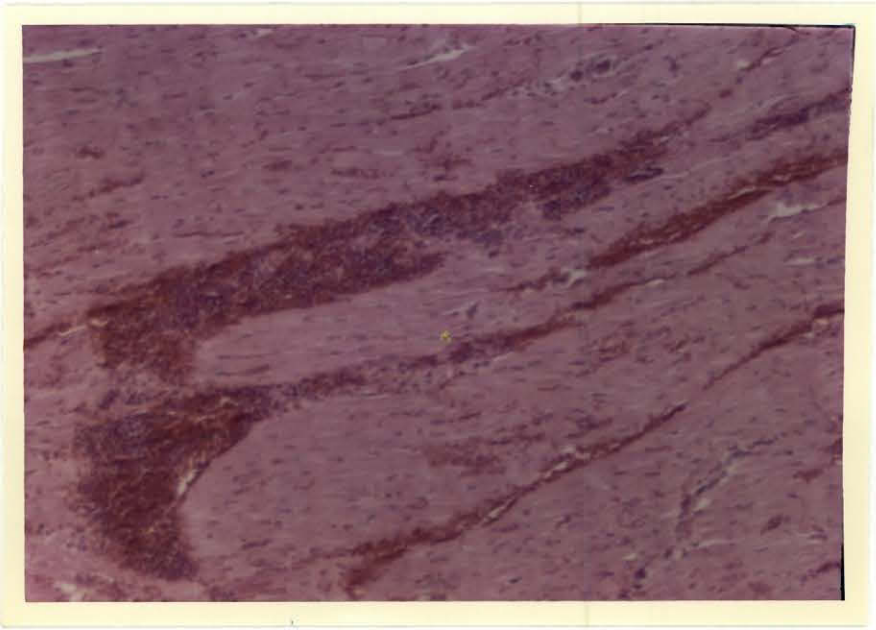


Figure 23 - Hematoxylin-eosin stained section of left ventricular wall (x 100). This demonstrates the foci of lymphocytes and polymorphs related to areas of damaged myocardium.

Figure 24 - Hematoxylin-eosin stained section of left ventricular wall (x 1000). This demonstrates the swelling of individual myocardial fibres particularly in the region of the intercalated discs. There is also an area showing a loss of striations and actual disruption of myocardial fibres.

DISCUSSION

There is a definite decrease in myocardial contractility during the progression of hemorrhagic shock in the experimental model used in this study. The hemorrhagic shock model used was extremely severe, and all results must be considered in this light. It was necessary to employ this model in order to evaluate myocardial function during the development of irreversible hemorrhagic shock.

The model used employed general anesthesia, thoracotomy and pericardiotomy, all of which affect myocardial function. A general anesthetic was mandatory in this study which involved major surgical procedures.

Several different investigations have pointed out the fact that opening the chest changes extra-cardiac pressures, resulting in a decreased blood pressure and cardiac output.[49,50,51] This observation was confirmed in all three experimental groups used in this study. Sarnoff[41,42] Fermosa and others[21] have shown that thoracotomized animals still provide a useful model in the analysis of circulatory function. They point out the importance of using post-thoracotomy values as control or base line in evaluating changes in myocardial function. An open-chest model obviates the vagaries of measuring alterations in negative intra-thoracic pressure as required in a closed chest model.

It is also conceivable that an animal subjected to a general anesthetic, a major operative procedure and a five hour period of observation with an open chest might display a decline in myocardial function over this period. The animals in group III thus served as a double control of the operative

trauma induced during this study. The ventricular function curve obtained after the five hour observation period showed very little shift to the right of the initial post-thoracotomy curve. This indicated only a minimal decline in myocardial function, as a result of operative trauma alone.

The method used to evaluate myocardial contractility is open to criticism. The difficulties in assessing ventricular diastolic fibre length, to which the energy of contraction is related, are well known. One of the best methods of evaluating end diastolic fibre length is by using left ventricular end diastolic pressure. Selkurt[26] feels that in view of the importance of atrial contraction in ventricular filling,[41,42,52] left ventricular end diastolic pressure is a more valid index of end diastolic size than atrial pressures. Left atrial pressure was chosen as an index of end diastolic size in this study for several reasons: Firstly, during the course of hemorrhagic shock, a significant tachycardia results, which considerably impairs the accurate measurement of left ventricular end diastolic pressure; secondly, Sarnoff in his original work[41,42] on the use of ventricular function curves to assess myocardial contractility, utilized left atrial pressure; and thirdly Selkurt[26] in his studies on ventricular function curves in hemorrhagic shock, showed that left ventricular end diastolic pressure changes closely paralleled those of left atrial pressure.

Cardiac output is governed to some degree by aortic pressure, which in turn is the resultant of peripheral resistance as well as cardiac function; thus left ventricular stroke work per minute was used as a more comprehensive index of the functional capacity of the heart. The methods used allow a

reasonably precise measurement of external work performed by the left ventricle, but they do not measure the total energy liberated by the heart in doing this work. There is a significant amount of total energy spent on isometric contraction of the left ventricle, and this is not measured as work done.[41,42,53] No estimation of myocardial efficiency is obtained using this method.

An attempt was made to make all determinations after a steady state or equilibrium conditions had been reached, while obtaining the ventricular function curves in this study. In spite of this precaution, there may have been changes in the neural and hormonal elements of the autonomic nervous system, affecting myocardial contractility. This difficulty is impossible to overcome using a model with an intact circulation.

The use of ventricular function curves as a method of studying myocardial contractility is a well established method[41,42,26,52,54] in spite of the known limitations. The modifications of the classical ventricular function curves which were used in this study, allowed a rapid means of quantitating ventricular performance in terms of physiologically significant work under the existing experimental conditions.

It may be argued that a better evaluation of myocardial reserve or capacity could have been obtained by using a volume or pressure load at different phases of hemorrhagic shock, as proposed by Gomez.[21] This creates a situation which may be potentially dangerous in that it could change a heart from occult to frank myocardial failure, and possibly exert a detrimental effect itself. The use of a volume load also introduces a new therapeutic variable in a hemorrhagic shock model.

The problem of accurately defining cardiac failure appears very simple on the surface, however, there is still disagreement on a definition which includes all facets of this complex phenomenon. A physiologist defines cardiac failure as a declining cardiac output in the face of adequate or increasing atrial filling pressures. The biochemist describes myocardial failure in terms of a deficiency of or an inability to utilize high energy phosphate compounds as A.T.P. The electron microscopist describes myocardial failure by alterations in the contractile proteins myosin and actin. The clinician thinks of myocardial failure as a well known group of clinical findings which indicate myocardial decompensation. Mommaerts and Langer[55] in a recent review of this problem state, that "the sine qua non of heart failure is the inability of the cardiac chamber under consideration to prevent progressive increments in its diastolic volume in response to imposed overloads." Most authors[23,26] agree that in order to prove cardiac hypofunction it is necessary to show that for a given atrial pressure the heart does less external work than the normal or control heart. As more is learned about the dynamics of myocardial failure, it will undoubtedly be possible to more accurately describe the exact mechanism of cardiac failure in any given situation.

The ventricular function curves in group I following reinfusion show a marked shift to the right indicating a definite hypofunction or depression of myocardial contractility. This curve is similar to the ventricular function curve obtained after the final reinfusion of blood in group II. The initial ventricular function curves in group II, prior to the point at which the animal spontaneously took back blood from the reservoir,

demonstrated a shift to the right, but not to the degree as seen following final reinfusion. These initial curves are very similar to those obtained by Sarnoff [41] after decreasing left coronary artery flow, and this suggests myocardial ischemia. The modest elevations of left atrial pressure seen on these curves, are always associated with an increase above control of left ventricular minute work. These initial curves probably represent the result of two simultaneously acting variables. The depressed function curve related to a period of decreased coronary flow during hypotension is partly compensated for by the positive ionotropic effect of the marked increase [39,56] in circulating catecholamines which occur in this phase of hemorrhagic shock. This may explain the elevation above control of left ventricular minute work, seen in the early ventricular function curves, in spite of the shift to the right.

The very marked shift to the right seen with the final reinfusion in groups I and II suggests that other factors in addition to myocardial ischemia now operate in order to produce this profound depression in myocardial contractility. The terminal ventricular function curves demonstrate that in spite of marked increases above control of left atrial pressures, left ventricular minute work remains below control. The relation between left atrial pressure and left ventricular minute work in terminal hemorrhagic shock deteriorates, in that work continues to decline as atrial pressures increase. This results in a descending limb on the ventricular function curve, which Sarnoff [41] found to occur in vivo only under extreme conditions, as severe restriction of coronary flow, severe anemias and pronounced cardiac irregularities. The depression in left ventricular work can be

explained in part by alterations in heart rate during hemorrhagic shock. There is a well known heart rate-determined ionotropic mechanism affecting cardiac output, which is an intrinsic property of the myocardium. The mechanism is not clear as recently discussed by Mitchell[57] and others,[55] but the myocardium appears to function at an optimum heart rate. Cardiac output increases as this rate is approached, and decreases as heart rate is increased above the optimum because of the reduced time for diastolic filling. A marked reduction in heart rate below the optimum rate will also result in a decrease in cardiac output. The marked bradycardia and the gross arrhythmias would undoubtedly explain some of the depression of myocardial work seen in terminal hemorrhagic shock, and contribute to the descending limb of this curve.

These results are in agreement with those of Crowell, Guyton and Gomez[21,22,23] and confirm the original observations of Wiggers.[14] The above results are not entirely in agreement with those of Rothe and Selkurt[26] who concluded that not all animals subjected to irreversible shock developed myocardial failure terminally. They suggested that a decrease in venous return was a more important factor in the terminal decline of cardiac output. Selkurt and Rothe[26] used a closed chest model, and the duration of hypotension varied from the experimental model used in this study.

The results of this study are totally different from those of Simeone et al,[27] who used a Walton-Brodie strain gauge to assess myocardial contractility during hemorrhagic shock. They concluded that the contractile force of the myocardium remained near normal despite the progressive

decline in arterial blood pressure as the animal deteriorates. The measurement of myocardial contractility with this device is somewhat artificial and does not relate changes in contractility to usefuk external work or to changes in left atrial pressure.

The left atrial pressure following final reinfusion in Groups I and II declined significantly, but never reached control values. Crowell[22,23] also noted this decline in atrial pressure which appears to be mainly due to loss of central blood volume. He also noted that a transfusion at this point again increased left atrial pressure to a higher level on a hypo-responsive function curve, only to decline again along this curve. he also demonstrated that in spite of massive transfusion of blood (three to five times the animal's original blood volume) it was impossible to maintain an effective cardiac output or alter survival rates. Crowell attributed part of this fall in atrial pressures to fluid loss, but he felt that "stress relaxation" also played a role. This phenomenon is not generally accepted and a more likely explanation is a loss of effective circulating blood volume. The animals in Groups I and II frequently demonstrated significant blood loss from the small bowel alone in the terminal phases of hemorrhagic shock. The changes in hematocrit during the progression of hemorrhagic shock in these dogs also suggests a loss of plasma and extracellular fluid resulting in the hemoconcentration. The terminal hematocrit values were noted to increase in the face of active bleeding from the small bowel lesions. Liklehei[58] and others[59,60] have demonstrated as much as a 28% decrease in plasma volume after reinfusion. Shires[61], Crenshaw [62], have both demonstrated a definite decrease in

extracellular volume in man and in the dog, as a result of severe hemorrhagic shock. A change in venomotor tone [63] may also be a contributing factor in this decline in left atrial pressure shortly after reinfusion.

Total peripheral resistance increased markedly with hemorrhage in groups I and II, as reported by most investigators. [64,65] The total peripheral resistance reached 203% of control at the point of maximum bled volume. There was a minimal decline in peripheral resistance as hypotension progressed, but just prior to reinfusion, total peripheral resistance had again risen to 229% of control. Reinfusion of shed blood resulted in a return to nearly normal, only to increase again as the terminal circulatory decline developed. The finding that peripheral resistance returned to normal with reinfusion, and increased again as blood pressure and cardiac output fell, would indicate that even in late hemorrhagic shock, the vascular bed is still capable of increasing resistance as a homeostatic mechanism. This measurement is only a gross estimation, and it must be remembered that total peripheral resistance is determined by numerous regional resistances arranged in parallel ($1/T.P.R. = 1/R1 + 1/R2 \ldots\ldots 1/Rn$). Thus the measurement of total resistance could very easily mask regional changes in resistance. These results are essentially the same as recorded by other investigators [64,66,67]. These findings imply that neither loss of effective blood volume or failure of the peripheral vascular system could be the sole cause of irreversibility, as massive transfusion results in only temporary improvement.

The E.C.G. changes seen in groups I and II definitely suggest myocardial

ischemia. The initial RS-T segment depression was usually seen at the time maximum bled volume was reached. The progressive nature of these changes suggests that myocardial ischemia was becoming more pronounced, and in some cases evidence of myocardial injury was observed. The fact that the majority of the animals showed definite improvement of their E.C.G. following reinfusion, indicates that the ischemic changes were not irreversible at this stage. The early reappearance of signs of myocardial ischemia following reinfusion emphasizes the fact that the myocardium appears to be operating on a borderline nutritional blood supply.

The T wave changes seen following reinfusion are very similar to those seen with hyperkalemia. The T waves also showed bizarre changes terminally which were difficult to interpret. There was a poor correlation between the pathological changes seen at autopsy, and the E.C.G. changes observed in the individual animal. The dogs which developed pathological changes at autopsy occasionally did not demonstrate E.C.G. evidence for this lesion. This is partly explained by the limited electrocardiographic studies done on these animals. In retrospect, a better correlation would have resulted if all leads had been examined, according to the studies of Wiggers[14,15] and Isquieta[29].

The marked prolongation of the QT interval, and the resulting bradycardia definitely suggests a loss of neurogenic control of the cardiovascular system. The bizarre E.C.G. configurations and arrhythmias seen terminally are probably a reflection of an anoxic myocardium with superimposed alterations in myocardial environment including severe acidosis and hyperkalemia.

The fact that such a large number of dogs died of ventricular fibrillation early in the course of hemorrhagic hypotension (dogs not included in results for groups I and II), further attests to the severity of the model. Ventricular fibrillation was also a common terminal event, following the development of marked arrhythmias. This is not a surprising finding as several authors have demonstrated that both a decreased coronary flow [68,69] and any form of metabolic acidosis will decrease the ventricular fibrillation threshold, resulting in an increased incidence of fibrillation. Local accumulation of toxic metabolites, particularly potassium and lactates, has also been incrimminated in lowering the ventricular fibrillation threshold.

The electrocardiographic findings in the animals in this study are not unlike those observed by Master [30] in his study on humans suffering from hemorrhagic shock. Master noted that in over 100 patients studied, ranging from 18 to 79 years, 60% presented clinical and or electrocardiographic evidence of acute coronary insufficiency. Conjestive heart failure was precipitated in 10% of this group of patients.

The pathological changes seen in the myocardium of the animals in groups I and II, are almost identical in nature and location to those described by Master in humans who died following an episode of hemorrhagic shock. Myasnikov [70] also described comparable lesions in the myocardium secondary to acute coronary occlusion associated with hypotension. He concluded that the conditions which develop following decreased tissue perfusion may exert an unfavorable influence on the predamaged myocardium causing these additional necrotic foci.

The anatomical location of the myocardial lesions in shock supports the concept that these changes may be secondary to a period of relative anoxia. The endocardial region is the most distal portion of the myocardium in relation to its nutritive blood supply.

Many authors [71,72,73,74] have noted the similar pattern of hemorrhagic and necrotic lesions seen in dogs given prolonged high doses of pressor amines particularly nor-epinephrine. Regan [71,72] has demonstrated a biphasic response of the myocardium to sustained intracoronary infusion of epinephrine. The initial period of positive inotropic effect was followed by a progressive decline in contractility. He has pointed out the fact that the prolonged high levels of circulating catecholamines seen in hemorrhagic shock may have a similar effect on the myocardium. Klouda et al [74] have queried whether the catecholamine level is in fact directly related to the production of subendocardial lesions or whether the lesions are secondary to mechanical injury associated with extremely high intraventricular pressures and low end diastolic volumes. They demonstrated that the severity of these lesions could be modified by partial cross clamping of the aorta, thus increasing end diastolic volumes.

The subendocardial hemorrhages and necrosis were always intimately related to the subendocardial Purkinje network. The possibility that a a period of hypotension may selectively effect this type of myocardial fibre must be considered. The subendocardial hemorrhages could also exert a detrimental mechanical effect on the conducting system. These two factors may partially explain the marked bradycardia and arrhythmias which develop in late hemorrhagic shock.

The preponderance of hemorrhagic subendocardial lesions compared to simple necrosis in the experimental animals used in this study, raises the possibility that the heparin used may have accentuated the hemorrhagic nature of the myocardial lesions.

The fact that anatomical changes result, following a prolonged period of hemorrhagic shock, definitely suggests that functional alterations may occur and be of paramount importance in the so called irreversible state of shock.

The majority of the pathological changes in the lung are undoubtedly terminal events. The thickening of the alveolar capillary membrane and the patchy atelectasis suggest however, that lung function may also be impaired in hemorrhagic shock.

The pathological changes seen in the small intestine in hemorrhagic shock have never been directly related to myocardial function until recently.[73] The work of Bounous[45] et al has demonstrated that the barrier function of the small bowel is definitely altered following hemorrhagic hypotension. The possibility that the metabolically depressed intestinal mucosa seen in hemorrhagic shock may allow the passage of a cardio toxic substance into the circulation, must be seriously considered.

The above studies have shown that cardiac output and blood pressure both decline rapidly after reinfusion of shed blood, following a critical period of hypotension. The peripheral vascular bed, although seriously injured, was still able to maintain total vascular resistance during the terminal decline in blood pressure. The cardiac output in the shocked dogs declined following reinfusion in the face of above control atrial filling

pressures. The heart was thus doing less external work at a given atrial pressure following the prolonged period of hypotension. The concurrent studies of myocardial contractility definitely suggest an early and progression decline in myocardial contractility as hemorrhagic shock progressed. These findings would support the hypothesis that myocardial function is significantly impaired following a prolonged period of hypotension, and may play a role in the syndrome of irreversible hemorrhagic shock in the dog.

CHAPTER II

INTRODUCTION

The majority of evidence in criminating the myocardium in irreversible shock, arises from studies of volume and pressures during the various phases of hemorrhagic shock. The foregoing studies confirm the suspicion that a deterioration of myocardial expulsive power contributes to the terminal circulatory failure following a prolonged period of hypotension. The ability of the heart to perform external work depends basically upon the biochemical activity which leads to muscular contraction. Therefore, any definite analysis of the phenomena of myocardial failure is dependent on a concurrent evaluation of myocardial blood supply and myocardial metabolism.

The first experimental studies on coronary flow during and following hemorrhagic shock, were carried out by Opdyke and Foreman.(80) Their estimations of coronary flow were hampered considerably by technical difficulties. They observed that coronary flow decreased 30 to 60% of control values during hemorrhagic hypotension (30-50 mm of Hg). Reinfusion of the withdrawn blood usually restored blood pressure to control values and increased coronary flow to 121-420% of control values. The augmented coronary flow was maintained until after circulatory failure had intervened. It was concluded from these studies, that the circulatory failure which follows a prolonged period of hypotension is not precipitated by an inadequate coronary blood flow.

The studies of Sarnoff et al[19], using an open chest hemorrhagic shock model, suggested that the myocardial failure seen following hemorrhagic shock was the result of an inadequate coronary flow. This conclusion was based on the observation that the rise in left auricular pressure and the cardiac dilation which followed reinfusion of shed blood in his model, could be rapidly reversed by augmenting left main coronary flow.

Edwards and Bing[81] in an extensive study of myocardial function in shock observed that coronary blood flow fell markedly during the oligemic phase of hemorrhagic shock. Coronary blood flow then rose during the normovolemic period, but never reached control values. These studies also demonstrated that as a result of the diminished coronary flow, myocardial oxygen usage was significantly reduced during oligemic and normovolemic shock.

Hackel and Goodale[82] using a nitrous oxide desaturation technique for measuring left coronary artery flow, concluded that coronary flow did not decrease despite the very low systemic arterial pressures, and low cardiac outputs during shock. A significant fall in coronary vascular resistance was observed following three hours of hemorrhagic shock.

Vowles et al[83] studied coronary blood flow during hemorrhagic shock by measuring coronary sinus flow. They observed that coronary flow decreases by approximately 50% during oligemic shock, in spite of compensatory coronary vasodilatation and peripheral vasoconstriction. Blood transfusion given early and late in the oligemic phase restored coronary flow to near normal values. The coronary flow in the period following reinfusion was not reported.

The above studies reveal that the pattern of changes in myocardial circulation following hemorrhagic shock, is not uniformly agreed upon.

The adequacy of coronary circulation in hemorrhagic hypotension has also been evaluated by indirect means. These include in vitro and in vivo studies of the availability of oxygen to the myocardium, as well as changes in myocardial metabolism as a result of varying periods of hemorrhagic shock.

Simeone et al (84) used a platinum electrode as a means of measuring the effectiveness of the circulation in maintaining an adequate supply of oxygen to tissues in order to permit normal cellular metabolism during hemorrhagic hypotension. The results of these studies suggested that a decrease in myocardial oxygen tension occurs during hypotension associated with bleeding. This fall in oxygen tension occurred despite the fact that the work of the heart during this period of hypotension is actually decreased. This suggests that the myocardial circulation during hypotension is deficient. Caliva et al (85) utilized an electropolarograph to study the efficiency of myocardial circulation in hemorrhagic shock. The electropolarograph provides a method for continuously recording the oxygen available between the capillary bed and the muscle cell. They concluded that the oxygen levels in the fluid pool between capillary and cell decreased significantly with hypotension induced by hemorrhage. This also suggests an insufficient coronary flow in hemorrhagic shock. They also observed that restoration of blood pressure by early reinfusion, or by the use of drugs resulted in the return of oxygen to near or above control values.

It is conceivable that a period of reduced blood supply to the myocardium could result in a decreased energy production and therefore a decrease in myocardial contractility. Burdette and Wilhelmi [87,88], studying respiratory rate and oxygen consumption of myocardial slices taken from rats during hemorrhagic hypotension, noted that the oxygen uptake in the shocked rats was significantly lower than that of control slices. They also observed that although the myocardium from the shocked rat was still able to utilize pyruvate, it was not as efficient as the utilization seen in slices from control animals.

Myocardial carbohydrate metabolism has been studied from several different aspects during hemorrhagic shock.

Edwards et al [81] in a detailed study of oxygen consumption and myocardial carbohydrate metabolism during hemorrhagic shock, demonstrated no significant change in myocardial oxygen extraction during oligemic shock. There was a decrease in total myocardial oxygen usage which is dependent upon the concurrent decrease in coronary blood flow. Both coronary flow and myocardial oxygen consumption remained below control levels after reinfusion of blood. During oligemia the heart also appeared to lose its ability to utilize glucose. Myocardial lactate extraction however, increased significantly during oligemia. A definite trend towards a negative myocardial extraction of pyruvate occurred during oligemia. The changes in glucose metabolism were completely abolished with reinfusion of blood. The myocardial extraction of lactate remained significantly elevated in the normovolemic phase, while the myocardial pyruvate extraction remained negative. Thus it appeared that the infusion of blood had failed

to correct the metabolic alterations initiated during the oligemic phases. Hackel and Goodale (88) studied myocardial carbohydrate metabolism in control dogs and those subjected to varying periods of hypotension. They concluded that a negative pyruvate extraction was the most consistent and striking abnormality found during hemorrhagic shock of three hours duration. Hackel (89) also compared the effects of reinfusion of blood with the use of l-norepinephrine on the myocardial metabolic pattern in hemorrhagic shock. The alteration in myocardial metabolism as a result of hemorrhagic shock was in part corrected by reinfusion of blood, but not altered by the use of l-norepinephrine.

It appears, from the foregoing observations that a study of coronary flow and myocardial metabolism concurrently could supplement the initial phase of this investigation and perhaps help to elucidate the etiology of the alterations in myocardial contractility after prolonged hemorrhagic shock. The following experimental studies were designed to investigate clause 3 of the original objectives:

"The study of changes in myocardial metabolism during hemorrhagic shock, and the attempt to correlate these changes with alterations in myocardial contractility."

METHODS

The experimental model used in this phase of the study was identical to that described in the initial methods, with the following additions:

1. Coronary sinus flow was determined at regular intervals during the course of each experiment. A number 14 Bardic catheter was introduced

into the coronary sinus via the right auricular appendage, and secured by means of a suture around the coronary sinus proximal to the middle cardiac vein. The catheter was then connected to a "y" tube which had one arm leading to a graduated cylinder, the other leading back to the right auricular appendage, and maintained with a purse string suture. The internal diameter of this tubing was 4 mm, and its free end which emptied into the graduated cylinder was maintained at a constant height to prevent variations in resistance to flow. Thus coronary sinus flow could be measured by clamping the return circuit to the right auricular appendage, and collecting the blood in a graduated cylinder for 30 second intervals. Each reading was repeated twice, and the mean value recorded.

2. Coronary sinus blood was obtained via the above system for measurement of O_2 content, lactate, and pyruvate levels at predetermined intervals.

3. Systemic arterial blood was obtained by a femoral artery catheter for measurement of O_2 content, lactate and pyruvate levels.

Myocardial extraction of oxygen, lactate and pyruvate was calculated by subtracting coronary sinus levels from coronary artery (systemic) levels. (90)

An approximate value for total uptake of oxygen, lactate, and pyruvate was obtained by the following formula:

Coronary sinus flow X (Coronary artery - coronary sinus level of substance in question).

The O_2 content of all samples was calculated using the Natelson microgasometer - model 600. Each determination was repeated twice and the mean value recorded.

The blood samples for measurement of lactate and pyruvate levels were

taken in a dry syringe, and 5 cc of blood was transferred immediately to 5 cc of ice cold 0.6N perchloric acid and thoroughly mixed. Lactate and pyruvate were measured using the Boehringer enzymatic test kits.

RESULTS: (8 dogs)

The mean control coronary sinus flow was 77 cc per minute. The changes occurring during hemorrhagic shock and reinfusion are shown in fig. 25.

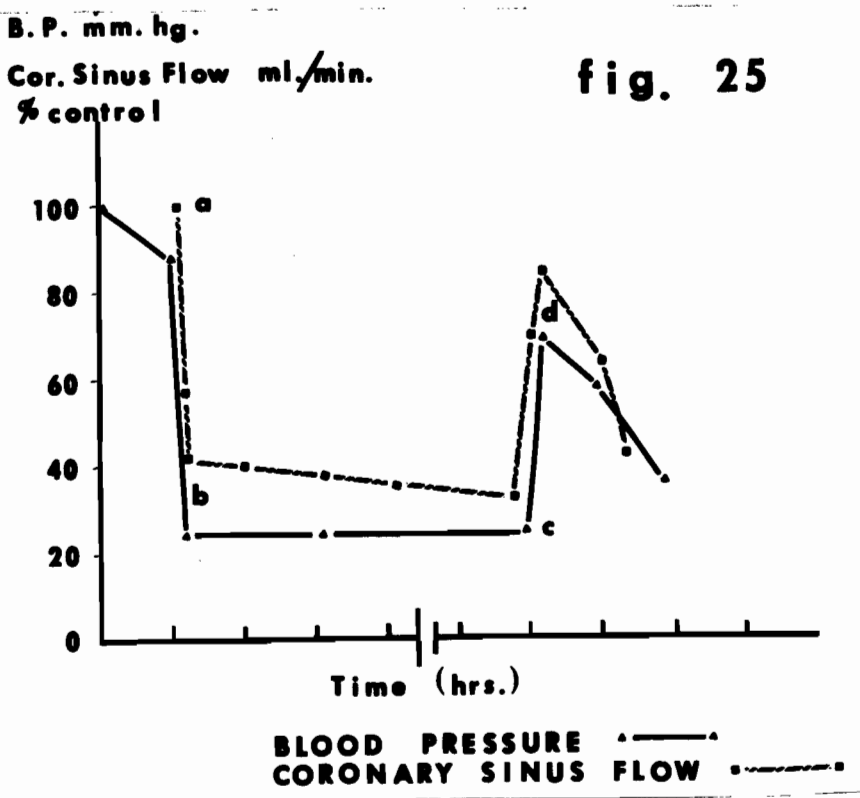
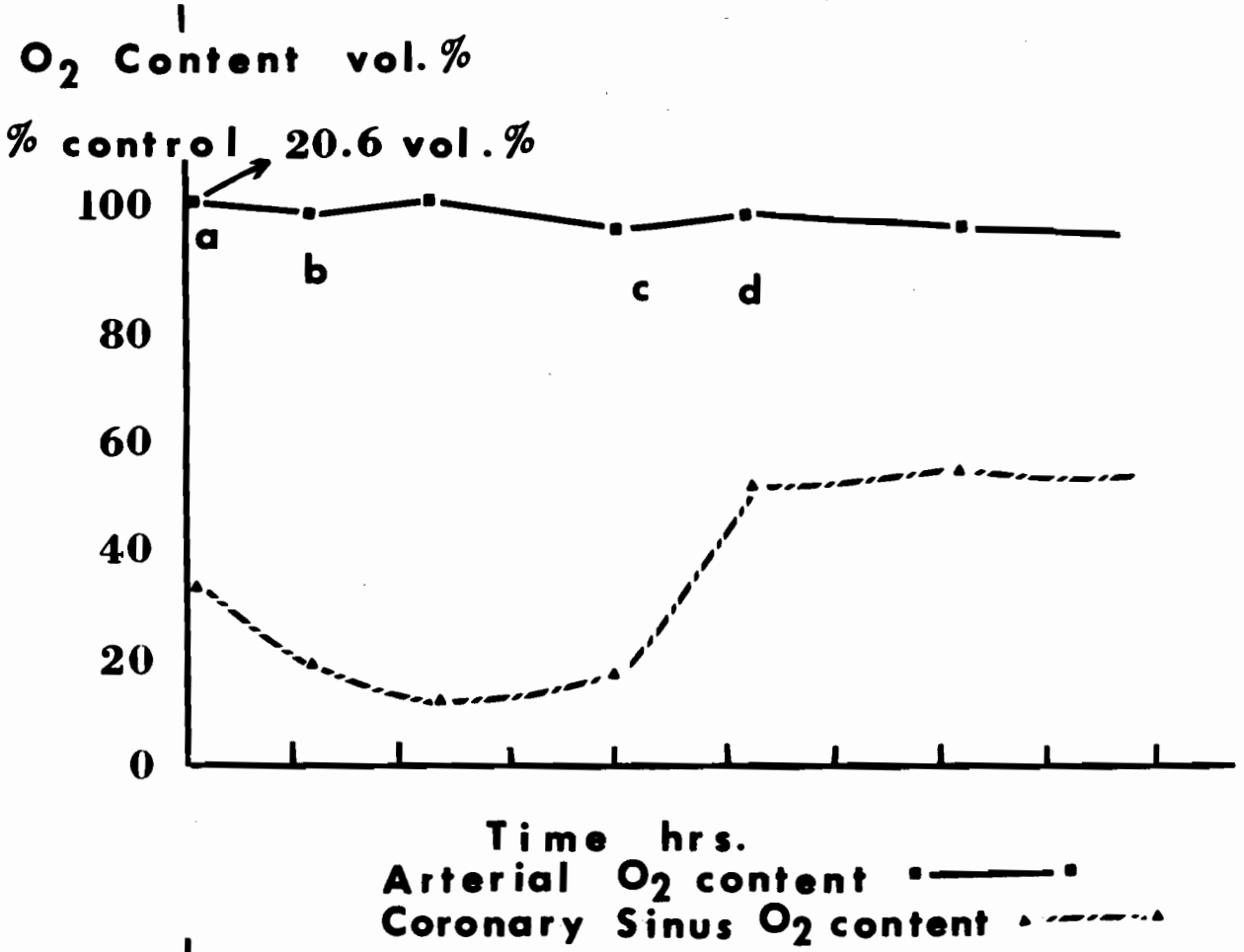


fig. 25

Coronary sinus flow fell with stepwise hemorrhage to 44% of the initial control value. As hypovolemia progressed, coronary sinus flow fell to 30% of control just prior to reinfusion of shed blood. Reinfusion of shed blood raised coronary sinus flow to 85% of the control value. It remained at this level for a very short period (20-30 minutes), and then declined rapidly. The decline in coronary sinus flow preceded the terminal decline in mean arterial blood pressure and cardiac output.


O2 Content vol.%
% control 20.6 vol.%
100
80
60
40
20
0
a
b
c
d
Time hrs.
Arterial O2 content
Coronary Sinus O2 content

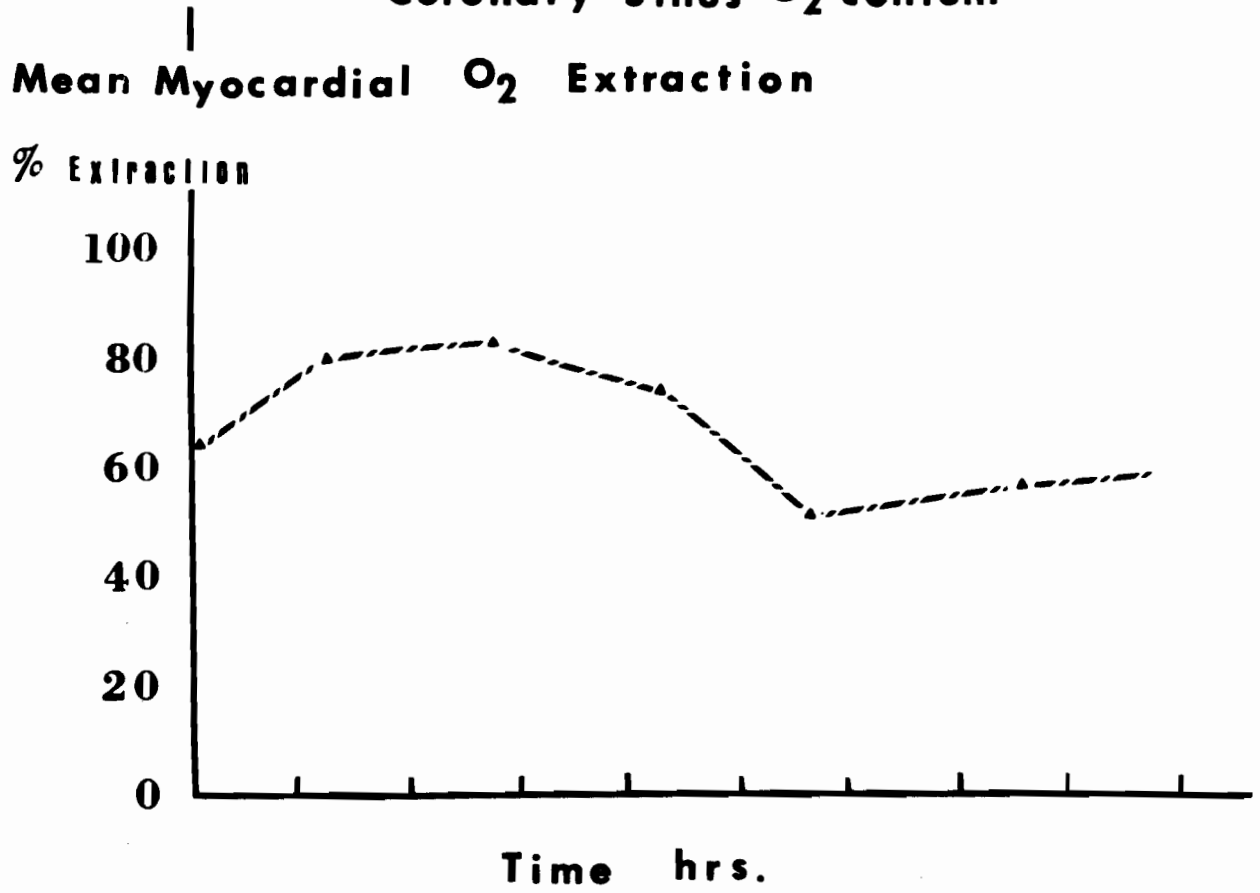
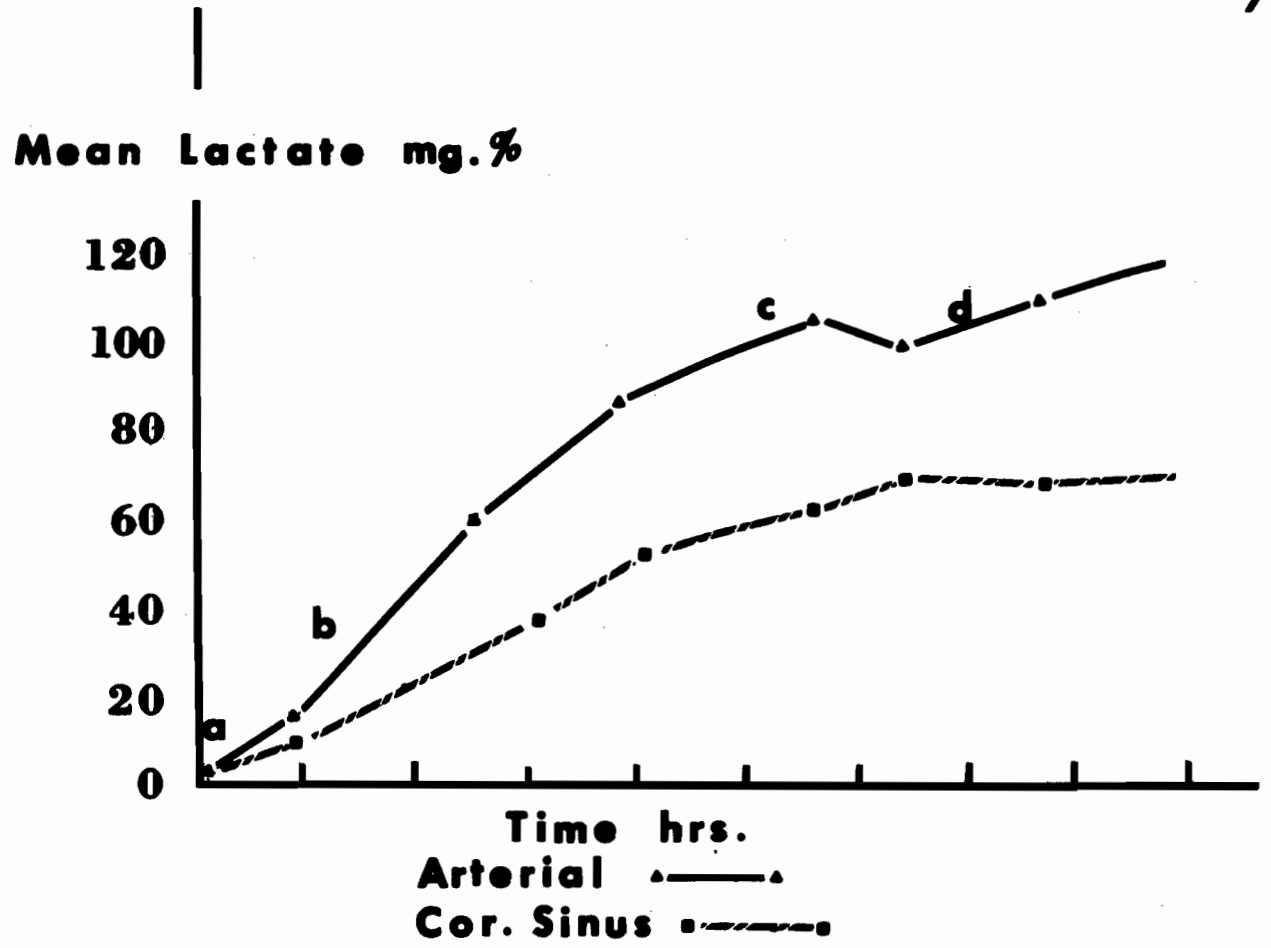

Mean Myocardial O2 Extraction
% Extraction
100
80
60
40
20
0
Time hrs.

FIGURE 26

The systemic arterial oxygen content was relatively well maintained throughout the course of all experiments. This is undoubtedly the result of the constant positive pressure respiratory support. The coronary sinus oxygen content was significantly decreased within 30 minutes following the induction of hemorrhagic shock. (Fig 26) Myocardial oxygen extraction thus increased from a control of 64% extraction to as high as 83% extraction after 2 hours of hypotension. After 30% of the shed blood spontaneously returned to the animal, the myocardial oxygen extraction had fallen to 50%. Reinfusion of all shed blood did not return myocardial oxygen extraction to control values, but instead the myocardial oxygen extraction remained at 52%. Myocardial oxygen extraction then fell as the animal deteriorated. One hour following reinfusion, mean myocardial oxygen extraction was 30%. Total myocardial utilization of oxygen however remained well below control throughout the hypotensive period due to the marked decrease in coronary flow during hypotension. The lowered myocardial extraction following reinfusion of shed blood, combined with the sub-control coronary flow maintained total myocardial oxygen utilization at low levels following reinfusion of shed blood.

The systemic arterial concentration of lactate rose from a mean control value of 2.1 mgm% to values as high as 140 mgm% terminally. The myocardial lactate extraction (Fig 27) increased progressively as hypotension progressed. The myocardial lactate extraction remained significantly elevated following reinfusion of all shed blood. The lactate concentration in the coronary sinus blood did not exceed arterial lactate levels at any time. Total myocardial utilization was not altered significantly despite the


Mean Lactate mg.%
120
100
80
60
40
20
0
a
b
c
d
Time hrs.
Arterial
Cor. Sinus

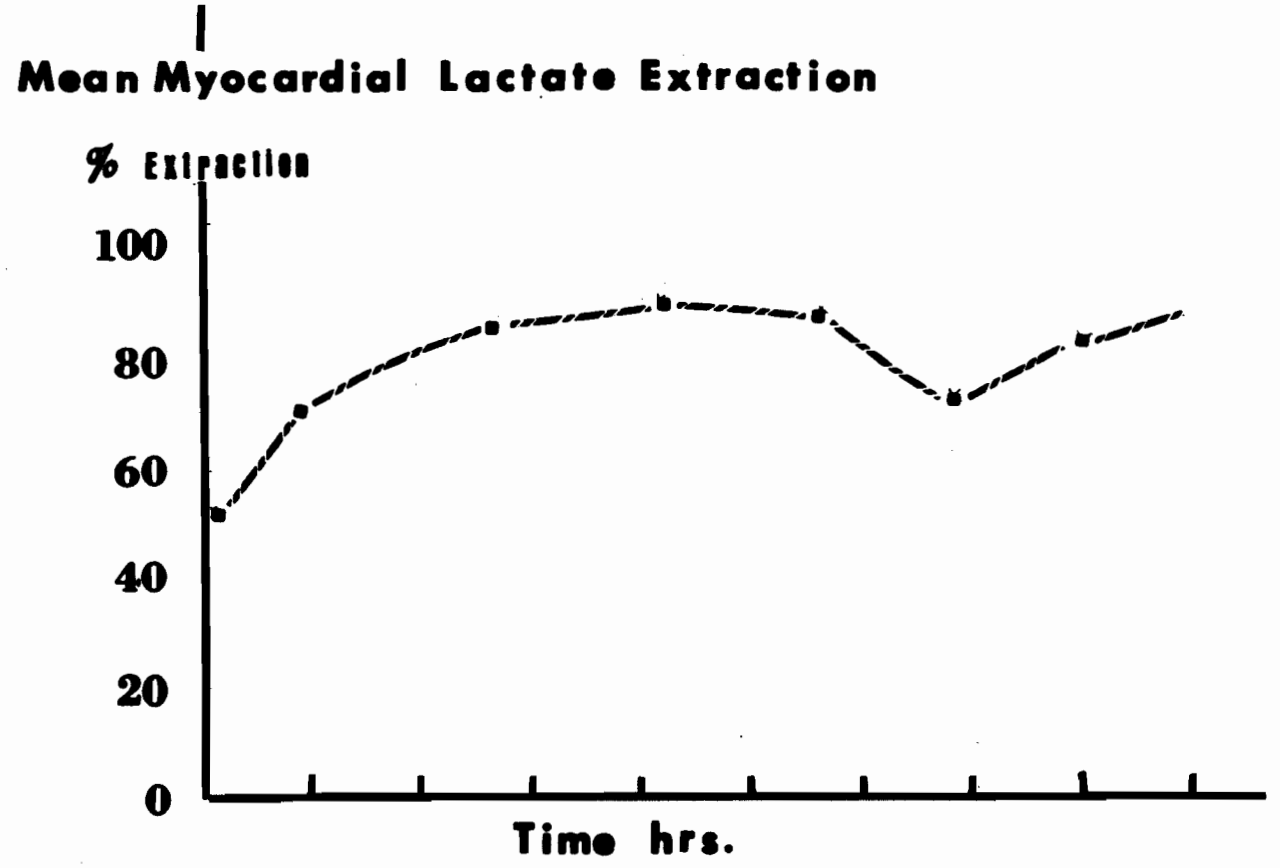
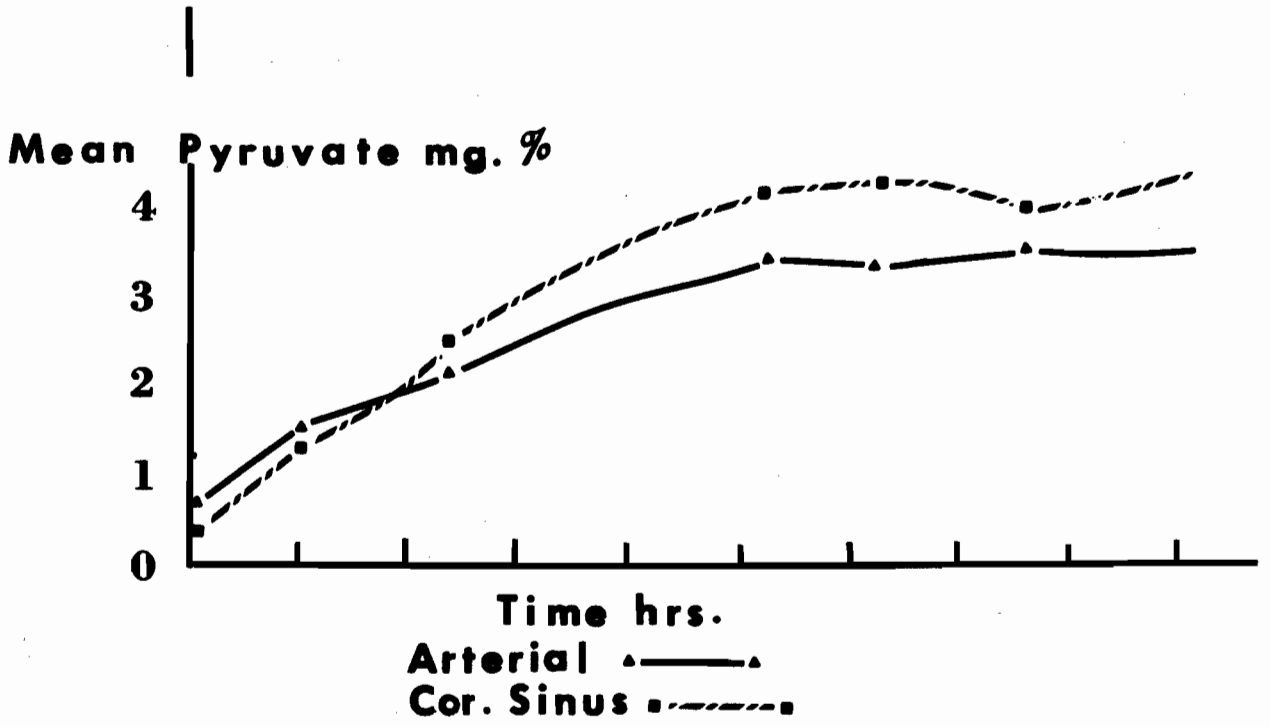

Mean Myocardial Lactate Extraction
% Extraction
100
80
60
40
20
0
Time hrs.

FIGURE 27


Mean Pyruvate mg. %
4
3
2
1
0
Time hrs.
Arterial
Cor. Sinus

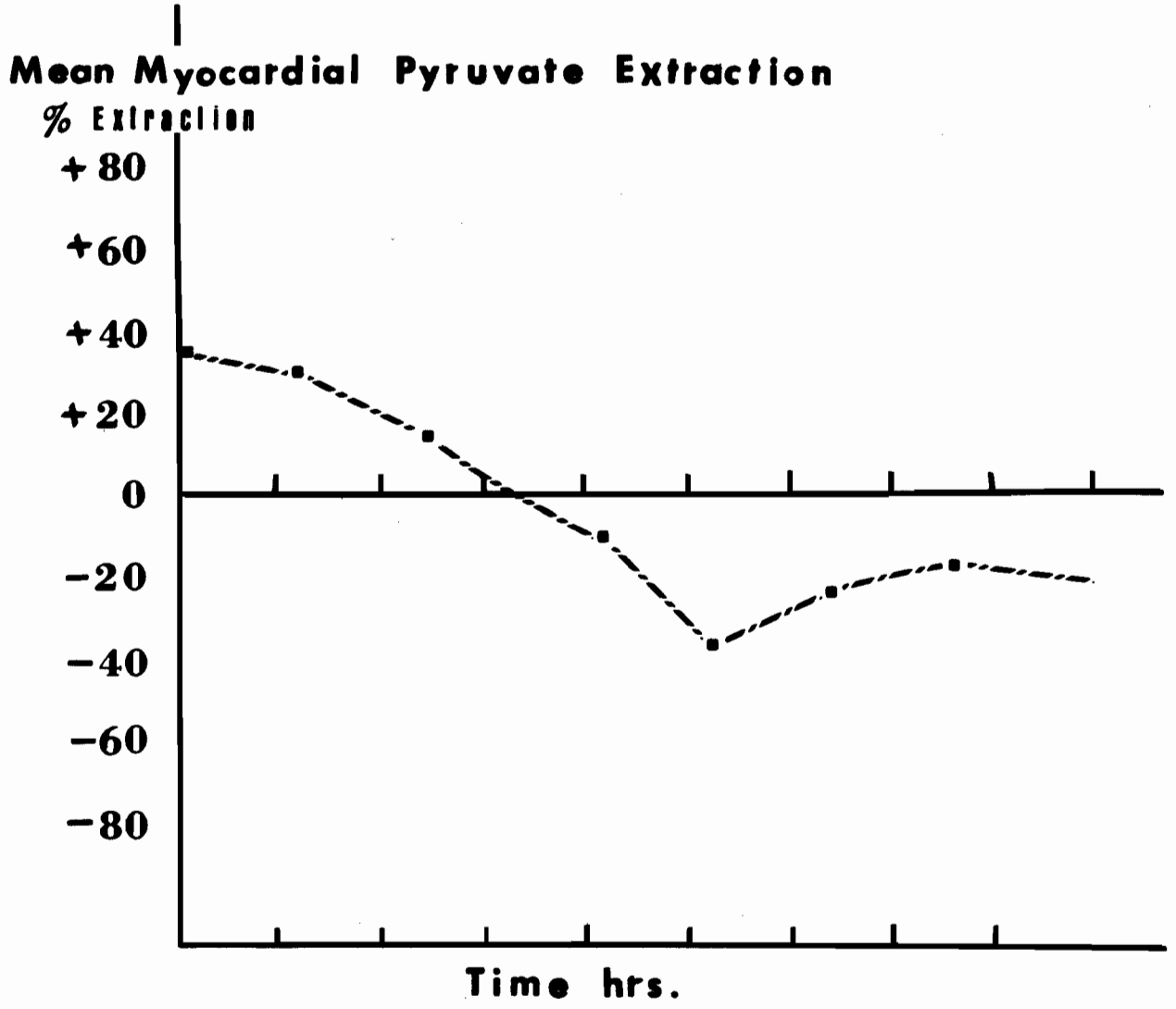

Mean Myocardial Pyruvate Extraction
% Extraction
+80
+60
+40
+20
0
-20
-40
-60
-80
Time hrs.

FIGURE 28

increased myocardial extraction. This is explained by the concurrent decrease in coronary flow, both during hypotension and following reinfusion.

The systemic arterial pyruvate levels also demonstrated a marked rise as hypotension progressed from a mean control of 0.79 mgm% to 3.34 mgm% terminally. The changes in myocardial pyruvate extraction during hypovolemia are illustrated in figure 28. There is an obvious progressive reduction in the myocardial pyruvate extraction after one hour of hypovolemia. The pyruvate extraction becomes negative just prior to reinfusion of shed blood. The coronary sinus levels of pyruvate were thus higher than the coronary artery levels of lactate, at the point of reinfusion. The myocardial extraction of pyruvate remained significantly reduced following reinfusion, and became even more negative as the animal declined terminally.

DISCUSSION

It appears that there is a significant fall in coronary blood flow following hemorrhage, when coronary sinus flow is used as an index of coronary flow. The coronary sinus flow does not return to control levels with the reinfusion of all shed blood.

There are definite criticisms and limitations to using coronary sinus flow as an index of coronary artery flow. Firstly, measurement of coronary sinus flow by catheter collection may not be an exact index of myocardial perfusion. Well described arterio venous shunts exist, but the exact conditions under which they function have not been defined. Secondly, balance studies of coronary inflow and outflow have shown that approximately 75% of blood entering the left coronary artery drains into the coronary

sinus,[90] but it is not known whether this proportion remains constant under changing conditions. One of the most commonly used methods of measuring coronary blood flow in the closed chest preparation is the nitrous oxide desaturation technique[91]. This however also depends upon a measure of coronary sinus flow, rather that of coronary arterial flow. As a result, the changes in coronary sinus flow cannot be considered as an absolute index of left coronary artery flow, but probably represents a good reflection of changes in coronary artery flow[83,90], during the course of this experiment.

The changes in coronary sinus flow, the E.C.G. changes and the alterations in myocardial contractility, definitely suggests that myocardial ischemia is present during oligemic shock, and reappears shortly after reinfusion of all shed blood. Similar conclusions have been reached by Sarnoff[19], Edwards et al[81], Vowles[83] and Opdyke[80]. It thus appears that myocardial ischemia during oligemia could result in adverse changes in contractility which are perpetuated following reinfusion and may contribute to the final fatal outcome following prolonged hemorrhagic shock in the dog. This further emphasizes the importance of rapid, accurate correction of any form of hypotension.

The increase in myocardial oxygen extraction shortly following the induction of hemorrhagic shock probably represents a compensatory mechanism as a result of decreased coronary flow. Marked coronary vasodilatation, with a fall in coronary vascular resistance has also been reported following hemorrhagic shock[80,81,83,88]. These two mechanisms would allow the myocardium to maintain aerobic metabolism in spite of a significant degree of

coronary insufficiency. An important factor in determining the metabolic response of the myocardium in the presence of reduced coronary flow is the ratio of oxygen demand of the myocardium, to its oxygen supply. If oxygen demand and supply are proportionally diminished, the metabolic effect of myocardial ischemia is minimal. As the animals began to spontaneously take back blood from the bleeding reservoir, myocardial oxygen extraction was reduced. The myocardial extraction of oxygen remained significantly reduced following reinfusion of all shed blood and as the animal declined. A reduction in oxygen consumption of the heart is not synonymous with myocardial anoxia. Following reinfusion, coronary flow remained below control, but systemic arterial oxygen content remained near normal, thus part of the decrease in oxygen extraction could be explained on the basis of myocardial ischemia. It is conceivable however, that a prolonged period of hypotension may have resulted in irreversible changes, making the myocardium unable to utilize oxygen. Another possibility is that circulating cardiotoxic products resulting from peripheral anoxia, may block enzyme systems preventing myocardial utilization of oxygen.

It is well known that the myocardium is able to choose its fuel from a variety of foodstuffs. It is possible to quantitatively determine the contribution of fat, carbohydrate, and protein to energy production under changing conditions. Lactate and pyruvate were utilized as an index for studying changes in myocardial metabolism for two reasons. Firstly, the myocardium is one of the major mammalian tissues known to utilize lactate as a substrate for energy production. Secondly, lactate and pyruvate hold a central position in anaerobic metabolism.

The marked elevation of both systemic lactate and pyruvate during oligemic shock, and persisting following reinfusion have been reported by several investigators (81,88) and probably reflects the general tissue anoxia seen in shock. A shift towards anaerobic met abolism in progressive shock is further suggested by an increase in the ratio of lactate to pyruvate in systemic blood. (92,92) If the myocardium responded to anoxia as other organs by an increased production of lactate via the usual glycolytic scheme, one would expect a decreased utilization of lactate and even an increase in the coronary venous lactate as compared to systemic arterial lactate. Instead, along with the increasing systemic arterial lactate, the myocardial extraction of lactate increased significantly both during oligemia, and following retransfusion. Total utilization of lactate was not significantly altered due to the concurrent fall in coronary flow. This increased lactate utilization may represent a biochemical compensatory mechanism to provide an additional source of energy in the face myocardial ischemia and anaerobic metabolism.

The most striking change in myocardial metabolism is the progressive trend toward a decreased extraction of pyruvate seen early in hypotension. This change becomes more pronounced with the progression of hypotension, and persists despite reinfusion of all shed blood. This change could possibly be related to a destruction of the co-enzyme cocarboxylase. Ochoa (94) first observed that cocarboxylase is destroyed under anaerobic conditions by an enzyme, probably a phosphatase. Greig and Govier (95) demonstrated a decrease in co-carboxylase content of muscle in dogs subjected to hemorrhagic hypotension. They postulated that the decrease in

co-carboxylase was a result of dephosphorylation, which occurred predominantly in muscle. They obtained similar results by rendering the dogs anoxic by inhalation of 10% oxygen mixtures. No measure of myocardial co-carboxylase was made in this study, although the finding of a negative myocardial pyruvate extraction is consistent with a disappearance of this enzyme in the myocardium. This destruction of cocarboxylase is very likely precipitated by a diminished coronary flow during hypotension.

Similar changes in myocardial lactate and pyruvate extraction in hemorrhagic shock have been demonstrated by Edwards et al (81) and Goodale (88). It is interesting that the changes in myocardial metabolism which developed during hypovolemia were not reversed with reinfusion of shed blood. Hackel et al (89) also showed that the administration of l-norepinephrine did not alter the pattern of myocardial metabolism despite the fact that both coronary flow and systemic blood pressure were returned towards control values. They concluded that l-norepinephrine did not correct the basic metabolic abnormality, and at the same time imposed a heavier burden of work on the heart. Some authors (72) have even suggested that the high circulating levels of catecholamines during hypotension may aggravate the altered metabolic pattern seen in the myocardium following hemorrhagic shock.

The above results demonstrate the metabolic response of the myocardium to a prolonged period of hypotension. These results suggest that myocardial ischemia secondary to a decreased coronary flow can initiate a specific pattern of changes in myocardial metabolism. The changes in myocardial metabolism are undoubtedly perpetuated by the degree of coronary insufficiency which persists following reinfusion of shed blood. The possibility that a circulating

cardiotoxin arising from peripheral anoxic areas further compounds these changes is postulated.

Thus, it may be reasonably postulated that a failure of myocardial energy production occurs following a prolonged period of hypotension, and contributes to the observed decline in myocardial contractility.

CHAPTER III

INTRODUCTION

The final result of the shock syndrome of any etiology is determined by several factors: the pre-shock status of the organism, the nature, intensity and duration of action of the etiological agent, the timing and effectiveness of the applied treatment. The ultimate aim of any form of treatment is to restore the pre-shock status and to correct the resulting deficiencies. An abundant supply of oxygenated blood at a high perfusing pressure is the most desirable form of treatment.

The results presented in this study suggest that the myocardium as well as the peripheral vascular bed declines functionally after a period of hypotension. It is conceivable that the myocardium in shock, could benefit from a period of mechanical support. The goal of such mechanical support would be to decrease the work load of the functionally deficient myocardium and at the same time artificially increase coronary blood flow. This artificial increase in coronary blood flow with the associated increased oxygenation should assist the myocardium toward recovery from injury and increase the production of useful myocardial energy.

The possibility of supporting the heart in failure by mechanical means has been proposed for several years. The four principal means of external support of the heart in failure are:

1. Total heart lung by pass with a pump and oxygenator (96,97,98). This method has the obvious disadvantages of requiring major surgery. There are

also significant hematocellular and metabolic changes to be considered, which limit the time during which external mechanical support can be maintained.

2. Veno-arterial pumping without oxygenation [99,100]. This method is readily carried out, with very few side effects in the normal individual. It has the disadvantages of low blood flow rates, and a markedly lowered peripheral resistance which would preclude its use in most shocked states. Patt et al [100] have demonstrated that this method of support could be fatal in the presence of cardiac failure.

3. Counter pulsation [101,102,103]. This method has been hampered by defects in synchronizing pump support with the electrocardiogram particularly in the presence of tachycardia or arrhythmias. Another disadvantage to the use of this method is the fact that alone, it may maintain existing blood pressure, but it cannot significantly elevate blood pressure. Counter-pulsation has been the subject of considerable recent research, [103] and with improved timing may represent a promising method for external circulatory support.

4. Left heart bypass. This method was developed by Dennis, Hall, Moreno and Senning [78,79], after Jonson and Karloff [104] perfected a transseptal approach to the left atrium for diagnostic methods. Dennis et al [78,79] demonstrated that left heart bypass was technically feasible, and appeared to reduce myocardial work, and decrease myocardial oxygen consumption. Keon [105] has recently reviewed the entire topic of left heart bypass, and applied the method to coronary shock, with promising results. He demonstrated that left heart bypass was capable of supporting systemic arterial blood

pressure, while maintaining adequate coronary flow. He also showed that oxygen supply to the myocardium was increased in excess of its requirements. This method of bypass diminishes the load of the left ventricle by bypassing the cardiac output. It then increases the cardiac output mechanically with oxygenated left atrial blood. It requires very minor surgical procedures, and could possibly be utilized clinically in cases of shock refractory to medical therapy.

The role of mechanical support to the myocardium following hemorrhagic shock, has been recently investigated by Callaghan et al[103]. They used an improved technique of counter pulsation on a hemorrhagic shock model. The animals in his study were rapidly bled a fixed volume of blood as determined by the I^{131} dilution technique, and then maintained in this hypovolemic state for 3 hours before the original shed blood was returned intravenously. A reduction of mortality rate from 70% in the control group, to 32% in the group treated with 60 minutes of counter pulsation was demonstrated. There was also a decline in blood lactate levels following the period of increased perfusion using counter pulsation.

It was of interest, therefore, to attempt an evaluation of the effects of a period of left heart bypass following prolonged hemorrhagic shock as proposed under section (4) of the original objectives: "An evaluation of the use of left heart bypass as a method of supporting the myocardium in dogs subjected to prolonged hemorrhagic hypotension, with particular emphasis on the effect it may have on myocardial metabolism and contractility." The methods necessary to carry out this part of the investigation were greatly facilitated by the work of Keon[105], who first utilized this procedure in this laboratory.

METHODS

Ten large mongrel dogs (average wt of 27 kg) were used in this phase of the investigation. The hemorrhagic shock model was identical to that described in detail in the first section of this study. Myocardial blood flow and metabolism were monitored as outlined in the second portion of this study.

The animals were subjected to stepwise hemorrhage, until a mean arterial blood pressure of 30 mm of Hg was reached. This blood pressure was maintained using the Lamson reservoir until the animal had spontaneously taken back 30% of the maximum bled volume. The animals then had all remaining shed blood reinfused over a 15 to 20 minute period. All experimental variables were documented at regular predetermined intervals, as in the first and second part of this study. The animals were then allowed 15 minutes to assume a "steady state", following which a 60 minute period of left heart bypass was carried out as described below. The animals were then monitored until death or marked circulatory depression had supervened.

During the initial cannulations for each experiment, in this group of dogs a silastic catheter (9 mm internal diameter) was inserted under direct vision into the left atrium, via the atrial appendage. This catheter was secured in position with a purse-string suture. The large silastic catheter had a smaller central polyvinyl catheter (PE 280) which ran from the left atrium to a transducer via a side arm in the silastic catheter. This allowed continuous monitoring of left atrial pressure. The tip of the large silastic cannula had a central orifice and four side orifices with a combined area 50% greater than the cross section of the lumen of

the shaft of the cannula. During the production of hemorrhagic shock in these dogs, the large silastic catheter was clamped, and only the central polyvinyl catheter utilized to monitor left atrial pressure. The large silastic catheter in the left atrium was adapted to the 10 mm vinyl tubing used for the extra-corporeal circuit.

The extra corporeal circuit consisted of a segment of vinyl tubing 150 cms in length (I.D. = 10 mm) which ran from the left atrial silastic catheter to a collapsible 500 cc vinyl bag which served as an expansion chamber. The bag was also connected via a 3 way stopcock to a blood reservoir. A second segment of vinyl tubing 200 cm. long connected the vinyl bag to a #14 Bardic catheter in one of the femoral arteries. This second segment of vinyl tubing was passed through a De Bakey roller pump. The priming volume of this circuit is 800 ml. This system allows blood to siphon from the left atrium to an expansible vinyl bag, and then to be pumped back into the femoral artery. This is a closed system, to which blood can be added at any time. The expansible bag was maintained in a water bath 80 cms below the operating table, helping to maintain blood temperature. The blood required to prime the circuit was obtained by bleeding another dog. The blood used in the first four dogs was collected in citrated bottles as by Abbott (Sodium citrate 1.32 grams, and citric acid anhydrous 0.44 grams). The blood used to prime the extra-corporeal circuit in the last 6 dogs was collected in 1000 cc siliconized bottles, filled with 75 cc of heparinized saline.

The extracorporeal circuit was primed with blood, and bypass was commenced at the appropriate time by releasing the clamp on the left atrial

cannula, and starting the roller pump. Bypass was carried out for a one hour period if possible. At the conclusion of this one hour period, left atrial, and femoral lines were then clamped, and the animals were monitored until death occurred. The pump flow rate was adjusted to maintain mean arterial blood pressure between 100 and 120 mm of Hg.

This group of dogs were also subjected to a careful autopsy.

RESULTS

The dogs responded to the prolonged period of hemorrhagic shock in precisely the same manner as described in detail in the first section of this study. Following complete reinfusion, arterial blood pressure was 70% of control, and cardiac output was 64% of control. This cardiac output was maintained at a significant elevation of left atrial pressure (144% of control), suggesting a definite degree of left ventricular failure.

The coronary sinus flow was 78% of control after complete reinfusion of all shed blood.

The pattern of change in myocardial metabolism was similar to that described in the second section of this study. The most striking change was the progressive trend to a negative myocardial pyruvate extraction.

The first four dogs placed on left heart bypass, all died within 20 minutes. The pattern of deterioration in these dogs was identical. They first developed a marked elevation in central venous pressure with an obvious gross dilatation of the right heart. The heart then became progressively more hypodynamic and asystole occurred within 20 minutes of the commencement of left heart bypass. It was impossible to maintain a mean arterial blood pressure of 90 mm of Hg. because of the progressive

elevation of central venous pressure. Any attempts to increase the flow rate resulted in further dilatation of the right heart. These four dogs all had the extra corporeal circulation primed with citrated blood. Serial determinations of serum K^+ and arterial pH (fig. 28) were documented in order to elucidate this rapid deterioration after the onset of left heart bypass. The possibility that the citrated blood used in the prime, played a role in the sudden death following bypass was considered.

Figure 29

Serum K^+ (meg./L)

	Control	Pre-bypass	Post-bypass
Dog I	4.2	4.6	6.4
Dog II	4.8	5.7	6.6
Dog III	4.4	4.3	6.7
Dog IV	4.4	4.1	9.5

Arterial pH

	Control	Pre-bypass	Post-bypass
Dog I	7.430	-	7.132
Dog II	7.320	7.176	7.056
Dog III	7.378	7.140	7.064
Dog IV	7.420	7.040	6.865

A random post bypass serum Ca^{++} on two dogs revealed moderate hypocalcemia (6.8 and 7.2 mgm/100 ml.)

The remaining six dogs underwent a full hour of left heart bypass, utilizing fresh heparinized blood to prime the extracorporeal circuit. Three of these dogs declined immediately after bypass was terminated. They died as soon after reinfusion as the dogs which were not bypassed.

These three dogs also demonstrated a marked elevation of central venous pressure in order to maintain a mean arterial blood pressure above 100 mm of Hg on bypass. This elevation of central venous pressure was associated with an obvious marked dilatation of the right atrium and the right ventricle.

The remaining three dogs demonstrated a degree of improvement following one hour of left heart bypass. There was only minimal elevation of central venous pressure in these three animals. Mean arterial blood pressure was elevated to an average of 78% of control compared to a pre-bypass level of 70% of control. Cardiac output averaged 76% of control post by-pass compared to 64% of control pre-bypass. The increase in cardiac output post bypass was in the face of a reduced left atrial pressure (pre-bypass 144% of control, post bypass 128% of control). These animals were able to maintain this improved status for an average of 90 minutes following bypass. These dogs then deteriorated slowly to die in an average of 4 hours. In only one of these dogs was there any evidence of return of reflexes following bypass.

There were no significant changes in the pattern of myocardial metabolism or oxygen consumption in any of the 10 dogs, following left heart bypass. The results were almost identical to those described in the second section of this study. Left heart bypass did not appear to influence the altered pattern of myocardial metabolism.

The coronary sinus flow while the animals were on left heart bypass was an average of 178% of control. Coronary sinus flow was markedly elevated in all 10 dogs while on left heart bypass.

There were no significant elevations of plasma hemoglobin following one hour of left heart bypass.

The six dogs which tolerated a full hour of left heart bypass following the prolonged period of hypotension, all demonstrated an increased bleeding tendency post bypass. It was necessary to add an average of 1400 cc to the blood reservoir in order to maintain a satisfactory flow rate.

The one hour period of left heart bypass did not alter the autopsy findings which were essentially the same as described in detail in the first section of this study. In particular there was no significant reduction in the occurrence of subendocardial hemorrhages and myocardial lesions.

DISCUSSION

The results of left heart bypass in this group of dogs were extremely disappointing, and somewhat difficult to explain. In retrospect, the model used in this study is the most severe possible. It is likely that any form of therapy following complete reinfusion of blood, would have been futile. The major criticism of most experimental models used in the study of left heart bypass is the inability to differentiate the effect of bypass on the myocardium from the beneficial effect on the peripheral circulation. It was felt that the model used in this study, monitoring changes in myocardial metabolism, would enable a selective evaluation of the effects of left heart bypass on the myocardium. The model as developed however proved to be too severe to evaluate any form of therapy.

The sudden deterioration of the expulsive power of the heart in the dogs bypassed while the extracorporeal circulation was primed with citrated blood is very interesting. Howland (106), Jennings et al (107) have both described a similar syndrome following massive transfusion of the shocked

dog with citrated bank blood. The end result is a combination of severe acidosis, hyper Kalemia and hypocalcemia which ends in progressive cardiac atony terminating in asystole. The endogenous trend towards acidosis in these severely shocked animals as a result of excess lactic acid from inadequate tissue perfusion and anaerobic metabolism was further compounded by the addition of a large volume of acid blood preserved with citrate. The findings of severe acidosis, hyper Kalemia and hypocalcemia following left heart bypass in the first four dogs suggests that the use of citrated blood in the prime may indeed contribute to the rapid cardiac atony which developed on bypass.

The increased perfusion associated with left heart bypass may produce a so-called "wash-out" acidosis as a result of the sudden mobilization of the products of anaerobic metabolism accumulated as a result of poor tissue perfusion.

In 7 of the 10 dogs which underwent left heart bypass, right heart failure was a limiting factor in maintaining a satisfactory flow rate. The presence of a normal right heart is absolutely essential for a satisfactory left heart bypass. The dogs utilized in this study developed predominately left heart failure, but undoubtedly suffered damage to the right heart also. It is difficult to predict the degree that right heart failure would be a limiting factor to left heart bypass in a less severe hemorrhagic shock model.

Technically the left heart bypass achieved in this group of dogs was satisfactory. In seven of the ten dogs, left heart bypass was able to maintain the systemic circulation and greatly augment coronary flow. The

fact that myocardial oxygen extraction and the altered myocardial metabolic pattern were not improved as a result of the markedly increased coronary flow, further attests to the irreversible myocardial changes in this model. The left heart appeared to be completely decompressed as a result of left heart bypass. There was no significant elevation of plasma hemoglobin as a result of a one hour period of left heart bypass. Excessive bleeding appeared to develop following a one hour period of bypass, despite complete reversal of heparin effect with protamine. This finding was not further investigated in this study.

It is impossible to draw any conclusions as to the effects of left heart bypass on the myocardium damaged by prolonged hemorrhagic shock, from this study. The evaluation of left heart bypass in a less severe hemorrhagic shock model is definitely indicated. The entire concept of pharmacologic and mechanical support to the circulation following hemorrhagic shock, warrants further study both experimentally and clinically.

SUMMARY AND CONCLUSIONS

A detailed investigation of myocardial function following a period of prolonged hemorrhagic shock has been carried out using an open chest canine experimental model. The study utilized left ventricular function curves to quantitate myocardial contractility. Simultaneous analyses of myocardial blood supply and metabolism were made during and following prolonged hemorrhagic shock. The possibility of utilizing left heart bypass as a method of supporting the circulation following hemorrhagic shock was investigated.

The following conclusions were made from the foregoing study:

(a) A significant decline in myocardial contractility occurs early following the induction of hemorrhagic shock. The decline in myocardial contractility persists following the reinfusion of all shed blood, and becomes more marked as the animal deteriorates terminally. Immediately following reinfusion of shed blood, left ventricular work was markedly below control values in spite of a significant elevation of left atrial pressure.

(b) There was a concurrent loss of effective circulating blood volume and a decreased venous return following prolonged hemorrhagic shock, as evidenced by the changes in central venous pressure and hematocrit. It is interesting to postulate that this loss of blood volume could mask or minimize the degree of myocardial failure observed.

(c) The changes in the electrocardiogram after the induction of hypotension, suggest myocardial ischemia. The changes become more pronounced suggesting myocardial necrosis as the duration of hypotension proceeded. The terminal changes indicate a complete loss of neurogenic control of the circulatory system.

(d) The dogs which die following prolonged hemorrhagic shock demonstrate a typical pattern of myocardial pathology. The lesions were primarily subendocardial in location and are characterized by a superficial hemorrhagic area, overlying varying degrees of myocardial necrosis, frequently involving adjacent conducting fibres.

(e) The indirect estimation of myocardial blood flow during hemorrhagic shock, support the hypothesis that there is a degree of coronary insufficiency shortly following induction of hypotension resulting in myocardial ischemia. This persists following the reinfusion of shed blood.

(f) A typical pattern of changes in myocardial metabolism develops with the induction of hemorrhagic shock. The changes become more marked as hypotension progresses, and remains unchanged following reinfusion of shed blood. The most striking change observed is the progressive decrease in myocardial pyruvate extraction, which becomes negative just prior to reinfusion of shed blood. This altered metabolic pattern suggests a reversion to myocardial anaerobic metabolism, compounded by the elevated lactate and pyruvate levels as a result of generalized decrease in tissue perfusion.

(g) The severe nature of the experimental model used in this study makes it impossible to draw any valid conclusions regarding the use of left heart bypass as a means of mechanical support to the myocardium following hemorrhagic shock.

The exact degree to which myocardial failure contributes to the final fatal outcome following prolonged hemorrhagic shock, remains to be elucidated. The results of this study, and recent clinical studies[37,38]

suggest that myocardial failure may play a significant role in refractory hypotension, particularly in the face of pre-existing coronary artery or myocardial insufficiency.

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