Oxygen Consumption, Oxygen Debt and Cardiac Output in Experimental Hemorrhagic Shock in Dogs

A Thesis submitted for the degree of Master of Science (Experimental Surgery)

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Short Title:

Oxygen Consumption and Debt,

and Cardiac Output in Shock

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PREFACE

This experimental work was carried out in the Surgical Research Laboratories of the Montreal General Hospital in July 1961 to June 1962 when the author was carrying out his Basic Science year of his Surgical Training.

The work was under the supervision of Dr. Fraser N. Gurd and Dr. L.G. Hampson. It was with their guidance that this work was completed.

In the original conception of this work it was planned to evaluate the use of the Davol Heart Pump in the treatment of shock. This work became very depressing when all the animals seemed to die from the effects of the pump. In order to obtain some data on the effects of the Pump cardiac output determination were made. This lead to the necessity of determining the oxygen consumption. In the development of a technique to measure oxygen consumption it became apparent that continuous recordings could be made. A plot of the oxygen consumption was found to resemble the curve of the blood pressure. It was in this manner that this particular work developed.

Dr. J. Trank, Associate Director of the Surgical Research Laboratories, greatly facilitated the use of the electronic equipment. He developed the apparatus

for the continuous recording of oxygen consumption. This experiment would not have been possible without his very kind and generous assistance.

I am greatly indebted to the laboratory technicians who carried out the blood oxygen determinations. They spent many long hours from early morning into the evening to provide me with the necessary data.

Mrs. Gogan, R.N., the Laboratory Charge Nurse provided sterile equipment and supplies for the procedure.

To the others of the Laboratory Staff who provided help with the animals, advice and criticism and humor when it was greatly needed, I also owe many thanks.

B. Gordon Thompson B.Sc. M.D.C.M.

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Introduction

Shock is a ubiquitous term! It is a term commonly heard in both scientific and non-scientific environments. It is a term so commonly used that it's meaning has become clouded. A perusal of scientific literature reveals a varied interpretation. This variety of opinion has led many to refrain from using the term, and some to suggest is abandonment.[44]

This situation leads one to confine one's thought to a specific area and to establish one's own working definition. The clinical observation of "shock" is made on the development of hypotension. The surgeon sees blood loss as the most common etiological agent. Shock, therefore, will be considered a state of hemorrhagic hypotension.

In clinical practice hemorrhagic hypotension which can be corrected by the restoration of blood volume with the subsequent survival of the patient is not a problem. The problem is the non-survival of the patient after the adequate restoration of blood volume. These two phases, reversible and irreversible, hemorrhagic hypotension form a spectrum of shock. The point, if there be a point, at which one passes from one into the other, is unknown.[14] The interest in this "point" is the hope to displace or to eliminate it.[31]

To transpose a clinical situation into an experimental model has many failings. Wiggers in his textbook, Physiology of Shock,[44] thoroughly discusses the problem of the criteria for experimental shock. The criterion of an acceptable experimental shock model must be that the clinical situation can be reproduced. It is not sufficient to induce hypotension to produce shock.[43] There must be a factor of time.[27] Together these factors, hypotension and time, can be controlled to produce an acceptable model of shock. This model is one in which survival or non-survival depends upon the point during the period of hypotension at which the blood volume is restored.

This investigation was carried out to study oxygen consumption and cardiac output in an experimental shock model. The concept of oxygen debt was employed to interpret the effects of shock.

Historical Review

The use of the term shock is obscured in antiquity. In 1815 Guthrie wrote and suggested the postponement of operations, "....until the alarm and shock have subsided."[44] Early authors in their descriptions of the effects of trauma used such terms as concussion, commotion, collapse, prostration, syncope and torpor. Later observations revealed that this "state" was found also in non-traumatic situations.

The development of the science of physiology and the application of experimental procedures lead to a more detailed study of shock and its causes. In 1899 Cirle treated experimentally induced shock with intravenous infusions.[44] He concluded that the cause of shock was peripheral vascular collapse. This concept is held widely today.[3] Furthermore, he suggested that the irreversibility of shock was a result of the failure of the vasomotor centers. Another concept still considered to be valid.[42]

Physiologists tend to support concepts of organ-system failure in the development of shock. Most, if not all, body systems have been investigated. At the present time there are at least three prominent areas of investigation.

Lillehei [17, 32] and Fine,[19] independently, believe that the gastrointestinal tract is the ultimate failing organ. In shock lethal endotoxins are produced, liberated and/or absorbed from the bowel. They have been able to protect animals from death due to shock by sterilization of the bowel, by perfusion of the bowel or liver, or by excision of the bowel.

This concept has been extended by others who suggest that it is the failure of the reticuloendothelial system to eliminate the toxins which is the ultimate cause of non-survival. It has been shown that blocking of the

reticuloendothelial system contributes to an early death in shock.[39]

In recent literature Hardway[30] has published data to suggest that the system of blood coagulation is ultimately responsible for shock fatality. The hypercoagulability of blood in the early stage of shock causes multiple minute thrombi to form. These thrombi accumulate in sufficient numbers to be fatal. Anti-coagulants have been employed with some success to combat the effects of shock.[12]

The cardiovascular system has been investigated from many aspects. Coronary blood flow[7], myocardial injury[18] and deterioration[21] have been subjects for study of the central element in this system. The investigation of the peripheral circulation and fluid shifts have been the subjects for others to study.[20, 26, 38] Guyton and Crowell have re-emphasized that the heart may be the central organ implicated in the production of and/or the perpetuation of shock.[24] Many workers[16, 25] have shown how the shock state can be controlled through changes in the "melieu interieur" or conditions of the myocardium.

Biochemists tend to support concepts of metabolic defects or derangements as the ultimate factors in the fatal outcome of shock. Many metabolites and electrolytes

have been measured in the various stages of shock. Most commonly measured factors are blood glucose, lactate, pyruvate, phosphate, sodium, potassium, bicarbonate and the pH.[10, 11, 41] The corticosteroid hormones and the natural occurring sympathomimetic substances have been investigated.[36] Others have advanced these developments to measure the metabolites in various tissues.

The metabolic state and requirements of many tissues during shock have been studied. Most of this work suggests that the metabolic state shifts from an aerobic to an anaerobic one.[5, 6] An oxygen deficit develops.[9] Each study reported provides information of a descriptive nature. Each report tends to clarify some facet of the shock problem. The central problem remains to be elucidated.

In 1960 Guyton and Crowell presented a paper in which they interpreted shock in terms of a total body oxygen debt. This concept of oxygen debt was defined as the calculated difference between the basal level and the actual, reduced, level of oxygen consumption in shock. They provided data to illustrate that in shock a total body oxygen debt develops which, beyond a specific limit, becomes the factor of irreversibility. They suggest, "....once damage has been done beyond a certain critical degree, the tissues deteriorate at a more rapid rate than they can be repaired."[24]

In addition they believe that the heart is the central organ implicated in the death of animals subjected to shock.[13] Sarnoff and his workers[4, 37] have demonstrated the effects of changes in the coronary blood flow on the function of the myocardium. Decreased coronary flow results in myocardial failure. Restoration of the blood volume after a period of hemorrhagic hypotension resulted in myocardial failure. This state could be relieved by coronary artery perfusion.

Edwards, Siegal and Bing[15, 16] measured cardiac output and myocardial oxygen consumption at various stages of shock. In the late normovolemic stage they found that the coronary blood flow and the myocardial oxygen consumption were below control levels. They report, "....that the coronary flow remains below control levels during the normovolemic phase contributing to the persistence of myocardial ischemia ."

This myocardial ischemia places the heart into a position of metabolic deficit.[5, 6] The mechanical efficiency of the heart is decreased.[2, 7, 25]

Another approach to this problem of shock has been the application of therapeutic measures.[22, 23] Many of these avenues of investigation are based on empirical knowledge.

Adrenaline and nor-adrenaline have been studied, both from the experimental and the clinical aspects.[36, 39]

These substances are present normally in the body. They increase in amount under stress and are vasoactive. The concept of shock as peripheral vascular collapse leads one naturally to the use of such vasoactive substances. The use of these agents has not been an unqualified success.[29] In many instances the use of such agents has been detrimental to the survival of the subject.

Hydrocortisone is a synthetic adrenal cortical steroid employed empirically in the treatment of shock.[35] It is reasoned that the patient or animal is subjected to great stress in shock. Therefore, to supplement the natural stress response should enhance the chances for survival. It has been the practice to give doses of steroids much in excess of therapeutic recommendations. The results have been variable.[29] Some report successful treatment. Others report failure.

A therapeutic concept directly opposed to that advocating the use of vasoactive substances has been advanced. The use of adrenolytic agents, in the form of adrenergic blocking substances, has been suggested. Hydralazine and dibenyline have been used in the treatment of shock.[29] The use of these substances has been suggested on the basis that there is marked vasoconstrictor activity throughout the body in shock. This activity shunts blood away from the areas which subsequently deteriorate to the detriment of the subject.

Many reports supporting the use of adrenergic blocking agents have been published. In 1955 Lotz, Beck and Stevenson reported the changes in oxygen consumption of shocked dogs treated with adrenergic blocking agents.[34] They noted that there was a significant increase in oxygen consumption and arterial oxygen transport in shocked animals following treatment with hydralazine.

In more recent years the application of the principles of the cardiopulmonary bypass have been attempted to solve the shock problem. A variety of approaches have been taken.[8, 11, 32] A certain degree of success has been reported. The work load of the heart can be reduced and life prolonged. The blood pressure and peripheral perfusion can be maintained under a variety of circumstances. The clinical application of the bypass has suggested that there is a beneficial effect.[1] Ultimate success still eludes the investigator.

Procedure

The technique to produce shock was one standardized in our laboratories. It was based on the Nickerson and Zingg modification of Fine's method.[45] This modification involves two periods of hypotension, one controlled and one uncontrolled, followed by the reinfusion of the shed blood. These periods are represented diagrammatically in Figure No. 1.

The mean aortic blood pressure was lowered by bleeding the animal into a sterile reservoir to which it was connected. The blood pressure was first maintained at thirty millimeters of mercury for sixty minutes. Then, it was raised to sixty millimeters of mercury for thirty minutes. These blood pressures were controlled by adjusting the level of blood reservoir. At the end of these ninety minutes, Period I, the bleeding line was clamped and the hypotensive state was uncontrolled for another ninety minutes, Period II. The shed blood then was reinfused under pressure within five to fifteen minutes. The data were recorded for another ninety minutes, Period III, at the end of which the animals' wounds were closed and the animals were returned to their cages. They were followed for forty-eight hours to ascertain survival.

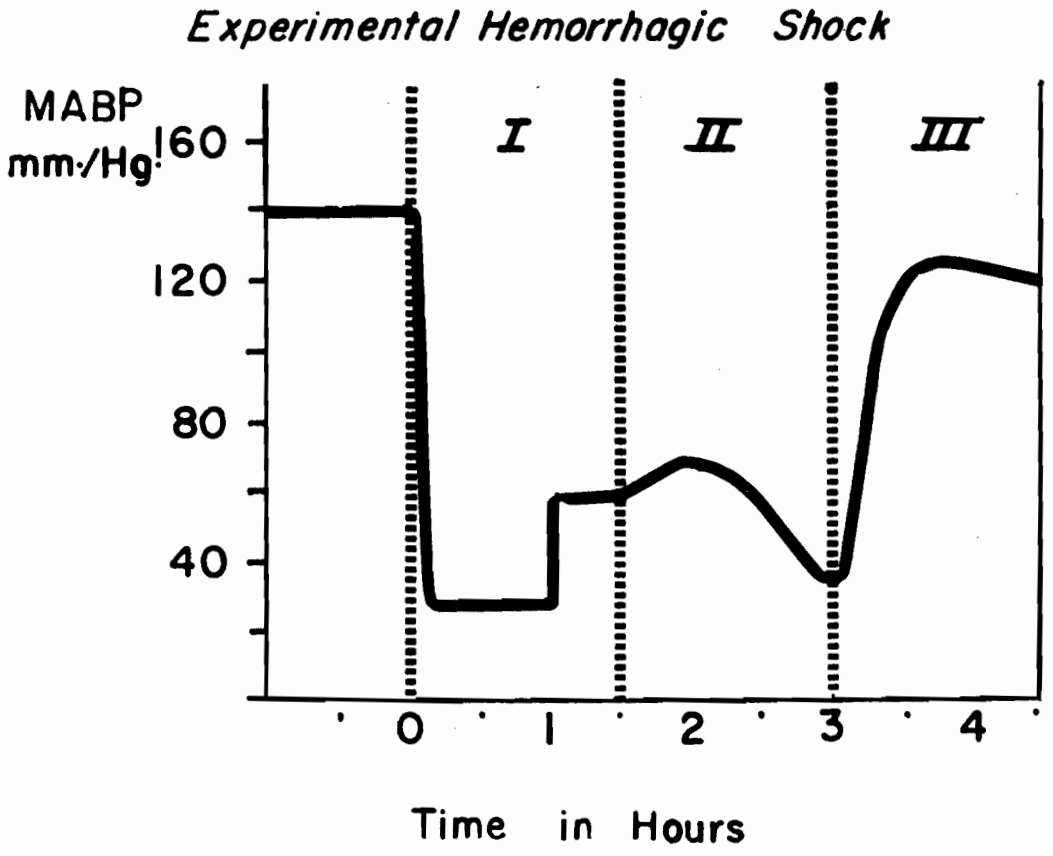

Figure No. 1

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

m.m./Hg - millimeters of mercury

Periods indicated by numerals I - controlled hypotension
II - uncontrolled hypotension
III - reinfusion

The oxygen consumption was recorded throughout the experiment in paired animals for alternate periods of fifteen minutes. A period, lasting from twenty to sixty minutes prior to hemorrhage served to provide data for the control level of oxygen consumption. All data were transferred to a block graph for each animal. An oxygen debt was calculated from the graph as a function of the area bordered by the control level and the actual level of oxygen consumption during the experiment. All data were compared on the basis of body weight in kilograms.

Central arterial and venous blood samples were taken for quantitive analysis of oxygen content. This work was performed by one of the laboratory technicians. Samples were obtained during the control period, at the end of both Periods I and II, and finally within fifteen minutes of reinfusion of the shed blood in Period III.

The cardiac output was calculated from the anterio-venous oxygen difference and the oxygen consumption.

Four therapeutic measures were attempted in this work. One animal of each pair was arbitrarily chosen as a test animal. The other animal served as a control. After adequate control data were obtained both animals were employed as test subjects. Two of these measures previously had been employed with success.[50] Hydralazine,

a ganglionic blocking agent was given in a single intravenous dosage, o.4 milligrams per kilogram of body weight at the beginning of Period II. In a similar manner a single dosage of 200 milligrams of hydrocortisone was given to other animals.

The two other forms of therapy were variations of an extracorporeal circulatory assistance. A Davol Heart Pump was employed in a bidirectional arterial circuit. An attempt was made to reduce the systolic pressure, and, therefore, the cardiac work, while maintaining the mean aortic blood pressure. This was carried out either during Period II or during Period III, following reinfusion of the shed blood.

Materials and Methods

Mongrel dogs, as supplied to the laboratory, were employed as test animals in pairs of approximately equal weights. They were of both sexes and ranged in weight from 9.6 to 19.0 kilograms. Their general state of health was variable depending upon the length of time the animals were maintained in the laboratory kennel before use. They were often subjected to experimentation on the day of their arrival in the kennels.

A continuous permanent recording of all data was made by a six channel Direct Writing Grass Polygraph. Aortic blood pressures were recorded through Statham arterial pressure transducers. Standard electrocardiographic leads were taken through Grass pre-amplifiers

Synchronization signals for the Davol Pump were obtained from the amplifier of the electrocardiogram.

A McKesson Bell Spirometer was employed to study the oxygen consumption. The spirometer tracing was recorded on the Polygraph. The oxygen consumption was calculated on the basis of a known quantity of oxygen inserted into the spirometer on a fixed bascline over a known time.

A unit of oxygen flowed into the bell whenever the bell reached a fixed level. The quantity of a unit of oxygen was adjusted by means of a flow meter attached to the standard wall supply of the hospital and a timer which activated the spirometer inflow valve. The volume was adjusted to 100 millileters of oxygen at standard temperature and pressure. Calibration of this method at the beginning and at the end of an experiment showed less than five percent variation.

The time factor was calculated on the distance the Polygraph tracing had moved, at a rate of 0.25 millimeters per second, during the consumption of a number of refill units.

Thus, the oxygen consumption was calculated from the volume of oxygen inserted into the bell, on the basis of the number of refills, and the period of time during which these refills were consumed, on the basis of the distance the recording paper had moved.

The blood oxygen quantity determinations were carried out on a Thomas Van Slyke Apparatus by the laboratory technician.

The drugs employed in therapy were obtained from the Hospital Pharmacy. Hydralazine was supplied as Apresoline, and hydrocortisone as Solucortef.

The Davol Heart Pump was under the joint ownership of the Medical and the Surgical Research Laboratories of the Montreal General Hospital. The pump was synchronized through the electrocardiogram recorded by the Polygraph. This synchronization was adjusted by following the changes of the aortic blood pressure tracing. The pump catheter was inserted through the femoral artery into the abdominal or thoracic aorta. The mode of pump action was to withdraw aortic blood during cardiac systole and to reinject it during cardiac diastole.

Polyethylene and Tygon tubing were employed as catheters.

The animals, in pairs of approximately equal weights, were anesthetized with intravenous pentobarbital. A state of light anesthesia was maintained with repeated small dosages of pentobarbital as required. The animals were placed on their back on tables and their legs tied to the table. Endotracheal tubes, with inflated cuffs were in place for connection to the spirometer.

The surgical procedures were carried out under semi-sterile technique. The neck and the groins were shaved and prepared with tincture of metaphen and rinsed with alchohol. Sterile drapes were placed to expose the right side of the neck and one of the groins.

The right external jugular vein, the right common carotid artery and one of the femoral arteries were isolated. Prior to the cannulations the animals were given an intra-arterial injection of heparin, 3 milligrams per kilogram.

A catheter was inserted through the right external jugular vein into the right atrium. This served for the infusion of five percent glucose and water throughout the experiment, the test drugs and Polybrene, a heparin antagonist, at the end of the experiment. Central venous blood samples were obtained through this catheter.

The aortic blood pressure and central arterial blood samples were obtained from a catheter inserted into the aortic arch through the right common carotid artery.

A large catheter in the femoral artery served as the bleeding line to the blood reservoir, and as the pumping catheter when required.

After completion of the necessary cannulations and connections the control data were obtained, i.e. oxygen consumption and blood for oxygen content determination.

The bleeding was carried out at a rate of twenty to thirty milliliters per minute. A blood pressure of thirty to thirty-five millimeters of mercury was obtained in fifteen to twenty minutes. The experiment was then carried out as outlined in the procedure.

Observations and Results

Experimental data on oxygen consumption were obtained from fourty-seven animals; of which nineteen were controls and twenty were treated. There were twenty-two survivors and twenty-five non-survivors. The overall mortality rate was 53.2%. Table I lists the number of animals, survivors and non-survivors, in the various test series.

The mortality rate of the control group was 31.5%. The rates for the test series were 62.5% with Hydralazine treatment, 50% with hydrocortisone treatment, 75% with Period II pumping and 100% with Period III pumping.

Most of the data on cardiac output was obtained from these animals. However, due to the difficulties in obtaining sufficient blood oxygen determinations, further data were collected from another series of animals subjected to the same procedure without continuous oxygen consumption recording.

Some general observations of the procedure and the results can be made. The hemorrhagic procedure has several characteristics. The initial period of controlled hypotension was characterized usually by a continuous

increase in the amount of shed blood. In the second period of controlled hypotension usually there was a slow decrease in the amount of shed blood. The animal took back its blood to maintain its blood pressure. Variations in these characteristics depended upon the severity to which the animal reacted to the shocking procedure. The more severe the animal's response, the greater was the uptake of shed blood.

In Period II, the uncontrolled hypotensive period, the blood pressure showed a slight temporary rise immediately after the bleeding line was clamped, after which a gradual decline occurred. The decline varied with the severity of the animal's state. An animal severely depressed responded with a rapid decline of blood pressure. This decline occasionally necessitated the restoration of the blood volume prior to the termination of the period to prevent sudden death.

The restoration of the blood volume in Period III, with reinfusion of the remainder of the shed blood restored the blood pressure. This restoration was to within control limits. The blood pressure then tended to drift downwards at a variable rate and to a variable extent. Figure No. 2 represents the comparison of the blood pressure curves and the curves of oxygen consumption in comparable control animals, one of which was a survivor and the other a non-survivor. Animals which ultimately survived tended to stabilize their blood

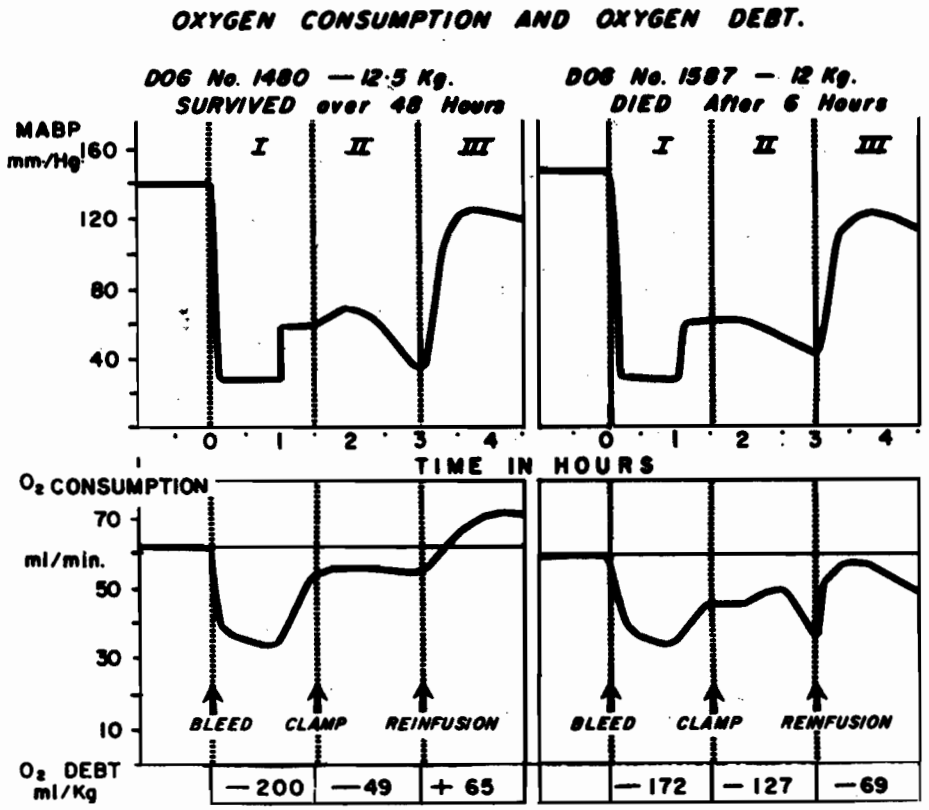

Figure No. 2

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

m.m./Hg - millimeters of mercury

Periods indicated by numerals I, II and III

ml./min. - milliliters per minute

ml./kg - milliliters per kilogram of body weight

pressure early. Those which failed to survive forty-eight hours exhibit a more marked decline of blood pressure over a period of several hours, and failed to stabilize. These animals often failed to recover consciousness.

The curve of the graph representing the oxygen consumption closely resembled that of the blood pressure curve. There was an initial marked decline of the oxygen consumption. The consumption increased as the blood pressure level was raised. The level of consumption varied in the period of uncontrolled hypotension. Reinfusion of shed blood was followed immediately by a marked increase in oxygen consumption. The level to which this increase reached often served as a factor for prognostication. The animals which survived usually increased their oxygen consumption to, or, in excess of, the control level. The non-survivors failed to respond in this manner.

Death usually occured within the first twenty-four hours.

Animals treated with hydralazine tend to show a more rapid decline of the blood pressure after its administration, than did the other animals. The pulse pressure of these treated animals markedly increased.

The animals treated with hydrocortisone or with the pump in Period II did not show any marked variation from the basic pattern of response.

Treatment of animals with the pump in Period III resulted in their early death. They died before the untreated control animals.

The electrocardiogram resembled a standard Lead I tracing. The changes noted during the hypotensive periods were those of myocardial ischemia. There were flattening and inversion of the T waves. The degree to which these changes occurred were related to the level of hypotension. The changes were more pronounced at the lower levels of hypotension.

Some animals had electrocardiographic recording of their deaths. The changes were of severe ischemia and anoxia immediately prior to death. Ventircular fibrillation took place. No resuscitation was attempted. It should be noted that during this period prior to death severe respiratory depression occurred. This was evidenced by a marked fall of the oxygen consumption and the respiratory rate and depth.

The pathological picture of the non-surviving animals was typical of that found in animals which have died from shock induced by any means. The feature most often remarked on is the bowel ulceration and hemorrhage. Submucosal, petechial hemorrhages were found in all viscera. The organs generally were pale. The spleen was most often

contracted. Occasionally it was congested along with the liver. The lungs showed marked congestion and hemorrhage. Pneumonia was frequently encountered.

The tabulation of the oxygen consumption for each animal is listed in Table II. The figures are comparable because the absolute values have been reduced to milliliters of oxygen consumed per kilogram of body weight per minute (ml./kg./min.).

The control values represent the basal level of oxygen consumption prior to the onset of hemorrhage. The actual level of oxygen consumption is for the 180 minute experimental period, Periods I and II, prior to the restoration of blood volume. The percentage the actual level of oxygen consumption is of the control level is listed.

The mean values of oxygen consumption are found in Table III. The survivors have a mean level of 5.5 ml./kg./min. and the non-survivors a mean level of 6.2 ml./kg./min. The significance of this apparent difference is not determined.

The mean values of the actual oxygen consumption in the various series, separated into the survivors and the non-survivors, show a very small range of 3.9 to 4.6 ml./kg./min. No remarkable difference is noted between the controls and the various treated groups. The Hydralazine treated groups have the highest level of actual oxygen consumption. This corresponds with the results of Lotz, Beck and Stevenson.[34]

The percentage the actual level of oxygen consumption is of the control level may indicate the significant factor. The mean percentage of the survivors is 77.1% and of the non-survivors is 62.7%. The range of the survivors is 70.6% to 106.1%, and of the non-survivors is 17.9% to 79.7%. This is the factor noted previously which served to prognosticate the survival or the death of an animal.

The reduction of the oxygen consumption below the basal control level produces a theoretical oxygen debt. This debt is defined as the difference between the projection of the control level of oxygen consumption and the actual level of consumption. This concept of oxygen debt is graphically represented in Figure No. 3. The mean level of the basal control oxygen consumption is indicated on the two graphs; one for the survivors and one for the non-survivors. The mean values of the actual level of oxygen consumption for the two groups are the lines below the shaded areas. The difference between the projected control levels and the actual levels, the oxygen debts, is indicated by the shaded area.

The total body oxygen debt of each animal is located in Table IV. The units employed are milliliters per kilogram of body weight. The "projected control" figures represents the theoretical oxygen consumption during the 180 minutes of Periods I and II. The actual oxygen consumption during the periods of hypotension and hypovolemia,

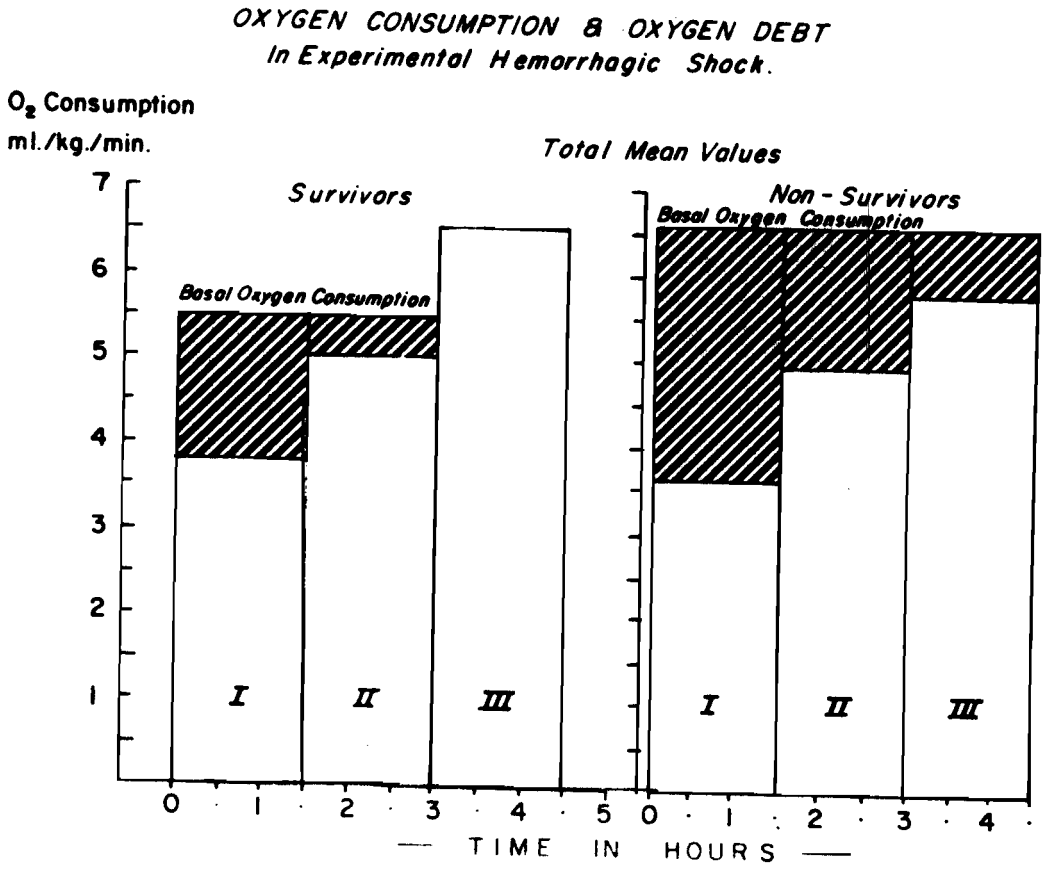

Figure No. 3

ml./kg./min. - milliliters per kilogram body weight per minute

Periods indicated by numerals I, II, III

Periods I and II, is listed in the second column. The difference between these two figures is the oxygen debt. One animal, a control-survivor on January 19, failed to develop a debt. The actual oxygen consumption for the period under study exceeded the projected value. This is indicated by a plus (+) sign in the table.

The final column of Table IV, listed as Period III, represents the difference between the projected basal level of oxygen consumption and the actual consumption during the ninety minute period following the restoration of the blood volume. This period was not extended to 180 minutes to compare with the period of the oxygen debt because it did not appear to provide any further useful information. The trend developed in the early phase of Period III was maintained. The figures designated with a minus (-) indicate a continuing oxygen debt. The figures without designation indicate that the oxygen consumption during this period exceeded the control level. The survivors, with two exceptions, had an oxygen consumption greater than the basal level. The non-survivors, with four exceptions, failed to develop a sufficient level of oxygen consumption to exceed the basal level. It can only be speculated that these six exceptions might have fallen into the general trend if the recording had been extended for a longer time.

The mean values of oxygen debt are compared in Table V. The mean value of the survivors is 196 ml./kg. and of the non-survivors, 330 ml./kg. The survivors showed a mean "recovery" value of 88 ml./kg. in Period III. At the same time the non-survivors continued to accumulate a debt with a mean value of 73 ml./kg.

The data obtained to calculate the cardiac output is listed in Tables VI to IX. Each of the four tables represents one point during the experimental procedure at which time the cardiac output was determined. Table VI represents the data obtained during the control period. The other tables represent output determinations at the end of Period II, at the beginning and at the end of Period III. The tabulation of the cardiac output for each animal is listed in Table X. Table XI lists the mean values for the various series.

The table of mean values indicates that there is little difference between the various comparable groups. The cardiac output is markedly reduced following a period of hypotension and hypovolemia. The output increases to values approximating, or in excess of, the control level after restoration of the blood volume. This is followed by a decrease in the output. There are insufficient values to determine whether or not this decrease is different in the survivors than in the non-survivors.

TABLE I

Experimental Hemorrhagic Shock

Numbers of Animals

Series	Survivors	Non-Survivors	Total
Control	13	6	19
Hydralazine	6	10	16
Hydrocortisone	2	2	4
Period II Pump	1	3	4
Period III Pump	0	4	4
Total	22	25	47

TABLE II

Oxygen Consumption
(explanation in text)
(ml./kg./min.)

Series	Date	Control	Actual	Actual %
Control: survivors	Jan. 12	4.1	3.4	82.2
	19	5.0	5.3	106.1
	22	2.8	2.2	78.3
	Feb. 2	4.8	3.4	71.2
	5	6.1	4.8	79.2
	7	6.5	5.1	72.3
	21	5.7	4.7	83.2
	Mar. 12	6.2	5.6	90.1
	16	4.3	3.7	86.0
	23	6.4	5.2	81.8
	28	4.7	3.2	67.8
	29	6.3	5.0	79.8
	Apr. 18	5.6	4.8	86.4
Control: non-survivors	Dec. 18	7.6	3.7	48.5
	Jan. 8 #1	7.6	1.4	17.9
	8 #2	4.7	3.3	70.9
	31	5.4	2.5	46.6
	Mar. 19	8.0	5.9	73.5
	26	5.0	3.3	66.7
Hydralazine: survivors	Jan. 22	3.0	2.5	83.3
	31	5.4	4.2	77.6
	Feb. 5	7.1	5.0	70.6
	21	7.6	4.9	77.3
	Mar. 28	5.0	4.1	81.3
	29	7.5	5.8	77.3

TABLE II
(Continued)
Oxygen Consumption

Series	Date	Control	Actual	Actual %
Hydralazine:				
non-survivors	Feb. 2	5.8	4.0	69.2
	7	6.8	3.5	51.2
	9	6.4	4.5	70.3
	19	7.5	4.4	58.4
	Mar. 12	9.1	5.7	63.1
	16	5.0	3.4	69.5
	23	4.6	2.9	64.0
	26	6.9	4.4	60.3
	Apr. 4	5.4	3.2	59.7
	6	5.4	4.1	75.9
Hydrocortisone:				
survivors	Apr. 13	5.0	4.1	82.4
	18	5.5	4.6	83.1
Hydrocortisone:				
non-survivors	Apr. 16 #1	5.8	3.6	61.7
	16 #2	6.0	4.8	79.7
Period II Pump:				
survivors	Apr. 9	5.6	4.1	73.1
Period II Pump:				
non-survivors	Jan. 19	6.4	3.3	50.9
	Apr. 4	8.0	4.9	60.8
	6	5.7	3.5	60.9
Period III Pump:				
non-survivors	Dec. 13	6.0	4.7	79.1
	18	6.9	5.1	69.3
	Jan. 12	5.7	3.9	69.1
	15	4.0	2.8	70.1

TABLE III

Oxygen Consumption
mean values
(ml./kg./min.)

Series	Control		Actual		Actual %	
	S	NS	S	NS	S	NS
C	5.3	6.4	4.4	3.5	81.9	54.0
H	5.9	6.3	4.6	4.4	77.7	64.2
HC	5.3	5.9	4.4	4.2	82.8	70.2
P II	5.6	6.7	4.1	3.9	73.1	57.5
P III	-	5.7	-	4.1	-	71.9

Key:
- C - Control
- H - Hydralazine
- HC - Hydrocortisone
- P II - Period II Pump
- P III - Period III Pump
- S - Survivors
- NS - Non-survivors

TABLE IV

Oxygen Debt
(Explanation in text)
(ml./kg.)

Series	Date	Projected Control	Actual	Debt	Period III
Control: survivors	Jan. 12	738	607	131	56
	19	900	955	± 55	154
	22	504	395	109	17
	Feb. 2	864	615	249	65
	5	1098	870	228	19
	7	1270	918	352	10
	21	1026	854	172	86
	Mar. 12	1116	1006	110	307
	16	774	666	108	207
	23	1152	942	210	429
	28	846	574	272	-103
	29	1134	905	229	37
	Apr. 18	1008	871	137	30
Control: non-survivors	Dec. 18	1368	663	705	-175
	Jan. 8#1	1368	244	1124	-337
	8#2	846	598	248	died
	31	972	453	519	-165
	Mar. 19	1440	1059	381	-185
	26	900	601	299	- 69
Hydralazine: survivors	Jan. 22	540	450	90	18
	31	972	754	218	255
	Feb. 5	1278	903	375	55
	21	1368	1058	310	57
	Mar. 28	900	732	168	69
	29	1350	1044	306	226
Hydralazine: non-survivors	Feb. 2	1044	722	322	- 15
	7	1224	627	597	- 84
	9	1152	810	342	- 47
	19	1350	790	560	- 49
	Mar. 12	1638	1033	605	-110
	16	900	608	292	- 96
	23	828	530	298	- 63
	26	1322	797	525	-165
	Apr. 4	972	580	392	± 84
	6	972	738	234	- 57

TABLE IV
(Continued)

Oxygen Debt
(Explanation in text)
(ml./kg.)

Series	Date	Projected Control	Actual	Debt	Period III
Hydrocortisone: survivors	Apr. 13	900	742	158	± 53
	18	990	823	167	± 27
Hydrocortisone: non-survivors	Apr. 16#1	1044	645	399	- 15
	16#2	1080	861	219	- 12
Period II Pump: survivors	Apr. 9	1008	737	271	- 27
Period II Pump: non-survivors	Jan. 19	1152	587	565	-184
	Apr. 4	1440	875	565	± 10
	6	1026	625	401	- 36
Period III Pump: non-survivors	Dec. 13	1080	854	226	±126
	18	1322	917	405	-220
	Jan. 12	1026	709	317	- 62
	15	720	505	215	± 7

TABLE V

Oxygen Debt

Mean Values
(ml./kg.)

Series	Debt		Period III	
	Survivors	Non-survivors	Survivors	Non-survivors
Control	172	546	93	-166
Hydralazine	245	417	113	-51
Hydrocortisone	163	310	40	-14
Period II Pump	271	510	-27	-70
Period III Pump	-	291	-	-37
Mean	196	330	±88	-73

Cardiac Output Data

Key to Tables VI to IX

Key:	Wt.	-	weight in kilograms
	A	-	arterial oxygen content in volumes per 100 milliliters of blood
	V	-	venous oxygen content in volumes per 100 milliliters of blood
	A-V	-	arterio-venous oxygen difference
	O_2	-	oxygen consumption in milliliters per minute
	CO	-	cardiac output in milliliters per kilogram of body weight per minute

TABLE VI

Cardiac Output Data
(Explanation in text)

Control Period

Series	Date	Wt.	A	V	A-V	O_2	CO
Control: survivors	Jan. 12	17.0	20.18	17.67	2.51	70	164
	19	16.0	22.10	16.27	5.83	80	86
	22	19.0	21.60	20.58	1.02	54	280
	Mar. 16	10.0	17.52	14.18	3.34	65	195
	23	11.0	12.17	9.52	2.65	74	254
	28	9.6	18.69	16.76	1.93	46	248
	29	11.0	17.55	13.43	4.12	70	155
	Apr. 18	12.0	21.18	15.47	5.71	67	98
Control: non-survivors	Nov. 1	16.0	18.64	14.45	4.19	148	221
	Dec. 18	15.5	18.05	11.45	6.60	118	115
	Jan. 8	17.0	16.16	10.35	5.81	85	86
	Mar. 19	10.0	18.64	13.71	4.93	80	162
	26	12.0	20.80	18.99	1.81	73	336
Hydralazine: survivors	Jan. 22	19.0	14.52	9.64	4.88	47	51
	Mar. 28	12.0	17.30	13.44	3.86	68	147
	29	12.0	14.26	11.72	2.54	100	328
Hydralazine: non-survivors	Mar. 16	10.0	18.65	13.68	4.97	67	135
	19	11.5	17.03	14.92	2.11	117	482
	23	11.0	14.80	10.46	4.34	51	107
	26	14.0	19.46	13.36	6.10	97	114
	Apr. 4	15.6	19.49	15.65	3.84	85	142
	6	14.0	18.52	14.92	3.60	83	165
Hydrocortisone: survivors	Apr. 13	15.0	19.57	16.37	3.20	66	137
	18	13.0	14.34	11.93	2.41	73	233
Hydrocortisone: non-survivors	Apr.16#1	14.4	21.22	17.93	3.29	104	253
	Apr.16#2	13.0	18.26	14.14	4.12	83	155

TABLE VI
(Continued)

Cardiac Output Data

Control Period

Series	Date	Wt.	A	V	A-V	O_2	CO
Period II Pump:							
non-survivors	Jan. 19	16.0	18.27	13.56	4.71	103	137
	Apr. 4	16.5	18.66	15.66	3.00	133	269
	6	14.0	18.86	16.87	1.99	80	287
Period III Pump:							
non-survivors	Dec. 13	14.0	20.21	15.47	4.74	85	128
	18	16.5	19.90	14.05	5.85	115	119
	Jan. 8	17.0	12.54	8.94	3.60	130	212
	12	18.0	18.85	15.64	3.21	105	182
	15	16.0	19.20	18.04	1.16	64	345

TABLE VII

Cardiac Output Data
Period II

Series	Date	Wt.	A	V	A-V	O_2	CO
Control:							
survivors	Jan. 19	16.0	17.66	5.73	11.93	98	51
	22	19.0	15.34	4.59	10.75	40	20
	Mar. 16	10.0	17.74	6.70	11.04	38	34
	23	11.0	10.84	4.43	6.41	71	101
	28	9.6	13.75	4.97	8.78	36	43
	29	11.0	18.40	1.56	16.84	44	23
	Apr. 18	12.0	21.85	11.16	10.69	69	54
Control							
non-survivors	Nov. 1	16.0	14.34	4.11	10.23	55	34
	Mar. 19	10.0	19.16	1.25	17.91	27	15
	26	12.0	14.34	3.73	10.61	39	31
Hydralazine:							
survivors	Jan. 22	19.0	14.88	2.87	12.01	38	17
	Mar. 28	12.0	13.53	4.11	9.42	60	53
	29	12.0	14.49	4.21	10.27	83	67
Hydralazine:							
non-survivors	Mar. 16	10.0	12.40	6.72	5.68	40	70
	19	11.5	17.08	3.52	13.56	86	55
	23	11.0	13.55	5.14	8.41	44	48
	26	14.0	21.45	5.66	15.79	47	21
	Apr. 4	15.6	19.54	4.37	15.17	60	25
	6	14.0	14.44	10.48	3.96	64	115
Hydrocortisone:							
survivors	Apr. 13	15.0	16.80	2.35	14.45	58	28
	18	13.0	12.63	2.61	10.02	75	58
Hydrocortisone:							
non-survivors	Apr.16 #1	14.4	21.19	6.10	15.09	70	32
	#2	13.0	18.36	3.77	14.59	67	35
Period II Pump:							
survivors	Apr. 9	16.5	13.52	2.43	11.09	63	34
Period II Pump:							
non-survivors	Jan. 19	16.0	10.93	0.63	10.30	29	18
	Apr. 4	16.5	18.25	6.38	11.87	100	51
	6	14.0	14.95	3.68	11.27	41	26

TABLE VIII

Cardiac Output Data
Period III
(early)

Series	Date	Wt.	A	V	A-V	O_2	CO
Control:							
survivors	Jan. 12	17.0	22.10	19.89	2.21	70	186
	19	16.0	23.35	21.01	2.34	129	345
	22	19.0	19.08	17.59	1.49	59	208
	Mar. 28	9.6	16.34	14.96	1.38	31	234
	29	11.0	17.17	15.86	1.31	82	569
	Apr. 18	12.0	22.21	20.08	2.13	83	325
Control:							
non-survivors	Nov. 1	16.0	19.48	15.70	3.78	94	155
	10	15.0	17.96	16.27	1.69	92	363
	15	15.0	21.62	19.28	2.34	100	285
	Dec. 18	15.5	17.59	11.36	6.23	90	93
	Jan. 8	17.0	2.72	1.31	1.41	52	217
	Mar. 26	12.0	16.37	12.36	4.01	80	166
Hydralazine:							
survivors	Jan. 22	19.0	17.19	15.30	1.89	53	148
	Mar. 28	12.0	17.56	14.61	2.95	70	198
	29	12.0	17.51	10.92	6.59	107	135
Hydralazine:							
non-survivors	Mar. 26	14.0	21.58	20.71	0.87	75	616
	Apr. 4	15.6	25.01	22.29	2.72	136	321
	6	14.0	18.85	16.10	2.75	66	171
Hydrocortisone:							
survivors	Apr. 13	15.0	20.03	18.71	1.32	83	419
	18	13.0	16.43	13.99	2.44	77	243
Hydrocortisone:							
non-survivors	Apr. 16#1	14.4	20.80	18.10	2.70	83	213
	16#2	13.0	18.17	15.01	3.16	76	185
Period II Pump:							
survivors	Apr. 9	16.5	16.46	15.64	0.82	88	650
Period II Pump:							
non-survivors	Jan. 19	16.0	17.15	14.76	2.39	88	230
	Apr. 4	16.5	21.74	20.17	1.57	143	552
	6	14.0	19.82	18.16	1.66	95	409

TABLE VIII
(Continued)

Cardiac Output Data
Period III
(early)

Series	Date	Wt.	A	V	A-V	O_2	CO
Period III Pump:							
non-survivors	Nov. 10	13.0	19.85	15.09	4.76	80	129
	Dec. 13	14.0	20.21	19.12	1.09	120	786
	18	16.5	18.63	8.63	9.99	79	48
	Jan. 8	17.0	13.57	9.87	3.70	70	111
	12	18.0	20.19	14.92	5.27	120	127
	15	16.0	21.01	18.09	2.92	68	146

TABLE IX

Cardiac Output Data
Period III
(late)

Series	Date	Wt.	A	V	A-V	O_2	CO
Control:							
survivors	Jan. 12	17.0	21.52	17.66	3.86	90	137
	19	16.0	27.40	18.55	8.85	95	67
	22	19.0	21.21	17.58	3.63	58	84
Control:							
non-survivors	Nov. 1	16.0	21.24	15.13	6.11	94	96
	10	15.0	17.87	6.92	10.95	80	49
	15	15.0	21.49	13.18	8.31	58	46
	Dec. 18	15.5	20.99	16.17	4.82	85	114
Hydralazine:							
survivors	Jan. 22	19.0	16.14	10.42	5.72	47	43
Period II Pump:							
non-survivors	Jan. 19	16.0	17.05	8.69	8.36	74	55
Period III Pump:							
non-survivors	Jan. 8	17.0	13.35	4.30	9.05	35	23
	12	18.0	14.86	0.84	14.02	55	22
	15	16.0	20.55	11.74	8.81	63	45

TABLE X
Cardiac Output
ml./kg./min.

Series	Date	Control	Period II	Period III (early)	Period III (late)
Control: survivors	Jan. 12	164	3	186	122
	19	86	34	345	67
	22	280	20	208	84
	Mar. 16	195	34	-	-
	23	254	101	-	-
	28	248	43	234	-
	29	155	23	569	-
	Apr. 18	98	54	325	-
Control: non-survivors	Nov. 1	221	34	155	96
	10	-	-	363	49
	15	-	-	285	46
	Dec. 18	115	-	93	33
	Jan. 8	86	-	217	-
	Mar. 19	162	15	-	-
	26	336	31	166	-
Hydralazine: survivors	Jan. 22	51	17	148	-
	Mar. 28	147	53	198	-
	29	328	67	135	-
Hydralazine: non-survivors	Mar. 16	135	70	-	-
	19	482	55	-	-
	23	107	48	-	-
	26	114	21	616	-
	Apr. 4	142	25	321	-
	6	165	115	171	-
Hydrocortisone: survivors	Apr. 13	137	28	419	-
	18	233	58	243	-
Hydrocortisone: non-survivors	Apr. 16#1	253	32	213	-
	16#2	155	35	185	-
Period II Pump: survivors	Apr. 9	-	34	650	-

TABLE X
(Continued)
Cardiac Output
ml./kg./min.

Series	Date	Control	Period II	Period III (early)	Period III (late)
Period II Pump:					
non-survivors	Jan. 19	137	46	230	55
	Apr. 4	269	51	552	-
	6	287	26	409	-
Period III Pump:					
non-survivors	Nov. 10	-	-	129	16
	Dec. 13	128	-	786	82
	18	119	-	48	128
	Jan. 8	212	-	111	23
	12	182	-	127	22
	15	345	-	146	51

TABLE XI

Cardiac Output
mean values
(ml./kg./min.)

Series	Control		Period II		Period III (early)		Period III (late)	
	S	NS	S	NS	S	NS	S	NS
C	185	184	44	23	311	213	91	56
H	175	191	46	56	160	369	-	-
HC	185	204	43	33	331	199	-	-
P II	-	231	34	32	650	397	-	55
PIII	-	211	-	34	-	192	-	77
Mean	183	211	44	37	306	264	91	67

Key:
- C - Control
- H - Hydralazine
- HC - Hydrocortisone
- P II - Period II Pump
- P III - Period III Pump
- S - Survivors
- NS - Non-survivors

Conclusions

An experimental hemorrhagic shock procedure was employed which created an overall mortality of 53.2%. The mortality of the Control series was 31.5%. The mortality of the Hydralazine treated animals was 62.5%. Arterio-arterial pumping after the reinfusion of shed blood appeared to create an adverse effect. There was 100% mortality. The deaths occurred at the end of the experimental procedure before any of the control animals died. No valid conclusions can be drawn for the other series because of insufficient numbers of animals.

The curve of the level of oxygen consumption during experimental hemorrhagic shock closely resembled the blood pressure curve.

The reduction of total oxygen consumption during the hypotensive period below 70.6% of the basal level was fatal to all animals. All animals with an oxygen consumption reduced less than 79.7% survived. There appears to be a critical range of reduced total oxygen consumption during the hypotensive period, below which no animal can survive. This range is 70.6% to 79.7% of the basal level.

The reduction of oxygen consumption during experimental hemorrhagic shock created a theoretical oxygen debt. This debt was greater in the non-survivors than in the non-survivors.

The oxygen consumption increased following restoration of blood volume. This increase for the survivors was to a level in excess of the basal consumption. The non-survivors failed to increase their oxygen consumption to the basal level. An oxygen debt continued to accumulate. There were six exceptions in fourty-seven animals to these general conclusions.

The cardiac output is greatly reduced after a period of experimental hemorrhagic shock. The cardiac output increases to levels similar to, or greater than, the control immediately after restoration of the blood volume. This increase is not sustained over a period of ninety minutes.

There is no apparent relationship between cardiac output and survival as measured in these experiments.

The measurement of blood pressure does not give an adequate picture of shock.

Discussion

This experimental study was designed to further explore the problems of hemorrhagic shock. Much work has been reported on the metabolic aspects of this problem. The changes from an aerobic metabolism to an anaerbic one are well documented.[11, 38, 39, 41] Myocardial respiration and oxygen consumption have been investigated under various conditions of shock.[2, 4, 5, 6, 9, 10, 15, 16, 25, 40] Only two reports [24, 34] were found at the

time of this study in which total body oxygen consumption was investigated.

Guyton and Crowell[24] developed a hemorrhagic preparation in which they recorded, by means of a computer, a continuous oxygen debt. They "shocked" the animals to a specific debt and re-infused the shed blood. They concluded that beyond a critical limit of oxygen debt an animal could not survive.

Lotz, Beck and Stevenson[34] recorded the changes of oxygen consumption in shocked animals treated with Hydralazine. They found an increase in the oxygen consumption in the treated animals. In addition the survival rate of the treated animals was greater than the controls.

Our study was designed to record the oxygen consumption in a standard hemorrhagic procedure and to compare the changes under various therapeutic measures. It soon became evident that the survival data did not compare with previous reports[29] in which the same hemorrhagic technique and therapy were employed.

It became apparent that the significant difference between our work and that of Hakstian et al.[29] was that our animals did not have the benefit of a two week period to acclimatize to the laboratory kennels and to stabilize their health. Haig[28] confirmed this fact in his own work. He was unable to develop a standard preparation

of pancreatitis until all animals were isolated and fed in the laboratory kennels for two weeks prior to experimentation.

It can only be concluded that our results would have shown less variability if it had been possible to provide a period of standardization. The availability of animals and space made this impractical.

The overall mortality was 53.2%. This provides a satisfactory distribution to compare survivors and non-survivors.

While we were concerned about the variability of results it became evident that the pattern of oxygen consumption in the survivors and the non-survivors might provide more interesting information. Therefore, the work was continued with the emphasis on the oxygen consumption and not on the therapy.

The oxygen consumption was an indirect measurement. The actual consumption was measured in alternate fifteen minute periods between two animals. This measurement was projected to thirty minutes and placed on a block graph. This graph was used to calculate total body oxygen consumption and oxygen debt.

A few animals had a continuous recording of oxygen consumption throughout the experimental procedure. These data were plotted on the same basis as for the other animals. A comparison of the two methods revealed that

the calculated oxygen consumption was ten percent greater than the actual consumption.

The system of mechanical and electrical equipment employed to measure the oxygen consumption was found to be stable. The variation in the amount of oxygen inflow throughout the five to six hours of the experimental procedure was less than five percent. The system was calibrated at the beginning and at the end of each experiment to maintain the accuracy.

The oxygen consumption of an animal maintained under light anesthesia for six hours ranged from 5.7 to 6.1 ml./kg./min. The body temperature of such an animal fell from 39.5 degrees centigrade to 38.5 degrees. This demonstration of the stability of basal oxygen consumption suggests that the changes recorded during the experimental procedure were a true representation of the effects of hemorrhage and hypotension.

The conclusion that an oxygen debt beyond a specific limit is fatal concurs with the work of Guyton. Figure No. 3 compares the mean values of oxygen consumption and debt between survivors and non-survivors. This same data may be represented on the basis of the percentage the actual consumption is of the basal level. Figure No. 4 clearly illustrates the difference between the survivors and the non-survivors.

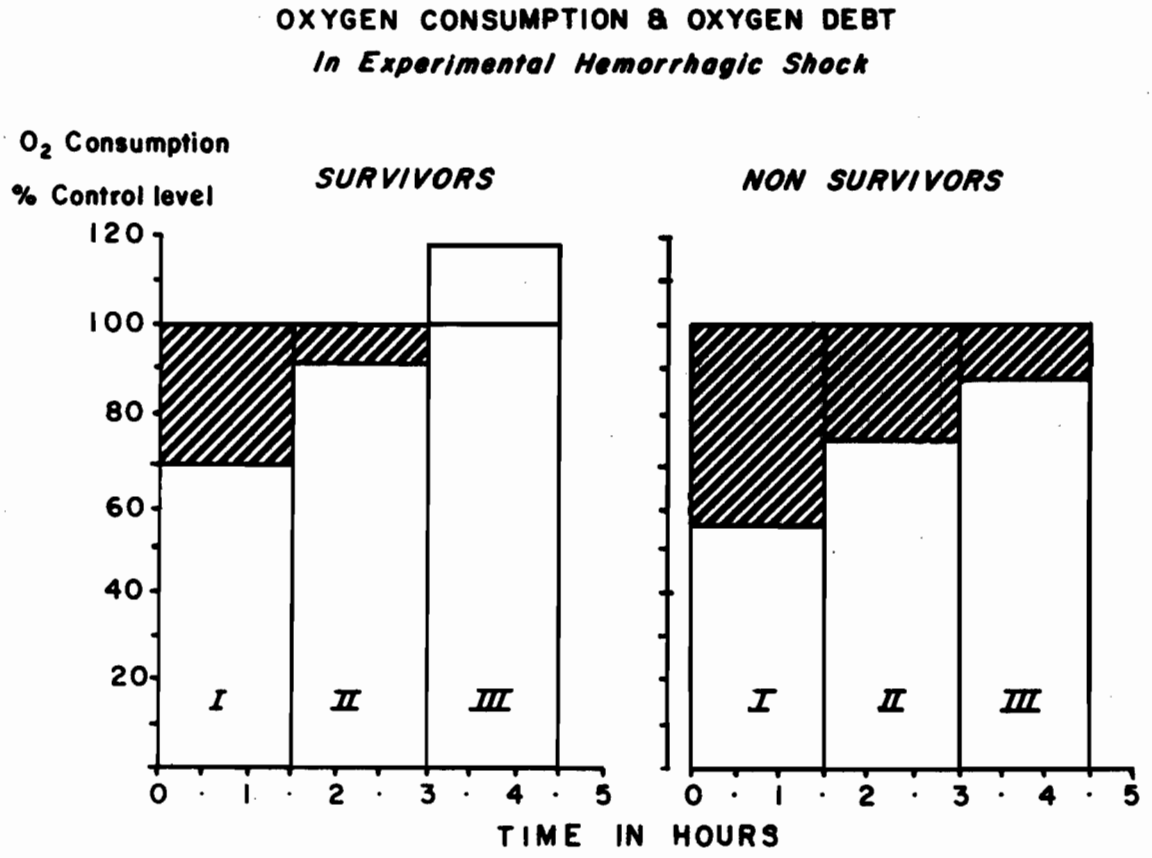

Figure No. 4

Periods indicated by numerals I, II, III

The cardiac output was calculated on the Fick Principle of the difference between the central arterial and venous oxygen content in relation to the oxygen consumption. Right atrial blood samples were used to determine the central venous oxygen content. It is known that this does not give a true central value. However, it is an acceptable value for comparison.

The determination of cardiac output requires a stable cardiovascular state. The determination early in Period III was made immediately after the reinfusion of shed blood. It was evident from the changing blood pressure that stability was not present. The results of the calculation of cardiac output at this time were variable.

In general discussion, it is noted that a fourty-eight hour period was chosen to determine survival. It is believed that this period covers the early and late deaths due to shock. No natural deaths occurred after fourty-eight hours. The survivors appeared healthy for several weeks. No remarkable pathological findings were observed in the survivors.

The survival of an animal did not appear to be related to any form of therapy. It may be assumed, in reference to this work, that the success of therapy by other authors was in fact the result of sublethal shock.

The point of irreversibility in shock may be the critical zone of reduced oxygen consumption. Therapy in this zone may be the answer to success.

Guyton expresses this idea in terms of an accumulated oxygen debt. It must be remembered that the reduced oxygen consumption is also an accumulated figure. It is more practical during an experimental procedure to determine an accumulated oxygen debt than the accumulated reduction of oxygen consumption.

Summary

A standardized hemorrhagic hypotensive procedure was developed which created a mortality of 53.2% in fourty-seven animals. There were nineteen control animals and twenty-eight test animals.

The test animals were treated in one of four ways. Hydralazine or hydrocortisone was given as a single injection at the mid point of the hypotensive period. Arterio-arterial pumping was attempted in other test animals, either during the second half of the hypotensive period or after the reinfusion of shed blood.

Total body oxygen consumption was measured for alternate periods of fifteen minutes in each pair of experimental animals throughout the procedure. Each measurement was projected to thirty minutes and placed on a block graph. The total oxygen consumption was calculated for the entire procedure. The basal oxygen consumption was projected on each graph. The survivors exhibited a mean oxygen consumption of 77.1% of the projected basal consumption; the non-survivors a mean value of 62.7%.

The difference between the projected basal oxygen consumption and the actual level was calculated as the oxygen debt. The mean oxygen debt of the survivors was 176 ml./kg.; of the non-survivors 330 ml./kg.

The oxygen consumption for the period following re-infusion of shed blood was also calculated. The survivors exhibited a mean consumption of 88 ml./kg. in excess of the basal level. The non-survivors continued to accumulate a mean oxygen debt of 73 ml./kg.

The cardiac output was measured at specific intervals during the procedure. Values were determined in the control period, at the end of the hypotensive period and after re-infusion of shed blood. Some values were obtained late in the experimental procedure. No relationship could be determined between the cardiac output and survival.

It would appear that there is a critical zone of reduced oxygen consumption; or, conversely, a critical amount of accumulated oxygen debt, which is responsible for the irreversibile state of shock.

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