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Cardiac Failure as a Terminal Event in Hemorrhagic Shock

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CARDIAC FAILURE AS A TERMINAL EVENT IN HEMORRHAGIC SHOCK

BY

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BIOGRAPHY

Joseph H. Traxler was born in Chicago, Illinois on December 14, 1940. He lived in Chicago until the age of nine and then moved to Glencoe, Illinois. He attended grade school there and was then graduated from New Trier High School in Winnetka, Illinois in 1958. That same year he entered Northwestern University in Evanston, Illinois and was a student there for three years.

In 1961 he entered the Stritch School of Medicine of Loyola University and received his M.D. degree in June, 1965. During his sophomore year of medical school he enrolled as a graduate student in the Department of Physiology of Loyola University. While he was a graduate student he was the recipient of a Lederle Foundation grant from 1962-1963 and was a Royal E. Gabel Fellow from 1963-1964.

Doctor Traxler has completed a straight surgical internship at the University of Illinois Research and Educational Hospitals and is now serving on two years of active duty with the U.S. Navy. He has been married to the former Joyce Merritt for two and one-half years.

INTRODUCTION

I. EARLY HISTORY OF SHOCK

The clinical picture of lost sensibility, pallor, nausea, muscle weakness, and syncope, as well as death, following the application of violent forces to the body was undoubtedly evident to the ancients. However, the first description of the clinical picture of shock, as we know it today, did not appear in the literature until the late 16th century. In 1575, Ambroise Paré commented on a deathlike state, which he called "commotion" and described as being "caused by falling from a high place on something solid and hard, or by blows causing contusions, such as stone or mass, or the blow of a lance, or an artillery blow, or thunder falling near a person, or other similar things". Moreover, Paré noted that convulsions followed the loss of blood, and death resulted if there was no replacement of blood. For the next one-hundred and fifty years, clinicians attempted vigorously, yet unsuccessfully to replace fluids by blood transfusions.

It was not until the early 18th century that the physician became more sophisticated in his physiological description and explanation of the shock-like state. In 1733 the Reverend Stephen Hales performed what are now regarded as his classical experiments upon animals. He became the first person to measure the venous pressure in animals in addition to recording

factors affecting blood pressure. He noted the presence of a marked vasoconstriction in exsanguination.

The French surgeon, LeDran, (1743) is credited with using the word "choc" for the first time. However, it is felt by most medical historians that he used it to designate the act of collision rather than the resulting functional damage. Yet, in spite of this discrepancy, the English translation of his work is very eloquent and surprisingly accurate. "The bullet... thrown by the gun powder acquires such rapid force that the whole animal machine participates in the shock and agitation. The vessels become constricted as if surrounded with a ligature, and hence the stream of animal spirits become intercepted or entirely suspended. There is a universal coldness due to this interruption of the fluids, and capillary flow is choked up. Syncope results due to three causes: 1. Sudden suspension of nervous fluid; 2. Spasmodic convulsion in the fibers of the heart; 3. Loss of fluid in hemorrhage. In shock the disorder of the machine may be increased by the succeeding pain, by want of sleep and rest, and by fluids extravasated into the circumference of the wound". He suggested transfusion to build up the patient's strength.

During the next one-hundred and fifty years more accurate clinical observations of shock were made. Moreover, it gradually came to be appreciated that shock-producing agents need not necessarily be violent or even obvious, although the

word shock was used in many instances where it would not apply in its modern usage today. Finally, the accumulation of physiological knowledge on the control of the circulation served to focus attention on circulatory failure as the important feature of shock. Paralysis or inhibition of the vasomotor center, pooling of blood in the abdominal vessels, and hypotension were regarded as sequential events. No consensus existed as to whether the nervous symptoms were primary or secondary to the fall of arterial pressure. Obviously, various hypothesis were suggested which were neither conclusive nor adequate. With the beginning of the twentieth century, investigators began to attempt to elucidate the subject of shock by experiments.

The first significant experiments were performed by Crile in 1899. He produced shock in various ways, and since the blood pressure could be quickly and temporarily restored by intravenous infusions, he concluded that the capacity of the heart to pump blood was not affected, and that peripheral circulatory failure was a major factor. He concluded that the vasomotor center must be exhausted. Henderson (1908,1910) studied various alterations of the circulation in shock produced by manipulating the intestines of anesthetized dogs. During the period that occurred preliminary to shock, the cardiac volume curve declined markedly because of inadequate diastolic filling, and that it occurred before any decline in

blood pressure. When blood flow had diminished to about 30% of normal, the arterial pressure began to fall rapidly. Infusions of saline solutions administered intravenously restored the volume curve and blood pressure to normal. Therefore, this decrease in cardiac output was not due to a decline in cardiac function, but to a diminished venous return to the heart.

Laboratory studies during the early 20th century and through World War I continued to indicate that the action of the heart and its innervation was not disturbed. Interest in this period focused chiefly on the location and nature of the peripheral vascular changes.

II. RECENT INVESTIGATIONS OF THE HEART IN SHOCK

However, with the outbreak of World War II, the development of more refined methods of measuring cardiac output, intracardiac pressures, and cardiac volume changes enabled the investigator to again focus his attention upon the hemodynamic changes in the heart in shock. These investigations were initiated by Wiggers and his co-workers. They found that animals kept for 90 and 45 minutes at mean blood pressure levels at 50 and 30 mm Hg respectively showed no reduction in the effective venous pressure despite the post-infusion decline in the cardiac output, which occurred when the animals were essentially normovolemic. Their animals

exhibited a "flattening" of the right ventricular pressure curve during the late oligemic and normovolemic stages, which they suggested to result from a reduction in the myocardial expulsive power during shock. Kohlstaedt and Page (1944), recording volume changes of the ventricles in the closed-chest animal by the technique of Boyd and Patras (1941), found that progressive bleeding led to a decrease in heart size. As circulatory failure progressed after the cessation of bleeding, both the systolic and the diastolic size increased, the former more rapidly than the latter. Thus the stroke volume was apparently less, the residual volume was augmented, and the ventricles dilated.

The appearance of myocardial failure was originally postulated by Wiggers (1944) to be due to coronary insufficiency, although Opdyke and Foreman (1947) suggested that despite a marked reduction in coronary flow, it was considered adequate in view of the reduction in cardiac work. However, Sarnoff et al (1954) presented evidence to show that a rise in left atrial pressure during hemorrhagic hypotension was reversed by perfusion of the left common coronary artery.

More recently, Crowell and Guyton (1961) found an increase in the left atrial pressure at the onset of autoinfusion, in dogs maintained at a mean blood pressure of 30 mm Hg for 90 minutes. In another series of experiments (1962) they observed that the infusion of large volumes of blood was incapable of

maintaining the cardiac output in a similar preparation despite marked increases in filling pressures. In two experiments, improvement was only manifested when the cardiac glycoside, Ouabain, was used. McPherson and Haller (1963), however, using essentially the same experimental procedures as Crowell and Guyton, found that the use of Ouabain did not correct, prevent, or significantly alter irreversible shock in dogs. Although they felt that myocardial failure occurs in shock, it did not appear to be related to the onset of irreversibility. They concluded that any correction of myocardial failure by Ouabain did not affect the course of irreversible shock. They did find, however, that dogs given Ouabain prophylactically had an increased survival time. Gomez and Hamilton (1962) also found evidence of cardiac failure in dogs maintained at a mean blood pressure level of 30 mm Hg for 90 minutes and then reinfused. Moreover, they observed that cross-clamping below the arch of the aorta for various periods of time resulted in peripheral hypotension that still produced irreversible shock and cardiac failure even though the brain and heart were perfused at mean pressures of 100 mm Hg. From these observations they concluded that the cardiac failure was secondary to a humoral agent from peripheral tissue.

Finally, Rothe and Selkurt (1964) found that various levels of hemorrhagic hypotension resulted in changes of cardiac performance in such a manner that the function of the

heart seemed to be inversely proportional to the severity or duration of hypotension.

METHODS AND PROCEDURES

Ten mongrel dogs, varying in weight from 13 to 21 kg were anesthetized with 30 mg/kg of sodium pentobarbital injected intravenously. The trachea was cannulated and attached to an Ensco respirator, which supplied continuous positive pressure respiration. A left thoracotomy was then performed through the 5th intercostal space and the exposure was increased by cutting the first through fifth ribs along the left sternal border. A pericardial cradle was then prepared to suspend and expose the atria and ventricles. Right and left atrial pressures were recorded from these appendages with short polyethylene (no. 19) catheters. Right and left ventricular pressures were recorded from catheters (no. 18) inserted through the walls of both chambers. The intracardiac catheters were connected to Statham pressure transducers (Model 21 Db), which in turn were recorded on a 4-channel Grass Polygraph. The left femoral artery and vein were exposed for bleeding and the infusion of blood respectively while the right femoral artery was cannulated and connected to a Hg manometer for visual monitoring of mean arterial blood pressure. The coagulation of blood was prevented by a priming dose of 5 mg/kg of Heparin followed by a maintenance dose of 2.5 mg/kg every hour during the course of the experiment.

After control records were taken, the dogs were bled to a mean blood pressure of 40 mm Hg, and were maintained at this

level from three to four hours, or until the animals no longer maintained this pressure with small infusions of blood. The total bled volume of blood was reinfused at room temperature at a rate of 30 ml. per minute. In two of the ten dogs the post-infusion pressure was followed until it declined to 40 mm Hg. Records of all pressure parameters were taken every 30 minutes during the oligemic period. During the postinfusion period, records were taken every 30 minutes or more often during the progressive fall of the arterial pressure in the terminal stage. At the conclusion of the experiment, the heights from the level of the pressure transducers to the point of insertion of the respective catheters in the myocardial walls were carefully measured. This was done to determine the hydrostatic factors, which were added to the recorded pressure to get the "true" intracardiac pressure. In four dogs, control experiments were performed to determine the effects of cardiac catherization for four to five hours in open-chest dogs not in shock.

In another group, six closed-chest dogs, anesthetized with sodium pentobarbital, were studied to determine the effects of the drug Ouabain on the heart in irreversible hemorrhagic shock. The shock procedure was the same as that described for the open-chest dogs with catherization of the cardiac chambers. The trachea was entubated and the left femoral artery was cannulated and connected to a mercury manometer for monitoring the mean blood pressures. Systolic and diastolic blood

pressures were measured from a Sanborn differential transducer (Model #267). The right external jugular vein was catherized with two radiopaque (no. 5) catheters, which were passed to the junction of the inferior and superior vena cavae as determined by the characteristic of the pressure pulse (Burch 1950). Verification was also obtained by postmorten examination. One catheter was used for recording the central venous pressure, while the other was used for the injection (1.25 mg) of the indocyanine green used for determining the cardiac output by the dye dilution method of Hamilton (1962) and Stewart. Blood was passed through a Gilford densitometer from a catheter passed into the left common carotid artery, and from the densitometer it was returned at a rate of 30 ml/min to a femoral vein by means of a Sigma motor pump. The mean arterial pressure, dye dilution curves, and the central venous pressures were recorded on a Sanborn Recorder, Model 150. When the animals were no longer able to maintain a mean blood pressure of 40 mm Hg pressure, they were divided into two groups. Three of the six dogs received 0.035 mgm/kg of Ouabain intravenously prior to the reinfusion of the bled volume, while in the remaining three dogs an equal does of Ouabain was administered 20 minutes after the reinfusion of the bled volume. Both groups of dogs were observed until the mean blood pressure had declined to approximately 40-30 mm Hg.

RESULTS

In Figure 1 changes in heart rate, mean blood pressure, right and left mean atrial pressures, and left and right ventricular systolic and end-diastolic pressures are shown for one dog during the oligemic, normovolemic, and terminal periods of hemorragic shock. The figure shows that during the oligemic stage all of the pressures dropped below control values, rose immediately after reinfusion, and subsequently declined again during the normovolemic or postinfusive stage. However, in the terminal stage of the experiment, when mean blood pressure had dropped to 30 mm Hg., ventricular systolic pressures continued to decrease, while ventricular end-diastolic pressures, as well as right and left mean atrial pressures rose rather significantly above control values until the heart fibrillated and the animal expired. Table #1 summarizes data in eight dogs recorded during the control period, two hours after bleeding, immediately prior to reinfusion, one-half and one hour after reinfusion and just prior to the death of the animals. The mean values for all of these parameters were calculated but they could not be subjected to statistical analysis because of the variation in pressures recorded in the respective experiments. While mean blood pressure dropped from an average control value of 97 mm Hg to a mean pressure of 40 mm Hg two hours after bleeding and remained there prior to reinfusion, the mean right atrial pressure dropped from a mean average of 3.0 mm Hg to a mean

average value of 2.4 mm Hg after two hours of oligemia and to an average of 2.2 mm Hg prior to reinfusion of blood. The right ventricular end-diastolic pressure showed no significant drop during the oligemic stage, staying at 2.4 mm Hg for two hours after bleeding and declining to only 2.2 mm Hg before reinfusion. Concurrently the right ventricular systolic pressure showed no marked decrease, and in fact increased from a control value of 20.0 mm Hg to 21.5 mm Hg just before the blood was returned. Unlike the right side of the heart, the left heart demonstrated almost a 50% decrease in the left atrial pressure, which fell from a mean pressure of 6.2 mm Hg to 3.4 mm Hg in the first half of the oligemic phase. The left ventricular systolic pressure during this period decreased from 107 mm Hg to a systolic pressure of 53.1 mm Hg. The left ventricular end-diastolic pressure fell from 3.5 mm Hg to 2.9 mm Hg and subsequently dropped to 2.5 mm Hg immediately before reinfusion. Recordings taken one-half hour after the reinfusion of the bled volume revealed an average mean blood pressure of 74 mm Hg and mean right and left atrial pressures averaged 2.4 and 4.6 mm Hg respectively. Right and left ventricular systolic pressures were observed to average 23.7 and 81.0 mm Hg respectively while right and left ventricular end-diastolic pressure levels averaged 1.7 and 3.2 mm Hg respectively. Within 30 minutes mean blood pressure had fallen to an average value of 55 mm Hg while right atrial pressures had dropped to an average of

1.7 mm Hg and the left atrial pressure remained at 4.6 mm Hg. The right and left ventricular systolic pressures fell on an average to 18.6 and 72.7 mm Hg respectively while the right ventricular end-diastolic pressure declined to an average of 1.5 mm Hg. The left ventricular end-diastolic pressure rose to the control average value of 3.5 mm Hg. However, during the terminal phases of the experiment, when mean blood pressure had fallen to an average value of 22 mm Hg, the right and left atrial pressures rose to an average of 3.1 and 5.5 mm Hg respectively. Ventricular end-diastolic pressures rose to an average of 2.6 (right) and 5.4 (left) mm Hg, while the ventricular systolic pressures declined to an average of 14.4 (right) and 25.8 (left) mm Hg.

Since significant changes in cardiac pressures indicating cardiac failure were only observed in the late normovolemic period, the observations for this stage have been summarized in Figure #2 where the mean blood pressure, atrial and ventricular end-diastolic pressures were plotted.

Of the eight experiments followed until the death of the animals, only two (Experiments #5 and #8) did not demonstrate significant rises in the atrial or ventricular end-diastolic pressures above the early normovolemic cardiac chamber pressures during the terminal phase 30 minutes before the death of the animals. These increases appeared to occur simultaneously with a rapid decline in mean arterial pressures. Unless a stroke by

stroke analysis were made of the heart, it would be difficult to determine if the fall in blood pressure preceded the rise in the atrial or end-diastolic ventricular pressures were followed by the decline in mean arterial pressures. The only striking example from this group, in addition to experiments number 5 and 8, where one or more intracardiac pressures did not increase, was in experiment #7 where the experiment was terminated when the mean blood pressure had declined to only 40 mm Hg. It would seem that a pertinent deduction from this experiment would be that the progressive decline in mean blood pressure leads to the rise in atrial and ventricular end-diastolic pressures from inadequate coronary perfusion.

The administration of Ouabain (0.035 mg/kg) either before or immediately after the reinfusion of blood did not increase the survival time of six closed-chest dogs in irreversible hemorrhagic shock. In two of the six dogs treated with Ouabain, the mean blood pressure, central venous pressure, and cardiac output and total peripheral resistance were graphed (Fig. 3). Contrary to what is expected in a failing heart from the action of the cardiac glycoside, cardiac output did not increase following the administration of Ouabain either before or after the return of the bled volume. In all of the dogs that received Ouabain, a transient increase in the mean blood pressure was noted following the administration of the drug. However, this occurred while the cardiac output either decreased or remained

stable. Therefore, this rise in mean blood pressure was attributed to an elevation in the peripheral resistance and not to an increase in the cardiac output. This phenomenon has been described previously in dogs not in cardiac failure, which were given Ouabain (Cotten, 1958). The rate of decrease in mean blood pressure was unaffected during the normovolemic period in the treated animals and eventually all of the dogs succumbed in a period of time approximately equal to the untreated open-chest dogs.

It is interesting to point out that despite the extensive surgical procedures used to measure cardiac chamber pressures in the open-chest dogs, the survival period from severe hemorrhagic hypotension and subsequent infusion of blood was approximately equal to the closed-chest dogs treated with the cardiac glycoside Ouabain. This possibly might be explained by the fact that the open-chest dogs had positive pressure respiration to maintain adequate oxygenation that was not available to the closed-chest dogs.

DISCUSSION

The purpose of this investigation was to assess the role of "myocardial depression" (deterioration in myocardial expulsive power) as a factor responsible for the irreversible phase of hemorrhagic shock. The hypothesis that "myocardial depression" is the precipitating factor in initiating irreversibility was based primarily on the findings of Wiggers and coworkers (1942, 1945, 1947, 1950). In these studies they found that dogs in experimental hemorrhagic shock were observed to exhibit an increase in right atrial pressure, a decrease in the force of ventricular contraction, and a decrease in the velocity of systolic ejection. These cardiodynamic findings were based on studies of the cardiac pressure and volume curves. Wiggers specified that although the evidence suggested that myocardial depression is a frequent and important factor, it might not be a major cause in all forms of shock. More recently, Crowell and Guyton (1961, 1962) more emphatically postulated that cardiac failure played the major role in the etiology of irreversible shock. They based their conclusions upon the observed increases in left atrial pressures during the onset of the irreversible period despite maintenance of the cardiac output by continuous infusion of whole blood. Moreover, the administration of Ouabain in their experiments decreased the atrial pressure, while increasing the cardiac output. Gomez and Hamilton (1964) implied that cardiac function was impaired during hypotension.

This implication was based upon the observation that the cardiac work load decreased when the left atrium was presented with a great load of blood. This was done after the animals were kept hypotensive for varying periods of time and then reinfused to normotensive pressure levels as opposed to the cardiac work of the hearts of control animals.

The results of the experiments reported in this work indicate that depression of myocardial function is not a significant factor in the decline of blood pressure associated with irreversible hemorrhagic shock. Reinfusion of the total volume of blood removed from the animals caused an immediate improvement in the circulatory response which could be attributed to the enhanced filling pressure. This would suggest that the heart in shock is capable of responding normally to an increased venous return at this stage of shock. It is obvious from these results that depression of cardiac function does occur in irreversible shock; but it does not appear to be present, as indicated by rises in atrial and/or end-diastolic pressures, until the terminal phases of the experiments. Moreover, this occurred only when the mean systemic blood pressure had already fallen to 40 mm Hg or below, when one might expect failure to result from an inadequate coronary perfusion pressure. Evidence of cardiac failure was not present even when blood was reinfused into a vascular space already increased by compensatory diffusion of fluid and therefore having a greater cardiac load

than during the control period.

These observations do not agree with those of Crowell and Guyton (1961-1962), who suggested that cardiac failure, determined by the rise in left atrial pressure at the onset of autoinfusion during the later part of the oligemic stage, is the etiology of irreversibility. In the present study, the rise in left or right atrial pressure occurred late in the post-infusion period. Although the onset of autoinfusion appears to signal the onset of irreversibility (Wiggers, H. C., 1946), these animals did not exhibit evidence of acute cardiac failure until much later. In their studies of the heart in shock, Gomez and Hamilton (1964) found that the work of the hearts exposed to hypotension decreased as opposed to hearts not exposed to hypotension. This occurred when an increased volume load was presented to the respective right atria. Moreover, the work was calculated primarily as a function of the left atrial pressure. While a designated load was not used in the present study, it is felt that the sum of the volumes of the reinfused blood and the compensatory increase in the plasma volume as a result of hemorrhage (Wiggers, 1950) provided a sufficient load on the heart. Yet, no evidence of cardiac malfunction was detected after reinfusion. Finally, it must be noted that the majority of the experiments (Wiggers, 1942, 1945, 1947, 1950; Crowell, 1961, 1962; Guyton, 1961; Gomez, 1962) reporting cardiac failure as the primary factor in the etiology of

irreversibility used a mean blood pressure of 30 mm Hg during the oligemic phase rather than a mean pressure of 40 mm Hg. This was the pressure exhibited by the majority of animals in this study during the normovolemic stage when evidence of cardiac failure first appeared.

Therefore, it is the conclusion of this study that previous works implicating myocardial failure as a predominant factor in irreversible hemorrhagic shock should be examined more carefully. At hypotensive levels of 30 mm Hg coronary perfusion was undoubtedly inadequate for maintaining myocardial function even at low cardiac outputs. This phenomenon has been reported by other investigators (Gregg, 1962; Case, 1953; Opdyke, 1946; Sarnoff, 1954). For example, Gregg found that the mean coronary flow decreased 70% during the initial phase of the oligemic phase, but during the hypotensive period it rose to approximately 50% of its control value and remained there until the blood pressure began to decline after reinfusion. These studies were done in dogs maintained at a mean blood pressure of 40 mm Hg during the oligemic stage. Therefore, it must be assumed that at pressures of 30 mm Hg the coronary flow would decrease even more significantly resulting in coronary insufficiency and acute cardiac failure. The indices of heart failure used in the experiments in the present study would be an elevated atrial or end-diastolic pressure, neither of which became apparent during oligemic hypotension. Similar results have been

reported by Rothe and Selkurt (1964), by McPherson and Haller (1963), and by Weidner, et al (1961).

In analyzing the results of these experiments, the effects of anesthetization with sodium pentobarbital, as well as continuous heparinization upon the course of the experiments, must be considered. However, many investigators have found that both of these factors have a negligible affect upon the eventual outcome (Ingraham, 1950; Smith, 1958; Wiggers, 1950).

In addition to the hemodynamic investigations, studies of the affect of a known cardiac stimulant (Ouabain) upon the heart in shock were performed. This was done on the premise that, if the heart is in actual failure, the cardiac output should increase and the central venous pressure should decrease. Moreover, the overall survival rate of the animals should be improved. However, instead of an increased cardiac output and decreased central venous pressure, just the opposite was observed. All of the dogs receiving Ouabain prior to reinfusion, which simulated the autoinfusion phase and the onset of irreversibility, or well after reinfusion, demonstrated a significant decrease or no change in the cardiac output. Moreover, the central venous pressure exhibited no decline and, in fact, rose in many of the animals. Finally, the only appreciable effect of the digitalis was the precipitous rise in the mean blood pressure immediately after administration. All of these phenomena (i.e. the rise in the blood pressure and

central venous pressure and the decline in cardiac output) have been observed by most of the investigators studying the effects of digitalis upon the non-failing heart (Cotten, 1958; Bloomfield, 1948; Cattell, 1938; Cohn and Steele, 1929; Cohn and Stewart, 1932). They attributed the affect of digitalis upon the non-failing heart to a marked arterial and venous constriction resulting in an increased systemic blood pressure. Moreover, cardiac filling is impeded by the venous constriction and cardiac output declines. Similar results with Ouabain in the heart in hemorrhagic shock were reported by McPherson and Haller (1963). They also found that the survival rates of animals given Ouabain while in shock did not improve except when the drug was given prophylactically. This same situation existed in the reported study.

The concept that functional myocardial failure plays an important role in the development of circulatory collapse in shock appears to be without foundation. The experiments described demonstrate that failure of the heart to expel blood is a contributing factor in irreversible shock, but does not manifest itself until the post-infusion blood pressure has declined to preinfusion levels. At this time there is an elevation in both atrial and ventricular end-diastolic pressures. It is concluded, therefore, that although cardiac involvement may become a significant factor leading to the demise of the animal, it does not appear to be a major factor in the

development of irreversibility.

SUMMARY

The concept of cardiac failure in irreversible hemorrhagic shock was investigated in ten open-chest dogs subjected to catherization of the four chambers of the heart and in six closed-chest dogs treated with the cardiac glyoside, Ouabain. In both groups of dogs anesthetized with sodium pentobarbital, shock was induced by bleeding the animals to a mean blood pressure of 40 mm Hg; this level of pressure was maintained for four hours and was then followed by reinfusion of the animal's blood.

Recordings of right and left intra-atrial pressures and right and left intraventricular pressures of the heart during the oligemic and normovolemic stages of hemorrhagic shock did not give evidence to relate the decline in blood pressure to cardiac failure. However, acute cardiac failure only became evident approximately thirty minutes before death, during which time a drop in mean arterial pressure to 30 mm Hg was accompanied by a rise in either right or left atrial pressures, as well as rises in the right or left end-diastolic pressures.

The possibility of a cardiac factor in hemorrhagic shock was further explored by measuring the myocardial responses to Ouabain (0.035 mg/kg) administered immediately after or just prior to the reinfusion of blood in dogs subjected to four hours of hemorrhagic hypotension. In the Ouabain-treated animals, recordings of cardiac output by the dye dilution

method, blood pressure, and central venous pressure show that after a transitory increase in blood pressure and a decrease in cardiac output, the eventual course of irreversible shock was not altered by the administration of Ouabain.

These results imply that heart failure may not play a significant role in the etiology of irreversible hemorrhagic shock. The onset of cardiac failure only occurred as a terminal event in the experiment when the blood pressure had decreased to the point where coronary flow was not sufficient to maintain cardiac function.

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TABLE #1

Blood Pressure, Heart Rate and Cardiac Chamber Pressures before and during Oligemic, Normovolemic and Terminal Phases of Hemorrhagic Shock

PERIOD	EXP. NO.	MBP	HR	RA	RVS	RVD	LA	LVS	LVD
Control	1	80	130	1.0	24.0	1.5	5.8	110	0.0
	2	97	162	3.2	20.8	4.8	5.1	130	5.7
	3	93	180	4.6	21.6	2.0	6.1	103	5.0
	4	120	210	2.5	21.9	0.0	6.7	124	3.2
	5	72	180	1.1	23.6	0.0	5.6	80	0.5
	6	86	156	6.4	18.7	6.2	7.8	98	9.2
	7	106	174	0.5	12.4	3.6	3.6	109	1.6
	8	118	174	4.9	17.6	2.0	8.9	121	5.7
Average		97	169	3.0	20.0	2.4	6.2	107	3.5
Two Hours Hypotension									
	1	40	180	2.0	20.0	1.5	1.0	75.0	0.5
	2	38	180	2.7	13.3	3.3	3.2	58.7	2.7
	3	40	180	1.6	28.0	0.4	5.9	43.0	2.2
	4	40	192	1.2	15.6	0.6	6.6	47.5	1.4
	5	40	174	2.2	27.0	5.3	3.9	70.0	4.0
	6	40	141	5.9	17.9	6.3	6.6	51.0	8.2
	7	40	156	0.1	21.4	-0.8	-0.9	64.0	-2.4
	8	42	144	4.2	10.1	0.1	1.7	45.7	5.7
Average		40	169	2.4	19.1	2.4	3.4	53.1	2.9

TABLE #1 - Continued

PERIOD	EXP. NO.	MBP	HR	RA	RVS	RVD	LA	LVS	LVD
Pre-Infusion									
	1	38	150	1.5	30.0	1.5	3.5	75.0	2.0
	2	40	170	2.8	17.6	2.7	3.5	73.7	1.2
	3	37	165	1.0	30.6	0.1	5.9	43.0	1.0
	4	42	175	1.2	19.4	1.9	6.7	32.6	1.4
	5	39	62	1.1	26.1	5.8	2.0	62.0	0.0
	6	40	141	5.9	17.9	6.3	6.6	51.0	8.2
	7	40	132	-0.3	19.9	-0.2	-0.9	56.6	-2.4
	8	40	132	4.2	10.6	0.0	2.0	37.7	5.7
Average		39	153	2.2	21.5	2.2	3.6	53.9	2.5
½ Hour Post-Infusion									
	1	48	150	0.0	28.0	1.3	5.0	70.0	1.5
	2	88	162	3.2	20.8	3.2	5.1	136.0	2.7
	3	60	155	2.1	45.0	0.0	6.0	80.0	0.8
	4	50	150	1.5	21.0	1.4	6.7	57.0	3.1
	5	50	156	1.1	26.1	1.1	3.3	64.0	4.5
	6	45	143	6.3	21.5	7.0	7.0	59.7	8.9
	7	100	138	0.4	29.0	-0.4	2.5	111.0	-0.9
	8	80	123	5.2	21.3	0.6	2.6	70.7	5.7
Average		74	146	2.4	23.7	1.7	4.6	81.0	3.2

TABLE #1 - Continued

PERIOD	EXP. NO.	MBP	HR	RA	RVS	RVD	LA	LVS	LVD
1 Hour Post-Infusion									
	1	30	150	-0.5	26.0	1.0	6.0	60.0	3.0
	2	83	165	2.3	15.9	2.1	4.1	117.0	1.3
	3	54	152	1.7	40.0	-0.1	6.0	81.0	0.3
	4*	-	-	-	-	-	-	-	-
	5*	-	-	-	-	-	-	-	-
	6	23	129	6.1	18.2	6.6	8.1	36.7	8.4
	7	90	144	-0.3	24.1	-0.9	0.9	99.1	-3.4
	8	50	126	4.6	18.4	0.0	2.6	42.7	5.7
Average		55	128	1.7	18.6	1.5	4.6	72.7	3.5
Terminal									
	1	25	130	-1.0	22.0	0.5	7.0	50.0	4.0
	2	30	165	2.5	15.8	3.9	5.6	19.0	14.6
	3	29	114	1.3	21.0	1.6	6.2	26.0	2.2
	4	20	102	3.1	10.9	1.4	6.8	29.0	3.2
	5	20	72	3.0	13.6	3.6	3.3	12.0	5.5
	6	15	84	8.8	15.0	8.2	8.5	21.7	8.7
	7	20	96	2.5	11.4	1.1	5.0	19.6	3.1
	8	20	96	4.2	5.4	0.8	1.4	22.2	3.2
Average		22	107	3.1	14.4	2.6	5.5	25.8	5.4

* These two animals expired within one hour after reinfusion.

MBP - Mean Blood Pressure
HR - Heart Rate
RA - Right Atrium (Mean Pressure)
RVS - Right Ventricular Systolic Pressure
RVD - Right Ventricular End-Diastolic Pressure
LA - Left Atrium (Mean Pressure)
LVS - Left Ventricular Systolic Pressure
LVD - Left Ventricular End-Diastolic Pressure

TABLE #2

Individual Experiments Showing Blood Pressure and Intracardiac Pressures

EXP. NO.	TIME	MBP	HR	RA	RVS	RVD	LA	LVS	LVD
1	Control	80	130	1.0	24.0	1.5	5.8	110.0	0.0
	2 Hr Hypotension	40	180	2.0	20.0	1.5	1.0	75.0	0.5
	Pre-Infusion	38	150	1.5	30.0	1.5	3.5	75.0	2.0
	½ Hr Post-Infusion	48	150	0.0	28.0	1.3	5.0	70.0	1.5
	1 Hr Post-Infusion	30	150	-0.5	26.0	1.0	6.0	60.0	3.0
	Termination	25	130	-1.0	22.0	0.5	7.0	50.0	4.0
2	Control	97	162	3.2	20.0	4.8	5.1	130.0	5.7
	2 Hr Hypotension	38	180	2.7	13.3	3.3	3.2	58.7	2.7
	Pre-Infusion	40	170	2.8	17.6	2.7	3.5	73.7	1.2
	½ Hr Post-Infusion	88	162	3.2	20.8	3.2	5.1	136.0	2.7
	1 Hr Post-Infusion	83	165	2.3	15.9	2.1	4.1	117.0	1.3
	Termination	30	165	2.5	15.8	3.9	5.6	19.0	4.6
3	Control	93	180	4.6	21.6	2.0	6.1	103.0	5.0
	2 Hr Hypotension	40	180	1.6	28.0	0.4	5.9	43.0	2.2
	Pre-Infusion	37	165	1.0	30.6	0.1	5.9	43.0	1.0
	½ Hr Post-Infusion	60	155	2.1	45.0	0.0	6.0	80.0	0.8
	1 Hr Post-Infusion	54	152	1.7	40.0	-0.1	6.0	81.0	0.3
	Termination	20	114	1.3	21.0	1.6	6.2	26.0	2.2
4*	Control	120	210	2.5	21.9	0.0	6.7	124.0	3.2
	2 Hr Hypotension	40	192	1.2	15.6	0.6	6.6	47.5	1.4
	Pre-Infusion	42	175	1.2	19.4	1.9	6.7	32.6	1.4
	½ Hr Post-Infusion	50	150	1.5	21.0	1.4	6.7	57.0	3.1
	1 Hr Post-Infusion	-	-	-	-	-	-	-	-
	Termination	20	102	3.1	10.9	1.4	6.8	29.0	3.2

TABLE #2 - Continued

EXP. No.	TIME	MBP	HR	RA	RVS	RVD	LA	LVS	LVD
5*	Control	72	180	1.1	23.6	0.0	5.6	80.0	0.5
	2 Hr Hypotension	40	174	2.2	27.0	5.3	3.9	70.0	4.0
	Pre-Infusion	39	162	1.1	26.1	5.8	2.0	62.0	0.0
	½ Hr Post-Infusion	50	156	1.1	26.1	1.1	3.3	64.0	4.5
	1 Hr Post-Infusion	-	-	-	-	-	-	-	-
	Termination	20	72	3.0	13.6	3.6	3.3	12.0	5.5
6	Control	86	156	6.4	18.7	6.2	7.8	98.0	9.2
	2 Hr Hypotension	40	141	5.9	17.9	6.3	6.6	51.0	8.2
	Pre-Infusion	40	141	5.9	17.9	6.3	6.6	51.0	8.2
	½ Hr Post-Infusion	45	143	6.3	21.5	7.0	7.0	59.7	8.9
	1 Hr Post-Infusion	23	129	6.1	18.2	6.6	8.1	36.7	8.4
	Termination	15	84	8.8	15.0	8.2	8.5	21.7	8.7
7	Control	106	174	0.5	12.4	3.6	3.6	109.0	1.6
	2 Hr Hypotension	40	156	0.1	21.4	-0.8	-0.9	64.0	-2.4
	Pre-Infusion	40	132	-0.3	29.0	-0.2	-0.9	56.6	-2.4
	½ Hr Post-Infusion	100	138	0.4	18.4	-0.4	2.5	111.0	-0.9
	1 Hr Post-Infusion	90	144	-0.3	24.1	-0.9	0.9	99.1	-3.4
	Termination	20	96	2.5	11.4	1.1	5.0	19.6	3.2
8	Control	118	174	4.9	17.6	2.0	8.9	121.0	5.7
	2 Hr Hypotension	42	144	4.2	10.1	0.1	1.7	45.7	5.7
	Pre-Infusion	40	132	4.2	10.6	0.0	2.0	37.7	5.7
	½ Hr Post-Infusion	80	123	5.2	21.3	0.6	2.6	70.7	5.7
	1 Hr Post-Infusion	50	126	4.6	18.4	0.0	2.6	42.7	5.7
	Termination	20	96	4.2	5.4	0.8	1.4	22.2	3.2

* Animals expired within one hour after reinfusion

MBP - Mean Blood Pressure
HR - Heart Rate
RA - Right Atrium (Mean Pressure)
RVS - Right Ventricular Systolic Pressure
RVD - Right Ventricular End-Diastolic Pressure
LA - Left Atrium (Mean Pressure)
LVS - Left Ventricular Systolic Pressure
LVD - Left Ventricular End-Diastolic Pressure

TABLE #3

Two Experiments Showing Blood Pressure, Heart Rate and Cardiac Chamber Pressures for Two Hours of Normovolemic Shock

PERIODS	MBP	HR	RA	RVS	RVD	LA	LVS	LVD
Control	100	177	6.7	31.3	6.8	6.9	108	10.0
	105	162	1.2	21.3	2.5	3.3	105	10.5
Average	103	170	3.9	26.3	4.7	5.1	107	10.2
2 Hr Hypotension	40	138	5.7	22.5	4.4	4.4	43	2.6
	45	192	1.1	21.3	0.0	1.7	65	6.0
Average	43	165	3.4	21.9	2.2	3.1	54	4.3
Pre-Infusion	40	114	8.0	22.5	3.3	5.7	53	2.6
	44	168	2.4	21.3	0.0	2.0	65	6.0
Average	42	141	5.2	21.9	1.7	3.9	59	4.3
½ Hr Post-Infusion	65	108	6.7	32.0	3.8	5.0	88	2.6
	70	156	1.1	19.1	1.3	1.4	70	6.0
Average	67	132	3.9	26.0	2.5	3.2	79	4.3
1 Hr Post-Infusion	55	96	6.3	16.3	4.8	4.4	68	3.9
	50	162	1.1	18.8	1.3	1.5	58	5.3
Average	53	129	3.7	17.5	3.1	2.9	63	4.6
2 Hr Post-Infusion	40	99	5.7	21.3	5.3	5.4	48	5.2
	40	162	1.0	16.3	1.3	2.0	70	0.3
Average	40	130	3.4	18.8	3.3	3.7	59	2.8

MBP - Mean Blood Pressure
HR - Heart Rate
RA - Right Atrium (Mean Pressure)
RVS - Right Ventricular Systolic Pressure
RVD - Right Ventricular End-Diastolic Pressure
LA - Left Atrium (Mean Pressure)
LVS - Left Ventricular Systolic Pressure
LVD - Left Ventricular End-Diastolic Pressure

TABLE #4A

Effects of Ouabain on Circulatory Dynamics in Hemorrhagic Shock

Ouabain Prior to Reinfusion

Exp. No.	TIME	MBP	CVP (mm Hg)	CO (l/min)	TPR (mm Hg/ml/min)
1	Control	140	-0.25	2.17	0.064
	120 min.	40	-3.6	0.517	0.077
	175 min. O	43	-3.5	0.500	0.080
	180 min. T	85	-4.0	0.286	0.297
	210 min.	75	-4.0	0.250	0.300
2	Control	165	0.5	2.15	0.0767
	120 min.	40	-0.5	0.39	0.1020
	180 min.	40	-0.5	0.39	0.1015
	225 min.	40	0.0	0.45	0.0888
	230 min. O	60	0.0	0.44	0.1366
	250 min. T	95	0.25	1.62	0.0586
	310 min.	52	-1.00	0.53	0.0988
3	Control	132	-2.0	1.65	0.0300
	120 min.	40	-4.0	.59	0.0630
	180 min.	40	-4.0	.50	0.0795
	225 min. O	40	-6.5	.56	0.0719
	230 min. T	71	-4.5	.59	0.1185
	260 min.	60	-5.5	.50	0.1200

T - Reinfusion of Blood
MBP - Mean Blood Pressure
CVP - Central Venous Pressure
CO - Cardiac Output
TPR - Total Peripheral Resistance
O - Injection of 0.035 mgms/Kg Ouabain

TABLE #4B

Effects of Ouabain on Circulatory Dynamics in Hemorrhagic Shock

Ouabain After Reinfusion

Exp. No.	TIME	MBP	CVP	CO	TPR
1	Control	135 mm Hg	-2.25 mm Hg	1.85 l/mn	.073 mm Hg/cc/mn
	2 Hr Hypotension	36 mm Hg	-3.10 mm Hg	0.37 l/mn	.098 mm Hg/cc/mn
	3 Hr Hypotension	37 mm Hg	-3.00 mm Hg	0.42 l/mn	.088 mm Hg/cc/mn
	3 Hr 35' Hypo.	37 mm Hg	-3.00 mm Hg	0.45 l/mn	.083 mm Hg/cc/mn
	20' Post-Infus.	98 mm Hg	-2.00 mm Hg	1.27 l/mn	.077 mm Hg/cc/mn
O	30' Post-Infus	115 mm Hg	-1.50 mm Hg	1.19 l/mn	.097 mm Hg/cc/mn
	1 Hr Post-Infus.	85 mm Hg	-1.75 mm Hg	0.71 l/mn	.119 mm Hg/cc/mn
	2 Hr Post-Infus.	50 mm Hg	-1.75 mm Hg	0.59 l/mn	.085 mm Hg/cc/mn
	3 Hr Post-Infus.	35 mm Hg	-1.00 mm Hg	0.50 l/mn	.071 mm Hg/cc/mn
2	Control	142 mm Hg	-1.25 mm Hg	1.40 l/mn	.101 mm Hg/cc/mn
	2 Hr 10' Hypo.	35 mm Hg	-2.25 mm Hg	0.72 l/mn	.048 mm Hg/cc/mn
	20' Post-Infus.	121 mm Hg	-1.50 mm Hg	0.85 l/mn	.142 mm Hg/cc/mn
O	30' Post Infus.	141 mm Hg	- .150 mm Hg	0.78 l/mn	.180 mm Hg/cc/mn
	1 Hr Post-Infus.	125 mm Hg	-2.50 mm Hg	0.79 l/mn	.158 mm Hg/cc/mn
	2 Hr Post-Infus.	70 mm Hg	-2.30 mm Hg	0.70 l/mn	.100 mm Hg/cc/mn
3	Control	155 mm Hg	-1.25 mm Hg	2.05 l/mn	.076 mm/Hg/ml/mn
	2 Hr Hypotension	40 mm Hg	-2.50 mm Hg	0.632 l/mn	.063 mm/Hg/ml/mn
	2 Hr 50' Hypoten.	36 mm Hg	-2.25 mm Hg	0.798 l/mn	.045 mm/Hg/ml/mn
	20' Post-Infus.	60 mm Hg	-2.25 mm Hg	1.45 l/mn	.041 mm/Hg/ml/mn
	25' Post-Infus.	70 mm Hg	-2.50 mm Hg	1.120 l/mn	.062 mm/Hg/ml/mn
	30' Post-Infus.	48 mm Hg	-3.50 mm Hg	.646 l/mn	.074 mm/Hg/ml/mn

T - Reinfusion of Blood
MBP - Mean Blood Pressure
CVP - Central Venous Pressure
CO - Cardiac Output
TPR - Total Peripheral Resistance
O - Injection of 0.035 mgms/Kg Ouabain

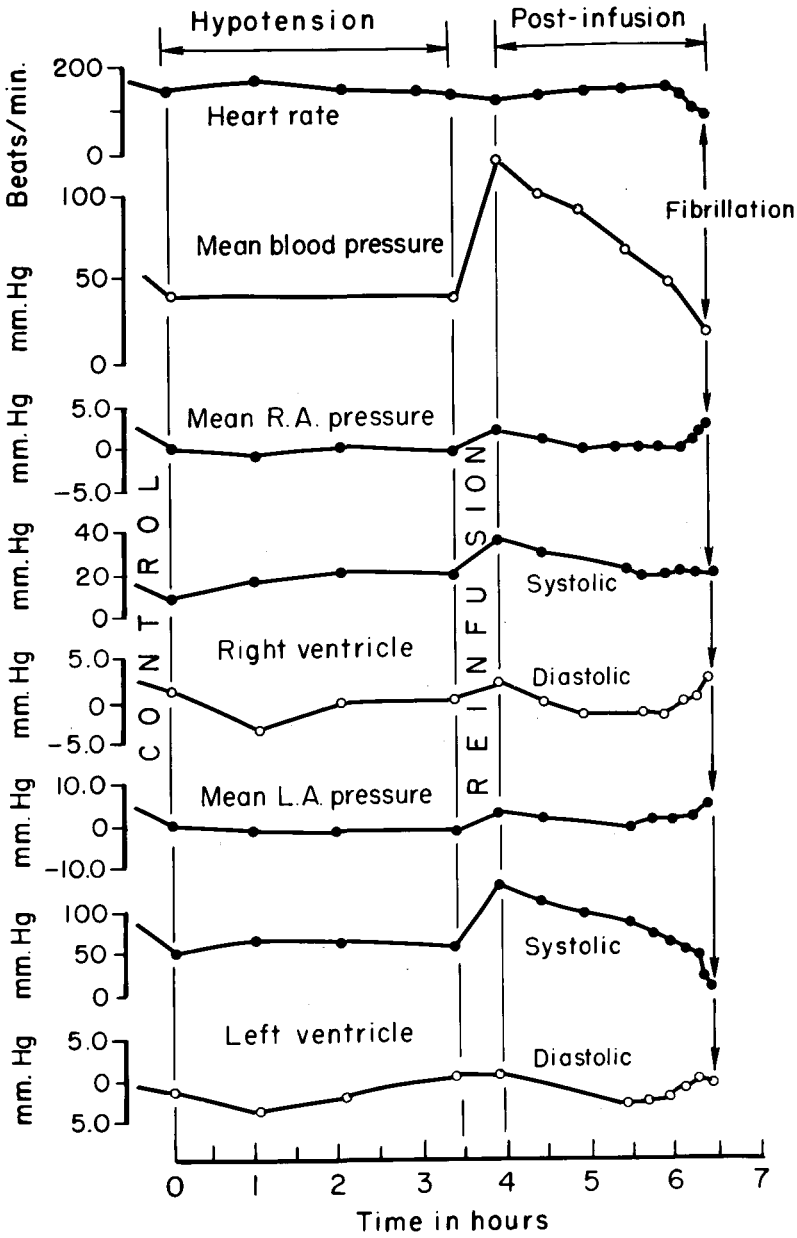

FIGURE 1

The Heart Rate, Mean Blood Pressure and the pressures in the Four Chambers of the Heart of a Dog in Hemorrhagic Shock

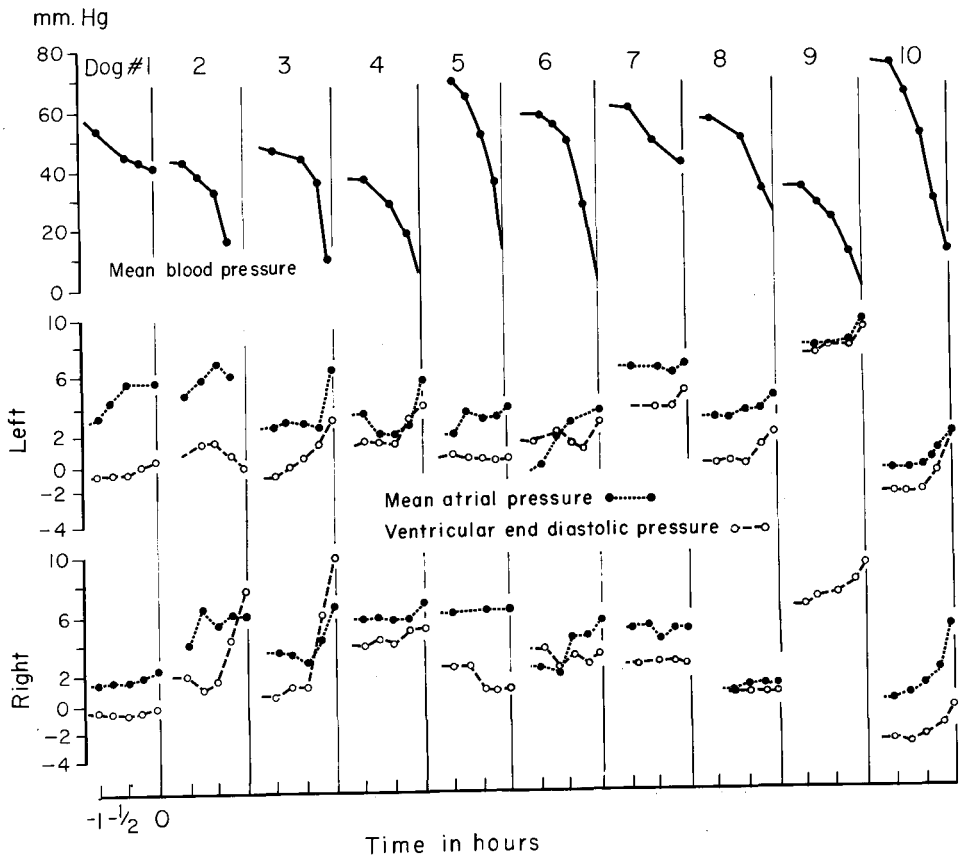

FIGURE 2

The Mean Blood Pressure and the Right and Left Mean Atrial and Ventricular End-Diastolic Pressures in the Last Hour of the Normovolemic Phase of Ten Dogs in Hemorrhagic Shock

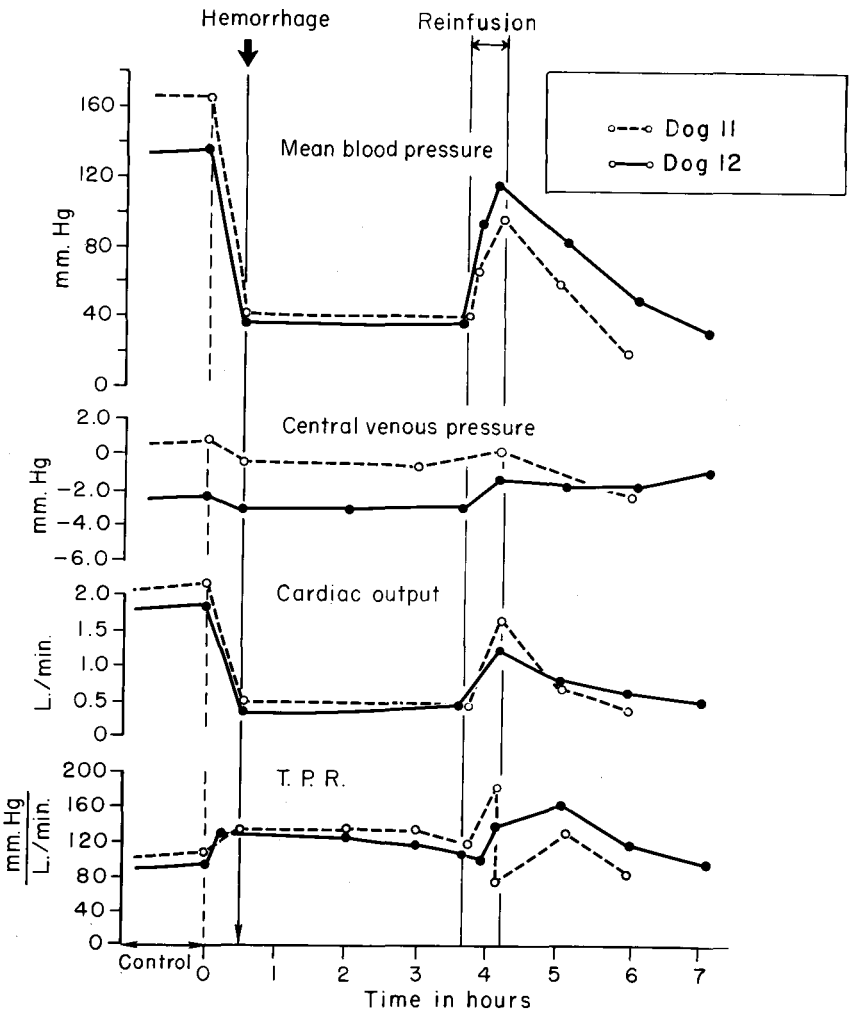

FIGURE 3

The Mean Blood Pressure, Central Venous Pressure, Cardiac Output and Total Peripheral Resistance in Two Dogs Receiving Ouabain during Hemorrhagic Shock

APPROVAL SHEET

The thesis submitted by Joseph H. Traxler has been read and approved by three members of the Department of Physiology.

The final copies have been examined by the advisor and director of the thesis and the signature which appears below verifies the fact that any necessary changes have been incorporated, and that the thesis is now given final approval with reference to content, form, and mechanical accuracy.

The thesis is therefore accepted in partial fulfillment of the requirements for the Degree of Master of Science.

January 4, 1947
Date

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Signature of Adviser