Pathophysiology and treatment of hemorrhagic shock

Jerry G. Schaaf
University of Nebraska Medical Center

This manuscript is historical in nature and may not reflect current medical research and practice. Search PubMed for current research.

Follow this and additional works at: https://digitalcommons.unmc.edu/mdtheses

Part of the Medical Education Commons

Recommended Citation
https://digitalcommons.unmc.edu/mdtheses/123

This Thesis is brought to you for free and open access by the Special Collections at DigitalCommons@UNMC. It has been accepted for inclusion in MD Theses by an authorized administrator of DigitalCommons@UNMC. For more information, please contact digitalcommons@unmc.edu.
Pathophysiology and Treatment of Hemorrhagic Shock

By

Jerry G. Schaaf

A THESIS

Presented to the Faculty of

The College of Medicine in the University of Nebraska

In Partial Fulfillment of Requirements

For the Degree of Doctor of Medicine

Under the Supervision of John R. Jones, M.D.

Omaha, Nebraska

February 24, 1969
Shock may be described as a syndrome of peripheral vascular insufficiency in which the effective circulating blood volume is reduced, accompanied by depression of many systems. The impaired general circulation causes diminished tissue perfusion and decompensation of the microcirculation. The result is a basic defect in cellular perfusion. Although the etiology and mechanism of shock may vary, the final common physiological lesion is cellular hypoxia. Hemorrhage or another type of metabolic insult may be the initial lesion, but regardless of etiology all types of shock rapidly form a similar syndrome since they share the same basic defect of cellular hypoxia. As stated by Haldane, "Anoxia not only stops the machine, but wrecks the machinery."

Hemorrhagic shock has been a misunderstood and frequently mistreated clinical syndrome. It is a complex entity that involves many etiologic factors, and becomes more complicated when combinations of these factors are the causes of circulatory collapse. Knowledge concerning shock has increased steadily over the years as research has improved our understanding of basic biochemical and physiologic mechanisms. New research tools and advanced methods of monitoring physiologic parameters have also allowed a more scientific approach to understanding the mechanisms and management of hemorrhagic shock. However, the growth of concepts leading to the present understanding of shock requires an appreciation of the historical
background involved.

HISTORY

The early definitions of shock were based entirely on clinical description and the initial usage of the term arose from observation of the wounded on the battlefield. Shock was used to denote a condition where the injury, on superficial examination appeared too small to account for the seeming collapse of vital processes. Warren's definition of shock, "A momentary pause in the act of death," implies that the study of shock is the study of impending death. Gradually the prostration, hypotension, pallor, coldness, moisture of the skin, collapse of superficial veins, suppression of urine formation, and obtund mental status seen in battle casualties came to be recognized in other conditions such as cholera. In 1831 Latta made a monumental contribution to the understanding of shock. Without precedent to direct him he proceeded to infuse 330 ounces of saline intravenously into a cholera patient in 12 hours, and reported dramatic clinical improvement.

The advent of experimental physiology and the use of the kymograph focused attention on the measurement of arterial blood pressure, and confirmed that hypotension was one of the most consistent accompaniments of shock. Recognition of the control of the heart and blood vessels by a vasomotor center acting by way of nervous pathways
prompted the concepts of vasomotor paralysis and of cardiac failure resulting from reflex vagal hyperactivity. This neurogenic definition of shock was summarized by Groenigen in 1885. He proposed that shock began as a state of intensive nervous stimulation and was followed by vasomotor exhaustion.

At the end of the 19th century Crile developed an experimental model of hemorrhagic shock. His work resulted in a systematic definition of shock in the experimental animal. He clearly documented the lowered venous pressure in hypovolemic shock, the acceleration and deepening of respiration following hemorrhage and the response of the shocked animals to infusion of warm saline. This latter response was an indication to Crile that the cardiac action was normal in shock and that the defect was largely one of impaired venous return.

War has almost invariably stimulated interest in the definition and therapy of shock, and the war of 1914-1918 was no exception. From observations made on the battlefield and in laboratory investigation, Cannon attempted to explain the hypotension of shock in terms of cardiac failure, loss of vasomotor tone, fall in blood volume, or stagnation in venous reservoirs. In 1917 Cannon used the then new Van Slyke apparatus to document a correlation between the low blood pressure and the reduction in alkali reserve. He believed that the fall in the alkali reserve was due to the accumulation of fixed acids, such as lactic
acid, and recognized that this was due to impaired oxygen transport. The acidosis was identified as a secondary phenomenon that was responsive to the administration of sodium bicarbonate. When the volume of the war wounded was studied by means of dye dilution methods, it was found that the severity of shock correlated with the reduction in blood volume. Cannon then defined wound shock as a discrepancy between blood volume and vascular capacity.

Other workers continued to add to the body of knowledge during the following years. Recent investigations have concentrated largely on the elucidation of the hemodynamic and biochemical events in experimental canine models using endotoxin or graded hemorrhage. Although a considerable body of knowledge has emerged from this work, much cannot be transposed readily from the artificial experimental model to the clinical situation. The complexities of human shock are in reality poorly defined. The age of the patient, past medical history, possibility of severe underlying disease, and the function of vital organs are variable factors that may contribute to circulatory collapse. All this information is not readily quantitatable nor transferable from one case to another, but is vital in the interpretation and analysis of shock data.

Traditionally, physicians regard shock from the circulatory viewpoint. Blood pressure, heart rate and
venous pressure are the three most readily measured, and hence, the most commonly considered variables. However, an absolute value of any one parameter is seldom a satisfactory basis for determining the presence or the severity of shock. Shock has often been regarded as a problem in arterial pressure when in fact a more satisfactory common denominator would appear to be cellular damage due to inadequate capillary flow and resulting hypoxia. While a falling blood pressure is almost invariable in shock, the hypotension may be a relatively late development in the course of events. Similarly, while the degree of hypotension often correlates with the severity of the shock, there may be exceptions. Conversely, in severely shocked patients the blood pressure may be raised with vasopressors to normal or hypertensive levels, but the tissue blood flow is progressively reduced. Distribution of blood flow to nutritive or non-nutritive vessels is just as important as arterial pressure or cardiac output.

In its simplest form shock is largely a problem of blood gas transport and exchange at the pulmonary and cellular levels. Although cellular disorganization produced by a prolonged decrease in blood flow may originate from the breakdown of mitochondrial enzyme systems or the release of hydrolases from lysosomes, it must be recognized clinically as a decrease in the function of an organ system such as the myocardium, the kidney, or
the lungs. Improvement in the care of the shock patient, therefore, can be achieved by close and continuous observation of the patient and the changing clinical picture, repeated measurements of organ system functions by available techniques, and the appropriate use of fluids, solutes, and drugs. The clinical management of shock demands unrelenting personal attention because of the need to continuously monitor and treat hypovolemia, respiratory disorders, myocardial decompensation, renal failure and so forth.

PATHOPHYSIOLOGY OF SHOCK

An understanding of the changes resulting in the progression of events resulting in shock is essential for proper therapy. Many of the changes are time related and variable, depending upon the extent of the injury.

In hemorrhagic shock the primary problem is hypovolemia or decreased effective circulating blood volume. There is decreased venous return.

Cardiac output is decreased and the arterial blood pressure falls causing stimulation of baroreceptors. This results in an increased heart rate and the myocardium contracts with increased force.

Decreased capillary blood flow occurs.

There is neuroendocrine stimulation resulting in release of antidiuretic hormone and adrenocorticotropic hormone. The output of 17-hydroxycorticoid, aldosterone
and catecholamines is increased. The renin-angiotensin mechanism is activated. Arterial and venous vasoconstriction are produced. Hepatic glycogen breakdown is stimulated producing hyperglycemia and eventually hyperkalemia and glycogen depletion. Hypoglycemia may occur in terminal stages, since histamine, serotonin, and vasoactive polypeptide release may increase.

Available cardiac output to skin, skeletal muscle, kidneys, and the splanchnic bed is redistributed by both arterial and venous vasoconstriction to the central circulation, especially the heart and brain.

Capillary refilling of plasma volume occurs with resulting hemodilution. Adrenal steroids and the renin-angiotensin mechanism may participate in this refilling. Hyperventilation occurs. Initially this is probably secondary to decreased central nervous system blood flow. Respiratory alkalosis may follow the initial hyperventilation and further decrease cerebral blood flow by a fall in arterial pCO₂. Later, hyperventilation from metabolic acidosis occurs.

Cellular hypoxia, decreased aerobic oxidation through the Krebs tricarboxylic acid cycle and the electron transport system and an increase in anaerobic glycolysis by the Embden-Meyerhoff pathway occurs. Blood levels of lactate and pyruvate are both increased initially, but later, blood lactate increases more than pyruvate. Increased acid metabolites produce metabolic acidosis and
blood pH and carbon dioxide content fall.

Tissue adenosine triphosphate stores decrease, and levels of inorganic phosphate increase. Glucose utilization is decreased, and alpha amino nitrogen levels increase. Hyponatremia and hyperkalemia are produced.

There is depression of the reticuloendothelial system with decreased phagocytosis. Sludging and intravascular red cell aggregation may occur. There may be morphologic intracellular changes of cytoplasm with edema and mitochondrial disorganization as well as increased levels of lysosomal hydrolase enzymes and proteases in peripheral blood.

Regional vasodilatation and pooling of blood along with the other changes eventually lead to cell death.

The effects of hemorrhage and decreased blood flow on various organs can be discussed only in general terms. In the individual patient, these will depend on the presence of pre-existing organ or vascular disease. However, every organ participates in the shock syndrome by altering its function as a defense against the metabolic insult.

During shock, renal blood flow is decreased due to vasoconstriction of the renal arteries. There is an intrarenal redistribution of blood flow from the cortex favoring the medulla. A decreased glomerular filtration rate and oliguria are noted. Hourly urine volumes fall below 30 milliliters. There is a decrease in medullary sodium with loss of the medullary hyperosmolar zone and
loss of the countercurrent concentrating system. Activation of the renin-angiotensin mechanism occurs. Eventually tubular necrosis accentuated by pigment excretion of myoglobin or hemoglobin, or total renal shutdown with azotemia, hyperkalemia, and acidosis occurs.

The initial cardiac response is a decrease in output. The normal heart responds to changing venous return by cardiac output adjustments, and over significant periods the venous return must equal cardiac output. When hemorrhage has occurred, venous return is altered by peripheral factors (constriction, aggregation) as well as by the volume lost, and cardiac output falls in response to diminished venous return. This is counteracted by the pressure receptors in the aortic arch and the carotid sinus which, in response to hypotension, induce a reflex increase in heart rate and stroke volume. The coronary circulation has an extraordinary capacity for oxygen extraction, but at low pressure levels it may not be able to deliver sufficient oxygen to the myocardium to maintain contractility. Endogenous norepinephrine will increase myocardial contractile force, but will also increase the oxygen requirements of the myocardium. Acidosis may cause further deterioration of myocardial function. Pre-existing coronary artery disease may lead to myocardial infarction.

Decreased pulmonary blood flow may contribute to hypoxia and carbon dioxide retention. As shock progresses there is a loss of pulmonary elasticity due to the
sequestration of fluid in the interstitial space and increased capillary permeability with pulmonary edema. Sequestration of red blood cells and intravascular coagulation within the pulmonary capillaries may occur.

In the liver there is a marked reduction in the stores of adenosine triphosphate and decreased ability to break down lactate and detoxify other substances. Decreased blood flow to the gastrointestinal tract during shock results in mucosal ischemia and a decrease in mucin production which favors peptic ulceration.

The changes occurring after hemorrhage in normal man have been extensively studied by Moore.

RECOGNITION

Pure hemorrhage is a frequent cause of shock in massive gastrointestinal bleeding, penetrating trauma with injury to solid viscera such as liver, spleen, kidney or artery, ruptured aneurysm, etc. The clinical findings in the resulting hypovolemic shock are based largely on generalized vasoconstriction in the periphery and diminished volume return to the right heart with decreased cardiac output. The effect of excess endogenous vasopressors explains the cool, clammy skin with sympathetic overactivity. Similarly, tachycardia, tachypnea, and diastolic hypertension are signs of maximal peripheral resistance compensating for the early modest decrease in cardiac output. However, continued fall in cardiac output causes
arterial hypotension unless treatment is undertaken.

Clinical assessment of the magnitude of the hemorrhage is useful in planning therapy. The capillary blanching test is performed by blanching the skin of the forehead or hypothenar eminence by thumb pressure; normal cutaneous circulation will return in 1.25 to 1.5 seconds. Delay in refill is a crude indication of 20 per cent blood volume deficit or greater. Patients in frank shock either have insufficient cutaneous circulation for blanching to be evident, or demonstrate marked delay in refill. Another guide to the scope of the bleeding which has occurred has to do with having the patient sit up suddenly; when blood losses in excess of 15 per cent of circulating volume exist, sudden cerebral ischemia with dizziness, nausea or fainting follows assumption of the upright position.

The following maneuvers may be undertaken when a patient is admitted to the hospital with massive bleeding:
1. Intravenous catheter(s) inserted.
2. Blood to be typed and cross-matched is obtained.
3. Fluid and solute replacement is started.
4. Urinary bladder catheter is inserted and hourly urine volume measured.
5. Nasogastric tube is placed if source of bleeding is obscure.
6. Vital signs including pulse pressure are measured and recorded at specific intervals.
7. Extent of trauma, if any, is evaluated.
8. Hematocrit is obtained. May consider obtaining blood volume if available.

9. Central venous pressure catheter is inserted if not previously done as part of 1. above.

CENTRAL VENOUS PRESSURE MONITORING

A valuable asset in the diagnosis and treatment of shock is a central venous catheter—a large caliber plastic catheter inserted into the superior vena cava by way of the antecubital, external jugular or subclavian vein. Central venous pressure measurement, along with arterial blood pressure and urine output measurements, has greatly improved the care of the patient in shock. An inferior vena cava catheter influenced by abdominal pressure or a catheter in the vein of an extremity do not accurately reflect right atrial pressure, and are not suitable for monitoring central venous pressure. The catheter can be used for fluid administration and blood sampling in addition to pressure measurements.

A central venous pressure catheter should be used whenever a patient does not respond rapidly to what is believed to be adequate replacement of vascular volume. Normal right atrial pressure is zero to 10 centimeters of water or 2 to 8 millimeters Hg. If a patient does not respond satisfactorily to volume replacement and the central venous pressure is low, volume restoration should be continued until the central venous pressure begins to rise.
It is difficult to give an absolute level that can be used as an end point, but 15 centimeters of water or above indicates beginning circulatory overload. This is usually due to myocardial failure and is not a reflection of hypervolemia. However, additional fluid administration must be carefully considered. Other measures such as digitalis, other drugs having an inotropic cardiac effect, or vasodilator agents may be required. The subject of central venous pressure monitoring has recently been reviewed by Borrow and Escaro.

Patients requiring positive pressure ventilation may have an elevated central venous pressure on this basis, even with persistent hypovolemia. Central venous pressure may also be normal or high in hypovolemic patients if there is poor coronary artery perfusion decreasing right ventricular function. As coronary perfusion is improved by volume replacement, central venous pressure may fall. There are other causes of a false elevation of central venous pressure which must be kept in mind: mechanical obstruction of the venous return, as seen in cardiac tamponade, mediastinal compression, or venous thrombosis; hemothorax and pneumothorax; the administration of vasoconstrictors; and improper placement of the catheter. All of these factors will produce a high central venous pressure.

REPLACEMENT OF BLOOD, FLUID AND VOLUME
Hypovolemia must be considered initially with shock from any cause, since fluid or blood administration may be helpful even if no losses are suspected or can be documented. A helpful concept that has evolved is to achieve an effective circulating blood volume. It is the best guide to the volume of blood and fluids needed, and one of the most common problems in the treatment of shock caused by hypovolemia is inadequate volume replacement.

The vascular space is not a static volume. Vasoconstriction of resistance vessels, terminal arteries and arterioles, may divert blood from various regions, but the largest change in vascular bed volume probably occurs in capacitance vessels, the capillaries, venules, and veins. Constriction of capacitance vessels in shock reduces the peripheral vascular volume and increases the central volume to a variable extent.

Treatment is best based on giving enough volume replacement to achieve a reasonable arterial blood pressure, good urine output, and good peripheral perfusion as judged by palpable peripheral pulses and warm, dry skin without elevation of right atrial pressure. This represents an effective circulating blood volume.

The significance of a median venous pressure, 6 to 10 centimeters of water, can be determined by a test infusion of fluid. An electrolyte solution is administered fairly rapidly and the central venous pressure is measured after every 100 cubic centimeters of fluid has been administered.
If the central venous pressure does not increase more than 5 centimeters during the infusion of the first 500 centimeters and returns to within 2 to 3 centimeters after 15 minutes of infusion, this would suggest that the heart tolerates the increase well and that further fluid is most likely required. On the other hand, an increase in central venous pressure would indicate that the heart is not capable of handling these additional quantities of fluid.

Estimation of blood loss following trauma is difficult. Hidden loss after injury, particularly with fractures of the femur or pelvis and with retroperitoneal hematomas, often escapes attention. Replacement is better based upon achieving an effective circulating blood volume than upon attempts at calculation with a balance sheet.

Volume replacement should be provided as rapidly as it is needed and tolerated. The urgency of fluid or blood administration to the hypovolemic patient must be stressed, since the longer shock persists, the more devastating its effect and the more difficult treatment becomes. Isotonic saline, Ringer's lactate solution, or clinical dextran can be given while blood is being properly cross-matched. Giving such fluids in the interim period with moderate hemorrhage may have additional advantages. It has been found that cardiac output and oxygen consumption are more rapidly increased by giving fluids containing no red cells in the initial treatment of shock. This may be due to decreased viscosity of the blood and better flow.
characteristics with hemodilution. With exsanguinating hemorrhage, type O Rh-negative blood with a low antibody titer can be used immediately if needed. Several infusion sites with large catheters and pumping devices may be required.

While shock is being treated, definitive treatment of the wounds or sites of hemorrhage must be started. It may not be possible to achieve normal cardiovascular function if blood loss continues. Circulatory support must be sufficient to maintain coronary, cerebral, and renal function while the patient is transported to the operating room or other suitable facility.

The treatment of blood loss is with blood transfusion, but blood alone may not be the best replacement solution. Saline solutions in addition seem to be helpful, since there seems to be an increased capacity or increased requirement of the circulation for blood volume to maintain pressure and flow in late or severe shock. The reasons for this have been summarized by Moore. It has been hypothesized that the increased sodium space and need for saline solutions with trauma and shock may be from a take-up of sodium salts and water by extravascular-extracellular tissue such as collagen and ground substance. Ringer's lactate has also been found helpful to the injured patient. Shires used Ringer's lactate solution initially in patients with hemorrhagic shock. One or two liters given rapidly to patients with marked hypotension often returned the blood
pressure to normal. If hemorrhage continued, blood was also given. One advantage to the use of Ringer's lactate solution rather than isotonic saline is the prevention of a further reduction in pH, which occurs with saline, by buffer dilution in an already acidotic patient. However, the question has been asked as to why give more lactate when the blood lactate is already elevated in shock. Studies have found that when Ringer's lactate solution is given to an animal in shock, the blood lactate level rapidly decreases if blood flow and cardiac output are improved. The excess levels of lactate quickly return to normal.

When blood loss is replaced with electrolyte or colloid solutions it is at the expense of reduction of protein concentration, hematocrit, and oxygen-carrying capacity. There is little known about the potential difficulties of protein dilution except that edema may result due to hypoproteinemia. It has been found that when blood volume is restored with Ringer's lactate solution, as compared with blood, a marked reduction in red cell mass did not inhibit improvement in oxidative metabolism.

Blood as commonly preserved and stored in a blood bank is an unphysiologic solution. It is frequently stored in acid-citrate-dextrose solution, and when received for use it is usually cold. The pH ranges from 6.6 to 7, and there is no ionized calcium due to a 30% excess of citrate. The plasma potassium levels may also be elevated. These abnormalities present no problem when small quantities
of blood are given. Citrate can be rapidly metabolized by the liver to bicarbonate and calcium is mobilized from body stores. The potassium is rapidly distributed in body fluids. In patients requiring massive or continuing blood replacement, or where shock is complicated by hepatic or renal disease, citrate is not metabolized rapidly and may decrease ionized calcium. Acidosis may be increased and the body temperature reduced. These abnormalities along with hyperkalemia, may not only reduce cardiac efficiency, but can produce cardiac arrest or ventricular fibrillation. 11 Bunker and his group found blood citrate levels sufficiently high to reduce ionized calcium in the blood in patients with hepatic disease or obstruction to hepatic circulation with multiple transfusions, or in any patient with extremely rapid or prolonged infusion of citrated blood. They also pointed out the difficulty of predicting when this would occur and the potential dangers of using calcium salts empirically. Rapid administration of calcium ion can produce increased ventricular excitability and ventricular fibrillation which is accentuated by decreased temperature. 28,33

MANNITOL

Mannitol is an agent frequently used in shock. It is helpful in protecting the kidneys and also in the diagnosis of acute renal failure. Mannitol is a six carbon alcohol which is not metabolized. It is readily filtered through
the glomerulus, and is not reabsorbed in the renal tubule. Even in patients with previously negligible urine output and maximal antidiuretic stimulation, it generally produces an osmotic diuresis with urine production. The functions of mannitol which are useful for the patient in shock are as a diagnostic test for acute renal failure in the patient with oliguria or anuria, and as a protection to the kidney when it is threatened with acute tubular necrosis from ischemia and nephrotoxic substances such as hemoglobin and myoglobin.

The rapid intravenous infusion of 12.5 to 25 grams of mannitol in the oliguric or anuric patient should produce an increase in urine flow unless there is acute organic renal failure. A lack of response to two such infusions within three hours is a strong indication of organic renal failure or acute tubular necrosis. It should be noted, however, that with severe persistent hypovolemia, mannitol may not induce a diuresis until this is partially corrected.

PLASMA EXPANDERS

Plasma expanders are colloid solutions which exert a colloid osmotic or oncotic pressure across the semipermeable capillary membrane and thus remain in the vascular compartment for a prolonged period. They may be necessary while blood is being prepared or secured since the first consideration in restitution of normal volume is not the infusion of red cells to increase oxygen-carrying capacity, but, rather, the re-establishment of normal circulating
volume. Colloids effective as plasma expanders are similar to albumin and should have a molecular weight above 50,000 so that they do not leave the circulation rapidly. Dextran is currently stockpiled by the Armed Forces and is the only plasma expander presently recommended by the National Research Council. The dextrans are long chain polysaccharides prepared by the growth of B-512 strain of Leuconostoc mesenteroides. They are hydrolyzed to various molecular weights with the average molecular weight being 78,000, and range of 45,000 to 180,000. They are inexpensive, chemically indifferent, and electrically uncharged.

When dextran is employed for plasma expansion, and transfusion of whole blood is anticipated, it is necessary to draw blood for typing and cross-matching prior to the dextran infusion, as this substance will cause some agglutination of red cells on the slide or in the test tube, making cross-matching difficult. Use of large volumes of dextran may result in hemodilution, reduced oxygen carrying capacity, and diminished erythrocyte buffering.

An increased bleeding tendency has been noted with dextran, particularly when large volumes are given. 6 Bloom found that a prolongation of bleeding time with dextran was related to expansion of the blood volume rather than the level of dextran and noted that this occurred with any plasma volume expander. Dilutional
hypoprothrombinemia, hypofibrinogenemia, and platelet coating with dextran may also play a part. This plus hemodilution limit the recommended total dose to one to two liters.

Pooled plasma has been considered excellent for emergency use as a volume expander. However, processing to eliminate the hepatitis virus through storage or heating have not proved completely effective. For this reason, the National Research Council Committee on Plasma and Plasma Substitutes recommends that the use of whole, pooled human plasma be discouraged or discontinued unless a clear-cut reason can be cited for its unique requirements. Human serum albumin would be excellent for volume expansion, but is almost never used for this purpose since it is expensive and may not be as readily available.

LOW MOLECULAR WEIGHT DEXTRAN

The microvasculature consists of all vessels of 100 microns or less in size. It consists of precapillary arterioles, capillaries, and venules. It is the part of the circulation that is involved with cell nutrition. Improvement of flow in this segment of the vascular bed is the primary aim in the treatment of shock. However, it was only recently realized that changes in the fluid structure of blood with cell aggregation or sludged blood could affect flow in this compartment. Blood is a viscid fluid, and in the microcirculation, where flow
may normally be slow or transiently stop, viscosity becomes important. Low molecular weight or low viscous dextran with an average molecular weight of 40,000 is of interest because it seems to have a beneficial effect on the microcirculation.

This effect of dextran of reversing cell aggregation and reducing blood viscosity seems to be caused by two principal mechanisms. One is a rapid increase in plasma volume by pulling interstitial water into the circulation, which produces hemodilution and reduces blood viscosity. The second is an influence on the red cell membrane by coating it or altering the protein envelope on aggregated cells.7

The effects of low molecular weight dextran on coagulation seem to be much the same as with clinical dextran. There is some prolongation of bleeding time because of increased tissue blood flow. Therefore, it must be used with caution or avoided in patients who are bleeding or might be bleeding, particularly if mechanical hemostasis is not possible. The final role of low molecular weight dextran in the treatment of shock has not been determined, but it has proved to be an interesting rheologic agent and has stimulated an entire field of worthwhile investigation.

OXYGEN AND VENTILATORY ASSISTANCE

One of the primary defects in shock is a reduced
oxygen supply to the tissues. Empirically, oxygen would seem to be indicated for all patients in shock. However, in the patient in shock with satisfactory ventilation, arterial oxygen saturation will be normal, and tissue oxygenation can only be improved by increasing blood flow and oxygen delivery. It is necessary to be certain that ventilation is adequate. Airway obstruction and inadequate ventilation require correction by endotracheal intubation, tracheostomy, or positive pressure ventilation.

Measurement of arterial blood gases and pH are necessary to determine carbon dioxide retention, hypoxemia, or acidosis which may precipitate or contribute to unresponsive shock. When pH is less than 7.35 and $P_{CO_2}$ exceeds 46 mm Hg, the patient has respiratory acidosis. For practical purposes, when the $P_{O_2}$ in arterial blood is less than 70 mm Hg (93% saturation), oxygen exchange is defective. Respiratory acidosis usually indicates either airway obstruction or inadequate bellows action because of neural, muscular, or mechanical deficit. Mechanical assistance of ventilation is usually needed. A sharp decline in oxygen tension or saturation usually indicates shunting through collapsed or consolidated lung. If this shunting effect is not promptly resolved after clearing obstructions or by mechanical ventilation, the concentration of oxygen in inspired air should be increased to 40% or greater. After oxygen content of arterial blood reaches normal levels, ischemic injury to organs and vital tissues,
including the heart, is minimized.

**VASOPRESSOR AND VASODILATOR AGENTS**

Sympathomimetic drugs are widely used by most clinically active physicians. Effects of these drugs comprise 4 broad types: constriction and dilation of resistance and capacitance vessels; inotropic and chronotropic actions; metabolic effects, such as glycogenolysis and lipolysis; and central nervous system stimulation. Sympatholytic drugs block one or more of these responses.

Vasopressor or constrictor drugs such as levarterenol (Levophed), metaraminol bitartrate (Aramine), and phenylephrine (Neosynephrine) have frequently been used in the treatment of shock, particularly when blood, fluids, and other measures do not raise the blood pressure to a satisfactory level. Such agents are practically always effective in elevating the blood pressure, at least transiently, even though the patient may ultimately not survive. There has been a fixation of the arterial blood pressure in shock, and frequently the blood pressure has been treated rather than the patient. However, this situation is now rapidly changing because of the knowledge that increased or prolonged vasoconstriction may be harmful and because of the availability of drugs which will increase blood flow rather than blood pressure. Cannon in 1923 wrote that increased arterial pressure was not what was needed in shock, but rather the need was for
increased capillary blood flow.

Sympathetic nervous system receptors may be divided into stimulatory or alpha receptors which produce vasoconstriction and peripheral inhibiting or beta receptors which vasodilate. Cardiac receptors are all stimulatory and are beta receptors which increase contractility, i.e., inotropic and rate chronotropic. Norepinephrine and metaraminol are alpha-stimulating drugs in the periphery, increasing resistance, and beta stimulating for the heart, increasing contractility and rate. Phenylephrine increases resistance with only a weak effect on the heart. Methoxamine hydrochloride (Vasoxy) and angiotensin II (Hypertensin) are pure alpha-stimulating drugs with no direct effect on the heart. Epinephrine (Adrenalin) has both alpha and beta stimulating effects which generally increase resistance and stimulate the heart. Isoproterenol hydrochloride (Isuprel hydrochloride) and mephentermine sulfate (Wyamine sulfate) are pure beta-stimulating drugs which vasodilate peripherally and stimulate the heart. Other classes of vasodilator agents are the alpha adrenergic blocking agents such as phenoxybenzamine hydrochloride (Dibenzyline) and ganglionic blocking agents such as trimethaphan camsylate (Arfonad camsylate).

In traumatic or hemorrhagic shock, there is only one potential physiologic indication for the use of vasoactive agents, and that is for temporary elevation of a markedly
reduced blood pressure which might produce cardiac arrest before blood and fluids can be given. Even then, a few hundred milliliters of saline solution will usually begin to elevate the blood pressure.

The significance of studies of blocking agents or vasodilators has been difficult to interpret in hemorrhagic shock because of decreased blood loss when the agent is given before the shock and the necessity to restore blood volume if such agents are given during shock. The beneficial effect of these agents has been thought to be due to reversal of the loss of plasma volume produced by vasoconstriction, decreased resistance with improved blood flow to tissues, and a decreased work load of the heart.

Lillehei has been one of the pioneers in the study and clinical use of phenoxybenzamine hydrochloride in shock when volume replacement has not produced improvement, and has reported clinical improvement and survival in otherwise unresponsive patients. He stresses the importance of adequate blood volume replacement with the use of the drug, which is given in a dose of one milligram per kilogram intravenously over an hour period. The effect of the drug persists for about 24 hours.

MacLean in studies of severe or unresponsive shock in man, found that isoproterenol was the drug of choice when volume replacement had elevated the central venous pressure but not improved arterial pressure and cardiac
output. Isoproterenol has a marked cardiac inotropic effect, increases heart rate, and produces vasodilatation. However, when it is given to the patient in shock with a high central venous pressure, blood pressure will frequently rise because of the improved cardiac output. One to two milligrams in 500 milliliters of dextrose and water is given at a slow rate not exceeding 15 to 20 drops per minute. Tachycardia may be a problem and careful titration is necessary.

In summary it may be said that the use of vasoconstrictor agents will probably decrease in the treatment of shock and that the vasoactive agents of choice will be drugs such as isoproterenol for patients unresponsive to volume replacement and other measures. The use of vasoactive agents is unsound if blood volume has not been adequately replaced as evidenced by central venous pressure measurement. However, they may be necessary for short term use when a fall in blood pressure has been so sudden and severe that cardiac arrest is imminent. In this instance a vasopressor agent may be lifesaving until fluids or blood can be given and other problems corrected.

METABOLIC ACIDOSIS

In shock there is a decreased carbon dioxide content of the blood. This was first confirmed in World War I casualties by Cannon. The metabolic acidosis produced during severe shock by cell hypoxia, anaerobic glycolysis,
and increased acid metabolites has been thought to be harmful and to further depress the circulation. As previously noted, the most important problem caused by acidosis in the human may be the propensity to cardiac arrest or ventricular fibrillation.

The arterial pH in patients in shock may be as low as 7.1, but is more frequently at levels of 7.25 to 7.35 because of respiratory compensation. Sodium bicarbonate is the most available and useful alkalinizing agent for treatment of acidosis, and some use it empirically in all patients with severe shock. Frequently this is not necessary, and documentation of the problem by measurement of pH and bicarbonate concentration or \( pCO_2 \) of arterial blood should be obtained whenever possible. Since large amounts of sodium bicarbonate with sizable sodium and water loads may be necessary to correct grossly abnormal pH, a more potent buffering agent, Tham or Tris buffer (tromethamine) has been studied. It has the ability to penetrate cells, but whether this intracellular buffering is advantageous is not known. It is, however, a potent hydrogen ion acceptor and has the distinct advantage of supplying buffer without sodium ion. It is also capable of promoting osmotic diuresis. Respiratory depression is common, and ventilatory support must be available. In a recent review, Bleich and Schwartz found nothing to recommend Tham over sodium bicarbonate in the treatment of metabolic acidosis. Hence, the place of Tham in the
treatment of shock is not definitely established, but it may be of some use.

STEROIDS

Hemorrhagic shock may develop in patients with adrenal insufficiency or those previously receiving steroids. Since a rare patient may have acute adrenal cortical insufficiency in such a situation and can be resuscitated by small doses of steroids, this empirical approach cannot be condemned in a desperate situation. A plasma sample for later corticosteroid determination may be helpful in proving the deficiency state. The use of massive doses of steroids in some forms of shock has become common practice, but will not be reviewed here.

OTHER CONSIDERATIONS

Digitalis. The physician treating a patient with high central venous pressure and inadequate cardiac output should consider the use of digitalis. Digitalization is justified in any patient in shock refractory to fluid therapy, beta inotropic cardiac stimulants, and alpha adrenolytic agents. Digitalis preparations are synergistic with isoproterenol.

Hypothermia. The potential usefulness of hypothermia in the treatment of shock has been demonstrated. An exponential fall in oxygen consumption occurs with decreasing body temperature indicating a decreased demand for oxygen by
by cells. Hypothermia, however, has not been used extensively. Two newer methods for reducing cellular oxygen demand are intravenous infusions of hypertonic glucose and magnesium. Neither method has had clinical application, but the concept of inducing a state of reduced oxygen demand may play a role in the future treatment of shock.

**Position of the Patient.** The Trendelenburg position has been used to treat shock, but vital capacity is decreased. The only reason for its use is to empty the veins of the legs, which may be the equivalent of a single blood transfusion. This can be quickly accomplished by raising the legs alone.

**SUMMARY**

Observations obtained from careful, partially controlled studies in humans with major bleeding have changed some classic concepts of shock management. The patient in shock must be observed by measurement of arterial blood pressure, urine output, and central venous pressure, in addition to general observations including skin color and capillary circulation. Essential laboratory studies for the difficult problem include determinations of serum electrolytes and arterial blood pH, pO₂, and pCO₂. Restoration and maintenance of an effective circulating blood volume should be carried out using whole blood, clinical dextran, saline, or Ringer's lactate solution. The use of saline solutions in addition to blood may be helpful.
If arterial pressure and urine output do not respond satisfactorily to volume replacement and central venous pressure rises, drugs which increase myocardial contractility such as isoproterenol and digitalis, should be considered. Drugs which produce vasoconstriction and increase myocardial contractility such as norepinephrine or aramine must be used cautiously in attempts to produce primarily an inotropic effect on the heart.

Improvement of alveolar ventilation, correction of metabolic acidosis, and replacement of continuing losses of blood and fluids may be critical. Mannitol seems to be helpful in protecting the kidneys, and low molecular weight dextran may help in improving blood flow in the microcirculation. The most frequent causes of lack of responsiveness to treatment are unrecognized volume deficits or continuing losses of blood volume, inadequate replacement of losses, myocardial failure, severe sepsis, peripheral pooling of blood volume, inadequate ventilation with hypoxia or carbon dioxide retention, or both, persistent metabolic acidosis, hyponatremia, hyperkalemia, hypocalcemia, and renal failure.

Measures directed at decreasing peripheral resistance, increasing cardiac output, and providing support for lung and kidney should be included in the treatment. Monitoring techniques have increased in sophistication, but intelligent, careful, minute-to-minute bedside observation remains the most important guide in care of the shock patient.
References


